Metabolic and Degenerative Diseases of the Central Nervous System

Pathology, Biochemistry, and Genetics

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PREFACE

The field of neuropathology has expanded recently with the addition of a considerable number of newly identified metabolic and degenerative diseases with numerous subtypes and variants, some of them affecting only a few families, or even individuals. This new information is dispersed in a large number of articles in a variety of scientific journals, some of which are difficult to obtain. In addition, taken individually, they do not offer clinicians, pathologists, or radiologists enough background for a sound interpretation of the pathogenetic mechanisms and natural history of each disease.

Clinicians often turn to neuropathologists with requests for information that may help them in solving difficult and complex diagnostic problems. General pathologists may experience difficulty in connecting the lesions in the nervous system with those found in other organs. Neuroradiologists must interpret the images obtained by modern diagnostic techniques in light of data obtained by anatomopathological observation. We trust that these specialists as well as others will find the information in this book sufficient and helpful in dealing with these problems.

Although there are many publications available on degenerative disorders of the central nervous system, they are generally proceedings of symposia dealing with specific diseases or a related group of disorders. Monographs devoted to metabolic disorders are less numerous, and most of them cover very distinct areas of the field. In compiling this book, based partly on personal experience and largely on studies of the literature, we have attempted to cover the current knowledge of the subject in a comprehensive manner, including recent advances, particularly in the fields of biochemistry and genetics.

A compilation of this type has involved an immense amount of work by both authors, extending over a number of years, yet we decided against allocating individual chapters to experts in their particular fields. Work carried out by two close collaborators offers distinct advantages: all chapters have been revised by both authors, ensuring uniformity of style and approach and avoiding overlaps or repetition. In multiauthor books overlap and repetition are unavoidable, as are differences of opinion and, occasionally, frank contra-

diction. In addition, it is often difficult to keep all contributors to a strict deadline, and delays by some authors render the work of others obsolete.

Needless to say this work could not have been carried out without considerable help. We are particularly grateful to Dr. K. Jendroska for advice on some aspects of brain pathology and to Dr. S. Patt for guidance on genetics. Several colleagues provided illustrations and are acknowledged in the legends. An immense amount of technical work was carried out cheerfully and efficiently by Mrs. Angela Becker, Dr. G. Hamdorf, Mrs. Katrin Kern, and Mrs. Angela Ludwig. Finally, our thanks to Academic Press, particularly Dr. Jasna Markovac and Mrs. Suzanne Miller, for their cooperation and efficient publication of this book.

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PRELIMINARY REMARKS

The juxtaposition of apparently disparate groups of disorders, metabolic and degenerative, requires justification. The diseases of the nervous system characterized by primary disturbance of metabolism form fairly well-defined entities, and their etiology and pathogenesis have been largely elucidated. On the other hand the pathogenesis of the so-called degenerative diseases remains obscure. The wide range of their clinical manifestations depends on the variable distribution of lesions. A common feature of both groups is the prevalence of genetic disorders. It used to be held that metabolic diseases manifested themselves in childhood, while degenerative disorders appeared at a later age. This is no longer true. An increasing number of metabolic diseases make their appearance in adult life, while a number of degenerations, particularly genetic ones, affect infants or children. The distinction based on age group has largely lost its validity.

The characteristic lesion of degenerative disorders is a more or less slowly progressive loss of the functional elements of the nervous system, leading to atrophy. This atrophy often involves specific circumscribed areas or systems. The metabolic disorders tend to have a ubiquitous distribution and involve all those elements of the central and peripheral nervous system that depend on the same metabolic processes. The deposition of products of disordered metabolism in the cytoplasm of nervous and other cells is a feature of many metabolic diseases, while we tend to encounter a simple loss of neurons followed by the formation of glial scars in degenerative disorders. Here again the differences are not clearly defined. Some degenerative diseases display an accumulation of pigments, particularly lipofuscin, and others may contain intracellular inclusions of a proteinaceous nature. Atrophy and glial scarring are often features of the end stage of metabolic disorders. Finally, no intracellular storage occurs in disorders of amino acid metabolism.

Not so very long ago the amaurotic idiocies, leukodystrophies, myoclonus epilepsies, etc., were classified among degenerative diseases. The distinction between lipidosis and leukodystrophies was based purely on the localization of lesions in the gray and white

matter, respectively. More recently the underlying metabolic defects of these disorders have been identified. It is of interest that W. R. Gowers (*Lancet*, **1**, 1003–1007, 1902) ascribed the distribution of lesions in system degenerations to disorders of metabolism affecting groups of neurons sharing a similar function. The coexistence of metabolic and degenerative changes in the same patients has been repeatedly pointed out and the presence of a metabolic disorder in a degenerative disease has been demonstrated in Parkinson's disease. Subsequent findings have provided further evidence of a connection between metabolism and degeneration in other diseases.

The elucidation of the pathogenesis of a large number of metabolic disorders has led to the concept of specific, genetically determined, enzyme defects, and these conditions are classified accordingly. The degenerative diseases are still classified on an anatomical basis, i.e., the distribution of lesions, although recent advances strongly suggest that this classification is only provisional. Recent experience has transferred a large group of leukodystrophies to the metabolic groups, and Creutzfeld–Jakob's disease to the infections group. There is increasing evidence that defective DNA repair may underlie some degenerations and this may well be the mechanism of a large number of degenerative disorders. In spite of this blurring of the boundaries it is still necessary in our present state of knowledge to retain the nosological distinction between metabolic and degenerative disorders, if only for the purpose of classification.

The number of mutants in mammalian species leading to metabolic or degenerative disorders has expanded enormously in recent years. A detailed description of these mutants and their pathology is outside the scope of this volume. They will, however, be considered, with appropriate references to the literature, whenever they shed any light on analogous human diseases.

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Introduction

Schwann (1839) was the first to use the term *metabolic phenomena*. He defined *metabolism* as "the sum total of chemical transformations which take place in living cells or in the surrounding internal environment through the activity of these cells." The term, or its vernacular equivalents, is now universally accepted. Discoveries in the field of biochemistry have led to a more precise definition of the concept while retaining the overall meaning of the word. A brief outline of the evolution of this concept is essential for understanding the pathophysiology of metabolic diseases.

Metabolism is confined to living organisms. The cell, as the smallest living unit, is the site of continuous metabolic activity. This consists of the synthesis (anabolism) and degradation (catabolism) of living constituents, as well as processes providing energy for various bodily functions. Most of these chemical reactions would run too slowly to be effective, if not accelerated by the catalytic action of enzymes. Over 1000 of these biological catalysts have been identified to date and more are discovered continuously. The enzymes have the structure of proteins of relatively high molecular weight. They are highly specific both antigenically and in their catalytic activities.

Enzymes, like other proteins, undergo continuous synthesis and degradation. Their synthesis is controlled by the genetic code enshrined in the structure of DNA, which forms the template for the amino acid sequence of the proteins.

The structure of proteins may be considered on several levels: the amino acid sequence of the polypeptide chain (primary structure), the helical or sheetlike configuration of the chain (secondary structure), the three-dimensional spatial arrangement of the chain (tertiary structure), and finally the linkage of several chains that form the subunits of a biologically active protein (quaternary structure). Even minor changes in the primary structure, such as the substitution of a single amino acid, may have far-reaching consequences for the tertiary and quaternary structures, and thus for the functional activity of the enzyme.

The enzyme systems are not uniformly distributed within the cells. Glycolytic enzymes are localized in the cytosol; those of the respiratory chain form part of the mitochondria,

while hydrolytic enzymes operate in the lysosomes. The enzymes form an integral part of the structures of the subcellular organelles; hence, alterations in enzyme structure may be reflected in morphological changes within the cell. Cellular structure and metabolism are so closely coordinated that certain specific structural changes may hint at the underlying metabolic error. While care must be taken not to confuse artifacts with genuine lesions, immunohistochemistry has revealed generally good preservation of molecular structures in routine histological preparations. The lysosomal and peroxisomal apparatus is well visualized by electron microscopy, which has given valuable insight into the pathogenetic mechanisms operating in some metabolic disorders.

Every disease may be accompanied by metabolic disturbances. Environmental factors (e.g., malnutrition, vitamin deficiencies, and poisons) and auxiliary mechanisms (e.g., disorders of absorption, transport, and excretion) must be distinguished from primary metabolic disorders due to the defective activity of one or more enzymes. The latter are discussed in this volume, inasmuch as they affect the central nervous system (CNS) and the peripheral nervous system. Most of these diseases are rare; some, exceedingly so.

Fundamentals of Metabolic Diseases

The maintenance of all vital functions depends on the integrity of metabolic processes. Atrophy and necrosis result from global impairment of metabolic functions, due to imbalance, or arrest, of the processes of synthesis and degradation. Metabolic diseases do not, as a rule, involve such global processes, but depend on the impairment of synthesis or breakdown of specific substances in the living cell. The intracellular deposition of abnormal substances, recognizable by routine histological methods and roughly identifiable chemically, led to the concept of storage disease.

The term *storage disease* was first applied by von Gierke (1929) to glycogenosis. The concept of true storage diseases was confined to disorders in which retention of intermediate products of cellular metabolism was an essential and irreversible feature (Siegmund, 1938; Giampalmo, 1951).

It is erroneous to consider storage to be a primary pathogenetic mechanism, however impressive it may be to the morphologist. Rather, it is an epiphenomenon of the underlying metabolic defect. Nevertheless, the chemical nature of the stored substances remains an essential criterion for the classification of the metabolic diseases, at least for the time being.

Lysosomal Storage Diseases

Lysosomes are organelles characterized by an extraordinary abundance of acid hydrolyses. The number of enzymes identified in the lysosomal fractions has increased considerably over the years. Increased activity of this enzyme is a common finding in lysosomal diseases in which acid phosphatase can be demonstrated histochemically.

The lysosomes are enveloped in a membrane corresponding in thickness to the plasma membrane of the cell surface (de Duve, 1969). They contain products of

degradation both in the normal process of catabolism and in pathological storage. In the latter situation the stored material is found in residual bodies (see below). The term *lysosomal storage disease* was introduced by Hers (1964) and is now generally accepted. The appearances of the lysosomes depend on the nature of the stored material, which, in some disorders, may be sufficiently characteristic to allow a morphological diagnosis.

The morphological heterogeneity of lysosomes is due to both the nature of the ingested material and its means of entry. The presentation of the material differs between heterophagy (the breakdown of exogenous substances) and autophagy (the breakdown of cell components). As a rule, heterophagy plays no part in most metabolic diseases.

The lysosomal degradation of a cell's own constituents is part of the normal turnover of cell components. This does not involve ingestion of materials from outside and can also be divided into three phases.

1. The sequestration of an area of cytoplasm leads to the formation of an autophagosome, which does not contain lytic enzymes. This involves the formation of a membrane demarcating the sequestrated portion (Pfeifer, 1987).
2. As the degradation proceeds a secondary lysosome is formed. As the process of autophagic digestion occurs continuously, one must postulate a cyclical turnover of lysosomes, in which newly formed ones may play a part.
3. In the process of digestion, all formed and unformed constituents are broken down into micromolecular fragments. After the completion of lysosomal degradation, the secondary lysosomes become telolysosomes (de Duve and Wattiaux, 1966). Secondary lysosomes that retain incompletely digested material are called residual bodies. They are the morphological substrate of the lysosomal storage diseases, but are also formed in nonpathological cells.

As autophagy is a continuous process in normal cells, they contain a normal complement of lysosomes. However, as metabolic processes differ in individual cell types, their residual bodies display qualitative and quantitative differences. Lipofuscin granules (Fig. 1A) are present in residual bodies in normal neurons. The residual bodies of oligodendrocytes contain "fingerprint" bodies (Fig. 2). The uniformity of these two types of residual bodies suggests that they are both autophagic in nature.

By contrast, the astrocytes, which are capable of heterophagy, contain highly pleomorphic residual bodies (Fig. 3). The pericytes of cerebral capillaries and the adventitial cells of arterioles and venules display characteristic globular lipid inclusions (Fig. 1B).

Transient overloading of lysosomes may occur when the uptake of substrate is greater than the lysosomes can digest. A good example is the accumulation of protein droplets absorbed by the proximal renal tubules.

Some proteins, such as immunoglobulins and collagen, are relatively resistant to the action of lysosomal proteases, and, under conditions of rapid endocytosis, many accumulate in secondary lysosomes. Intensification of autophagy may lead to a striking increase in the number of lysosomes. Glucagon stimulates a multiplication of autophagic vacuoles (Deter, 1971). Ionizing radiation also causes increased autophagy (Cervós-Navarro, 1964).

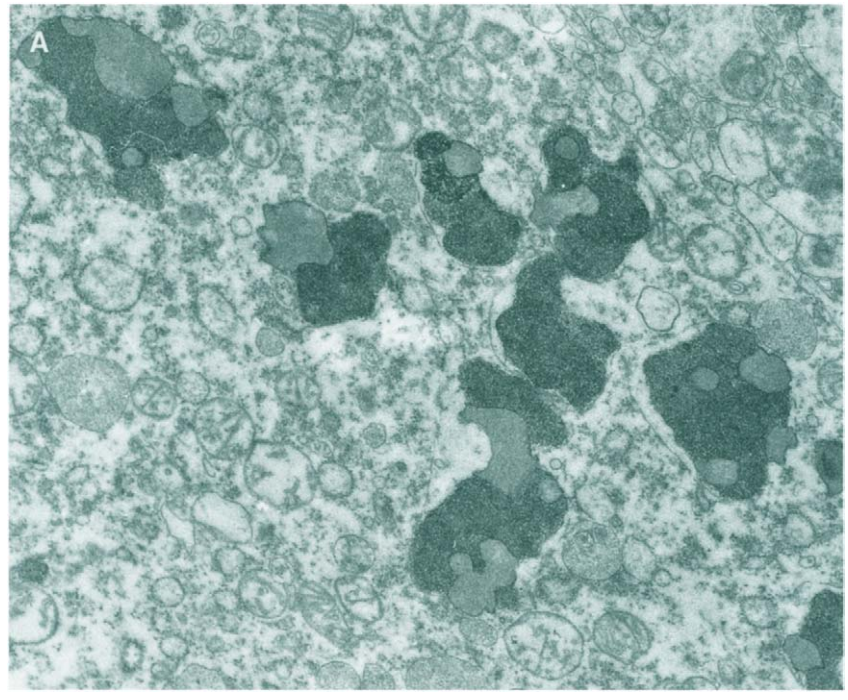


Fig. 1 (A) Lipofuscin granules, ×20,000.

Experimental inhibition of lysosomal enzymes leads to a temporary and reversible increase in the number of residual bodies (de Duve, 1983; Henell and Glamann, 1984). A permanent overload may occur in incomplete digestion, in which each cycle adds to the residue. This may occur when indigestible substances, such as dextran, find their way into lysosomes (Roberts *et al.*, 1976; Pfeifer *et al.*, 1984) or when an enzyme is missing, as in genetic storage diseases. In these situations the time factor must be taken into account, as a certain length of time is required for the accumulation to become morphologically appreciable.

Certain basic ultrastructural patterns may be identified (Figs. 4–9). Even if these patterns are not pathognomonic for any particular disease entity, they are at least partially specific and offer useful diagnostic pointers.

Disorders of Other Organelles

Although lysosomal diseases account for the bulk of metabolic disorders, many diseases are caused by the malfunction of other organelles and deficiencies in their enzymes. Abnormalities in mitochondrial and peroxisomal functions have attained increasing importance in recent years. The mitochondrial enzymes are predominantly dehydrogenases,

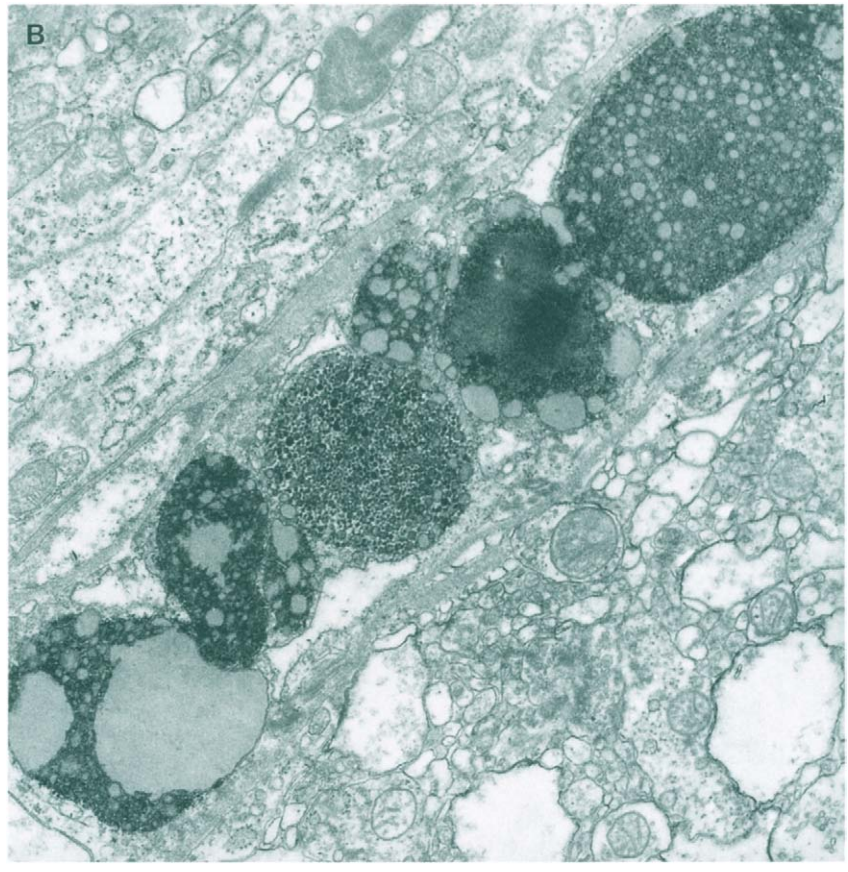


Fig. 1 Continued. (B) Lipophagosomal residual bodies, ×12,000.

primarily involved in oxidative phosphorylation. They are therefore responsible for the normal functioning of the respiratory chain, and deficiencies in these enzymes can lead to disease processes in which this metabolic cascade is interrupted.

Peroxisomes contain a great variety of enzymes, peroxidases, catalases, and several enzymes active in the degradation of very long-chain fatty acids. A deficiency of these enzymes can lead to several recently recognized diseases, the hallmark of which is storage of these fatty acids.

Enzymopathies

In a study of alkaptonuria, Garrod (1908) assumed a congenital absence of an enzyme and developed the concept of inborn errors of metabolism. Beadle and Tatum (1941)

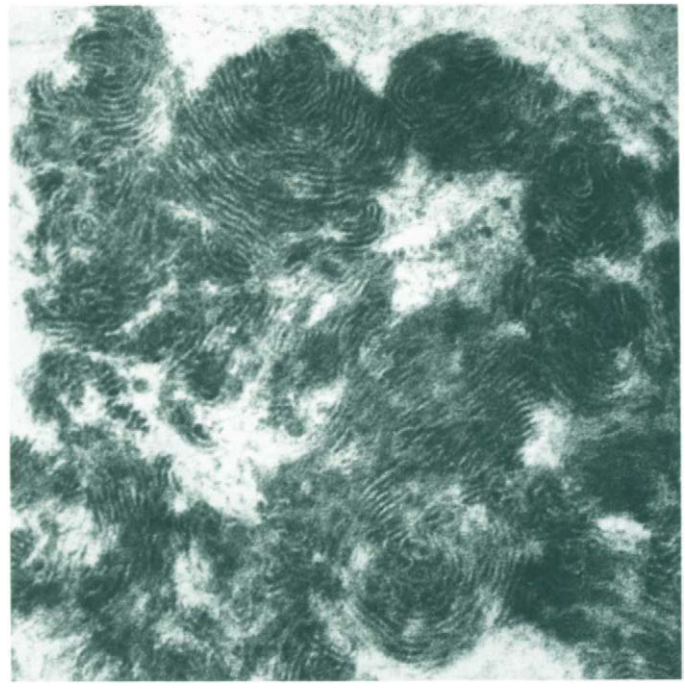


Fig. 2 "Fingerprint" bodies, ×125,000.

demonstrated in mutants of bread yeast (*Neurospora crassa*) that the genetic control of metabolism operates through the genetic control of enzyme synthesis. This confirmed Garrod's hypothesis and defined the inborn errors of metabolism as permanent, genetically conditioned, metabolic disorders caused by enzymatic defects.

The absence or functional insufficiency of a specific enzyme cannot always be reduced to a single "missing enzyme." The concept of enzymopathy is wider than that of a "defective enzyme" or a missing enzyme. In theory, at least, one can distinguish enzymopathies with reduced enzyme activity from those with increased activity. As a rule, only the former manifest themselves as diseases in which a definite metabolic function is abolished or inadequate. The formation or breakdown of a specific substance then becomes impossible or greatly impaired. A gradual reduction of enzyme activity and disturbances of interaction between enzyme and substrate are also included in the concept of enzymopathy. Enzymopathies may be inherited or acquired. Only the former represent the classical inborn errors of metabolism.

The activity of enzymes may be impaired or enhanced by a variety of factors (e.g., nutritional or hormonal). The synthesis may be subject to similar influences. The sequence of aminoacids in any specific enzyme is genetically determined and coded in the nucleic acid sequence of DNA (structural genes). It used to be assumed that a de-

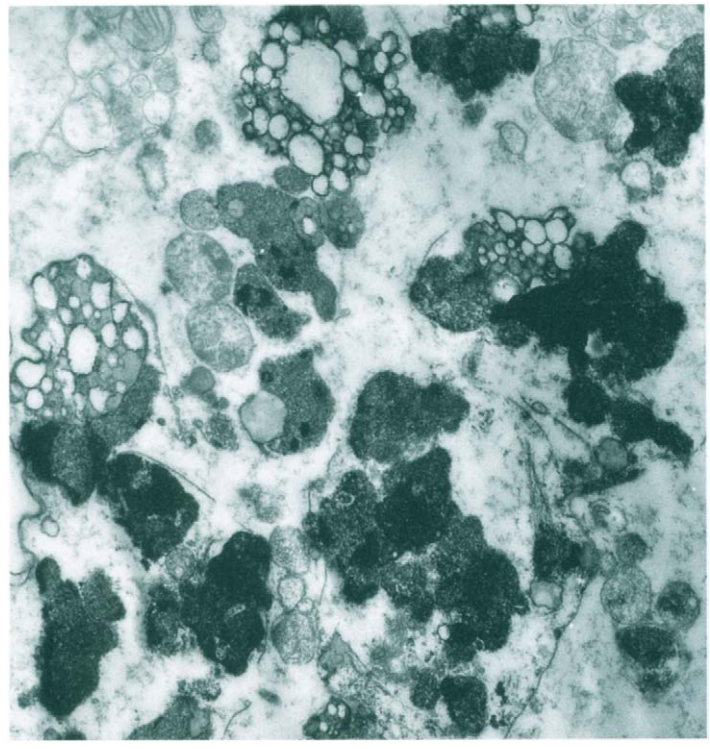


Fig. 3 Pleomorphic inclusions, ×12,500.

fective gene abolished the synthesis of the corresponding enzyme, which was therefore missing (Tatum, 1959). In many cases, however, a minor alteration of the DNA sequence will result in not a missing, but a modified, enzyme. Some enzymes are composed of several polypeptide chains, each of which is coded by a different gene. The integrity of such enzymes depends on the preservation of all relevant genes.

Most enzymopathies are due to mutations in structural genes, coding for specific enzymes, but other mechanisms may lead to impaired enzyme activity. A progressive loss of enzymes may be involved in muscular dystrophy, in which a defect in the cell membrane may lead to leakage of metabolic components from the interior of muscle cells. This may be compensated for some years by increased enzymatic synthesis of the lost components, but ultimately this fails, leading to an irreversible loss of tissue. The uptake of lysosomal enzymes depends on the presence of specific receptors (Neufeld *et al.*, 1977). Some lysosomal storage diseases may therefore be due to receptor defects.

Hydrolases, like all other enzymes, are hydrophilic. *In vitro*, they show little activity in the degradation of lipophilic substances. This is largely due to the fact that

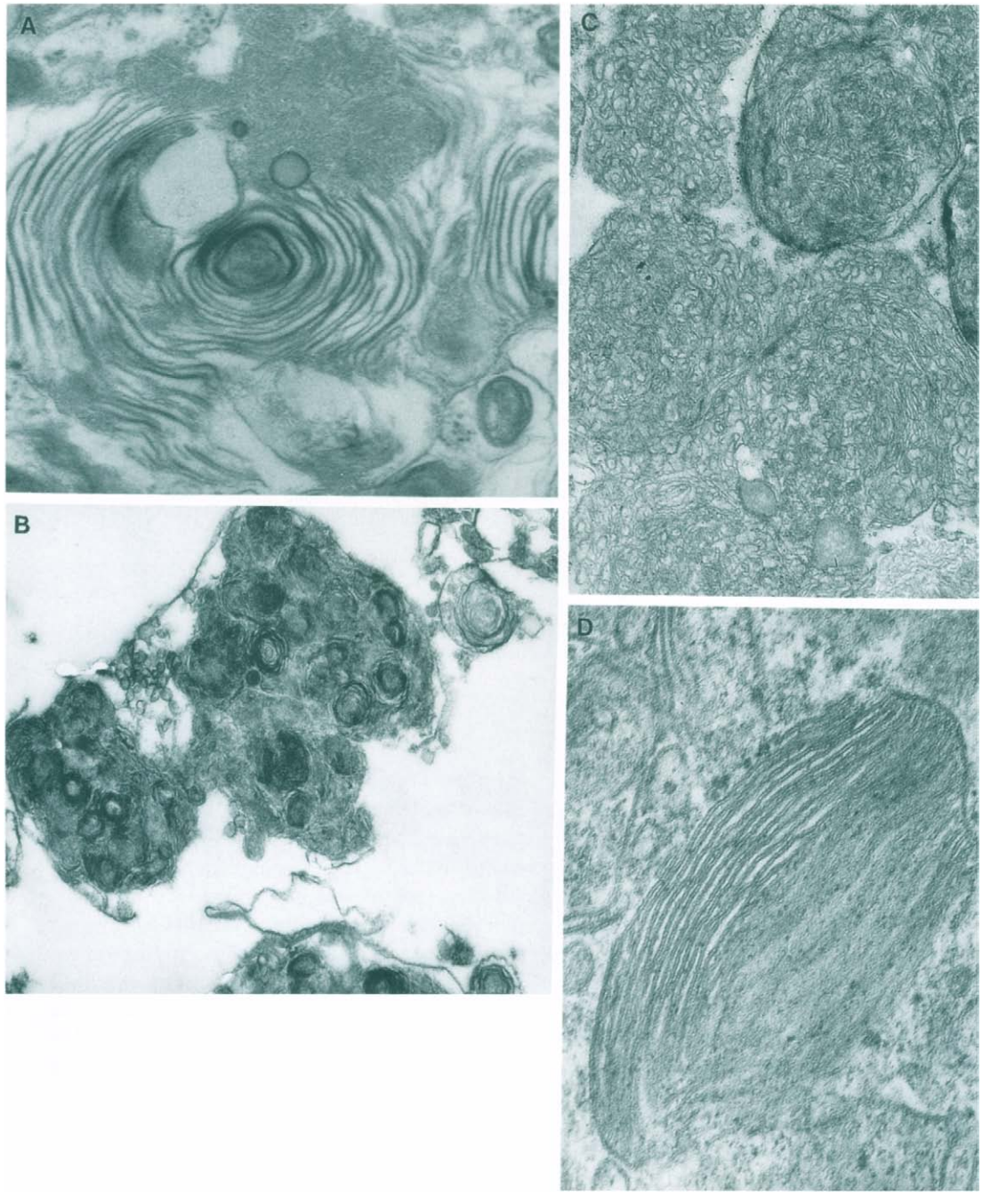


Fig. 4 Lamellar inclusions. (A) With concentric membranes, ×34,800. (B) With multiple small membranous whorls, ×10,440. (C) With irregular membranes, ×52,200. (D) With parallel bilaminar membranes, ×52,200.

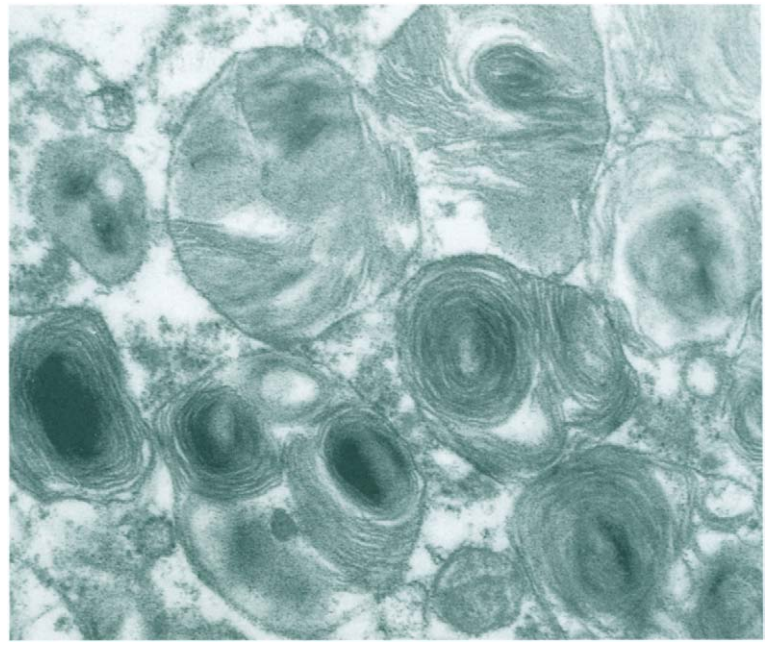


Fig. 5 Concentric lamellar inclusions with a dense center, ×38,000.

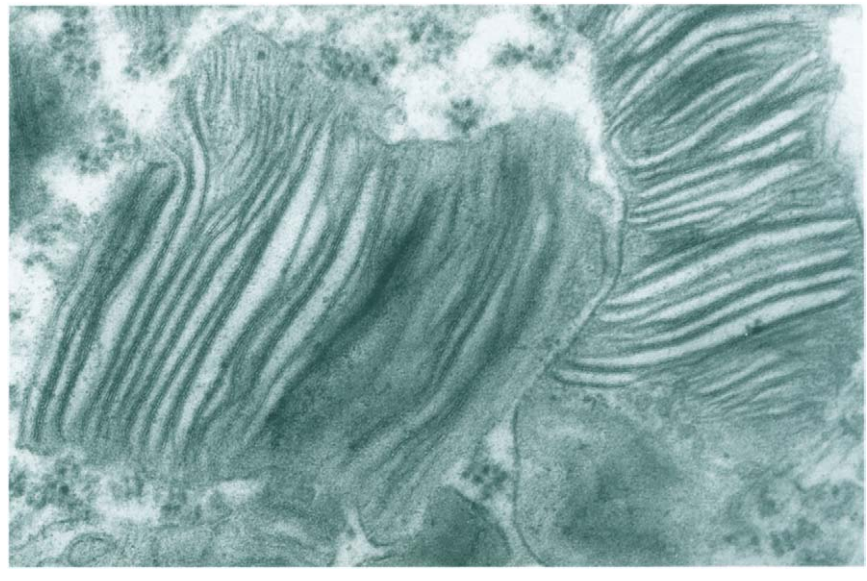


Fig. 6 Zebra bodies, ×40,000.

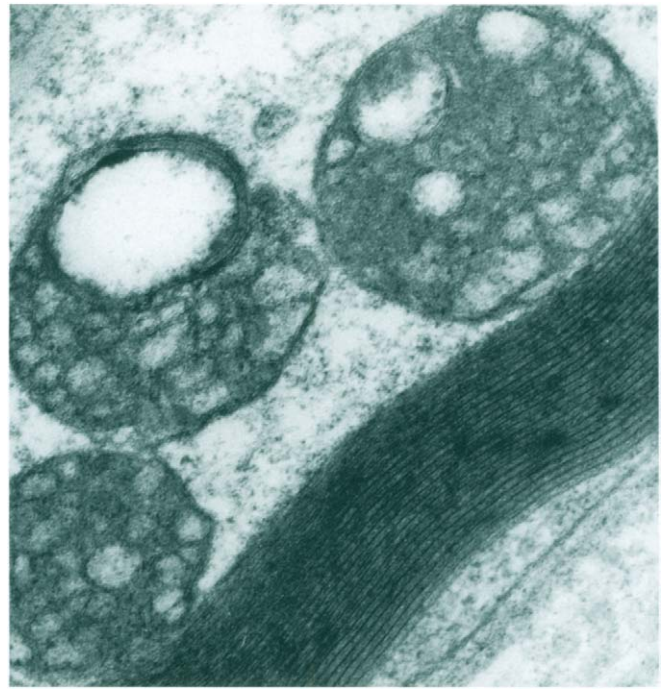


Fig. 7 Multivesicular bodies, ×40,000.

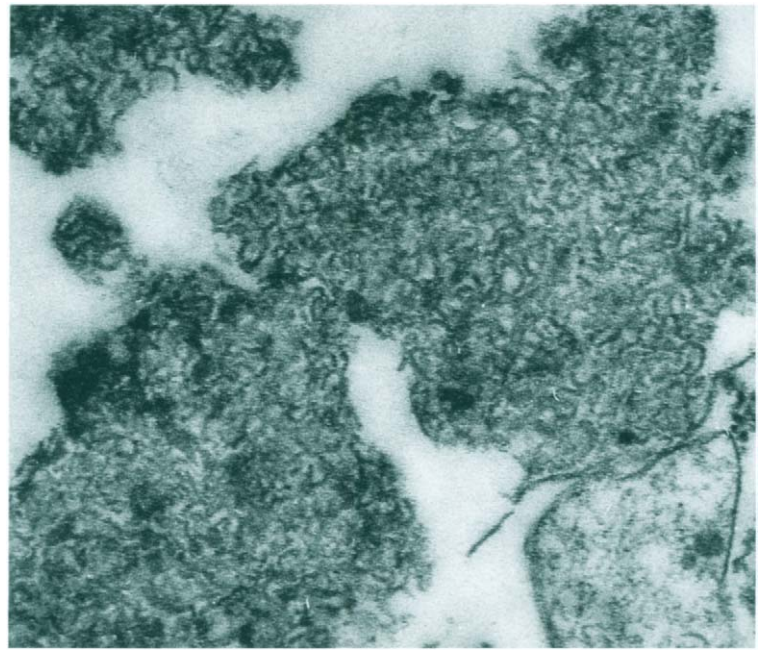


Fig. 8 Curvilinear inclusions, ×28,000.

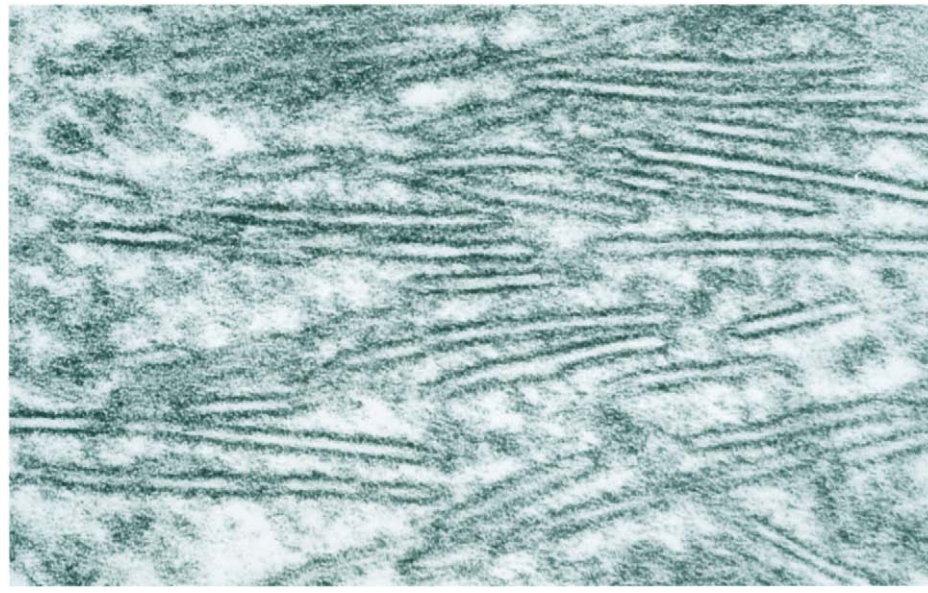


Fig. 9 Elongated bilaminar structures, ×10,000.

lipids, particularly apolar ones (e.g., triglycerides and cholesterol), form aggregates (micelles) that are impenetrable by the enzymes. The activity of the hydrolases was explained by the discovery of nonenzymatic protein activators. The first such activator, necessary for the degradation of sulfatides by arylsulfatase A, was isolated by Mehl and Jatzkewitz (1964). The activator forms a complex molecule with the lipid, converting it into a suitable substrate of the enzyme. The absence of appropriate activators explains the pathogenesis of some metabolic disorders in which storage occurs despite normal enzyme activity *in vitro*.

Classification of Metabolic Diseases

In spite of the recent contributions of molecular biology, our knowledge is still too limited for a classification based on identification of the enzyme. To provide a comprehensive classification of metabolic disorders, useful to both the clinician and the pathologist, a variety of criteria should be adopted.

A classification based on storage phenomena, however, is not universally applicable, as, in some conditions, there is no morphologically demonstrable storage of metabolites. This applies particularly to disorders in which the retained substrate is water soluble and extended in the urine. This, as well as the similarity of various storage diseases under light microscopy, renders a purely phenotypic classification system insufficient.

Electron microscopy has added a refinement to phenotypic classification when it became apparent that many stored substances had characteristic ultrastructural profiles. The chemical characterization of stored substances led to an improved classification of metabolic disorders based on classes of substances. Further investigations, however, have revealed that substances of different classes may be stored simultaneously. This may occur when a defective enzyme is responsible for the degradation of complex substances consisting of carbohydrates, amino acids, and/or lipids.

This characterization has already been achieved in many metabolic disorders and has been of great importance in the isolation of subtypes and variants. The identification of structural defects in enzymes plays an increasingly important role in the systematic classification of metabolic disorders. We are still faced with difficulties, however, as a large number of conditions continue to await identification of the responsible enzyme.

Genetics of Metabolic Diseases

The concepts of dominance and recessivity were originally defined by Mendel (1965). Recessive alleles are expressed only in homozygotes. Dominant alleles mask or suppress the expression of the other (recessive) allele of the same gene. These genes therefore express themselves in heterozygotes. It may be added that these concepts are not absolute and that a range of expressivity may be formed between the two extremes. The mechanism of recessive inheritance is generally better understood than that of dominance. Most enzymopathies are inherited as autosomal—some, as sex-linked—recessives. The gene expression is subject to a regulatory mechanism.

In all highly developed multicellular eukaryotes the cells undergo differentiation, leading to a multiplicity of cell types. In the human body there are about 200 different cell types, each of which contains an identical genome. Each cell synthesis yields between 10,000 and 20,000 different proteins, many of which are specific to a particular cell type. In this process only 7–10% of the entire genome is expressed in each cell. It is likely that the remaining 90–93% of the genes should be inactivated by specific repressor proteins. A regulatory mechanism must therefore exist to control correct gene expression.

The sequence of events leading to gene expression is now well understood, albeit with some gaps in our knowledge (Willman, 1993; Latchmann, 1993; Rosenthal, 1994). The human genome contains 100,000 distinct genes, encoding all structural and functional proteins. Every cell contains two alleles of these "single-copy" genes: one of maternal origin, the other of paternal origin. These single-copy genes compose only 3–5% of the 3.2 billion nucleotide base pairs (bp) that make up the nuclear human genome. The vast majority of the genome is composed of noncoding DNA, the function of which has not been fully elucidated.

Each gene consists of a DNA strand divided into several encoding sequences (exons) separated by nonencoding ones (introns). Attached to the 5′ end of the gene, there is a promoter, consisting of adenosine and thymidine nucleotides (the "TATA box")

and a variety of enhancers. Transcription starts by the action of the enzyme RNA polymerase associated with a number of transcription factors. The whole DNA sequence is transcribed to form the premessenger RNA. The transcript is then processed in several stages. A nucleotide cap is added to the 5′ end while several bases are trimmed from the 3′ end by the action of the RNA clipping enzyme. A polyadenosine tail is added to the trimmed 3′ end by the adenosine adding enzyme (terminal transferase). Spliceosomes then excise the introns and join the ends of the exons. Apart from this regular splicing, "alternative splicing" also occurs, by which the exons are rearranged and some are omitted. The mechanism of this process is not understood, but it enables each gene to code for several different, but related, proteins. The processed transcript becomes the messenger RNA, (mRNA) which leaves the nucleus for the cytoplasm, where it enters the ribosomes. The mRNA is then translated into proteins, each nucleotide triplet coding for a different amino acid. At the end of this chapter, abbreviations of the amino acids are listed. Posttranslational modifications may still alter the end product.

The whole process is regulated by other genes, enzymes, growth factors, inducers from neighboring cells or tissues, and hormones. In view of the complexity of the process, it is surprising that faulty end products are comparatively rare. The main types of genetic aberrations fall into the following groups: (1) point mutations, in which a substituted nucleotide in a triplet codes for a different amino acid; (2) deletions, in which an exon or part thereof is excised in the process of splicing, sometimes with the insertion of a foreign sequence; and (3) repeats, in which a nucleotide triplet is repeated sequentially, forming a long chain. All of these cause the formation of a missense or nonsense end product, whether it be an enzyme or a structural protein.

A small quantity of DNA is also present in mitochondria (mtDNA). The mitochondrial genome consists of about 16.5 kilobases (kb), arranged in two strands: a heavy one and a light one. Each strand has its own promoter that initiates transcription. The mitochondrial genome encodes for 13 structural proteins, two ribosomal RNAs (rRNAs), and 22 transfer RNAs (tRNAs). Each cell contains multiple mitochondria, and each mitochondrion includes several copies of its genome.

Mitochondria are inherited maternally, as only the naked nucleus of the spermatozoon enters the ovum during fertilization. During cell division mitochondria are distributed at random. In normal tissues all copies of the mitochondrial genome are identical (homoplasmy). In most pathological situations both normal and mutant genes may be present (heteroplasmy). A certain minimum number of mutant genes must be present in order to be expressed (the threshold effect). The threshold may vary in different tissues according to each tissue's energy requirements. Because of the random distribution of mitochondria, only some offspring of an affected mother may reach the threshold and express the pathological phenotype.

Several methods are now available for the localization or identification of abnormal genes. Naturally occurring variations in DNA sequence (polymorphisms) have been exploited in the identification of disease-associated genes. Polymorphisms in human DNA occur predominantly in two forms: (1) restriction fragment-length polymor-

phisms (RFLPs) and (2) variable-number tandem repeats. RFLPs are variations in DNA sequence between individuals, which abolish or create new restriction endonuclease clearage sites. Using DNA probes that are complementary to a polymorphic region of DNA, variation in a restriction endonuclease cleavage site in this region in different individuals can be detected by Southern blot analysis.

Polymorphisms in DNA sequence surrounding single-copy genes have no effect on gene function. However, if these polymorphisms are adjacent to (i.e., "tightly linked" with) a gene of interest (e.g., a gene for a distinct disease), they are said to be "informative" and may be used for disease diagnosis. In the study of a family with a genetic disease, it may be found that a polymorphism always cosegregates with the clinical manifestation of the disorder. This would imply that the particular polymorphism is lying near the gene containing the disease mutation. This polymorphism can then be used as a marker of the disease gene, even though the precise location, structure, sequence, and function of the disease gene are unknown. These disease genes, which are localized by polymorphic markers, can be produced in large amounts by molecular cloning and subsequently rapidly and easily sequenced. Thus, they can be identified.

Alterations in these genes, (e.g., mutations) can be studied by direct sequencing techniques of DNA fragments containing the mutations of interest or by other methods, for example, single-stranded conformation polymorphism analysis, which allows the detection of polymerase chain reaction-amplified DNA sequences containing single point mutations.

Phenotype and Genotype

Numerous diseases considered nosological entities have been shown in the last 20 years to be disease groups, consisting of a number of types clearly separable by clinical, biochemical, or genetic criteria. The pioneering work of Cori and Cori (1952) revealed that the glycogen storage disease of von Gierke was not a single entity, but a large group of glycogenoses, each of which depends on a different, specific, genetically determined enzyme defect. This development affected almost all aspects of clinical genetics. It is therefore difficult to deduce the nature of the genotype from the phenotype, all the more so if the latter is influenced by environmental factors. A good example is phenylketonuria (see p. 169), in which mental retardation and other stigmata of the disease, caused by a defect in phenylalanine hydroxylase, can be prevented by appropriate dietary treatment.

A single gene may affect more than one phenotypic feature, a situation known as pleotropism. A mutation in a pleotrophic gene may lead to multiple changes in the phenotype. On the other hand, an identical or similar phenotype may result from mutations at different gene loci (genocopy or heterogenesis). A similar phenotype may also arise from a variety of alleles at the same locus (genetic heterogeneity).

When the primary enzymatic defect is unknown, it may be difficult to decide between variants of a single entity and genetically distinct entities. Hybridization of some somatic cells in tissue cultures may help in solving these problems (Ruddle *et al.*, 1982).

Abbreviations of Amino Acids

The common abbreviations of amino acids use either three-letter or single-letter code.

Ala, or A	Alanine	Leu, or L	Leucine
Arg, or R	Arginine	Lys, or K	Lysine
Asn, or N	Asparagine	Met, or M	Methionine
Asp, or D	Aspartic acid	Phe, or F	Phenylalanine
Cys, or C	Cysteine	Pro, or P	Proline
Gln, or Q	Glutamine	Ser, or S	Serine
Glu, or E	Glutamic acid	Thr, or T	Threonine
Gly, or G	Glycine	Trp, or W	Tryptophan
His, or H	Histidine	Tyr, or Y	Tyrosine
Ile, or I	Isoleucine	Val, or V	Valine

Disorders of Carbohydrate Metabolism

This chapter deals with disorders that directly affect the metabolism of mono-, oligo- and polysaccharides. The oligosaccharides also form complex conjugates with proteins, called glycoproteins, which are important structural elements of the cell. In metabolic disorders of complex glycoproteins and glycolipids, the breakdown not only of carbohydrates, but also of the other catabolites, is impaired. Morphologically, these form an important group of storage diseases.

Monosaccharidoses

Under the category *monosaccharidoses* we include all conditions accompanied by alterations in glucose metabolism. This is justified by the central position of glucose in energy metabolism, which is affected in all disorders of monosaccharide turnover.

Energy Metabolism of the Nervous System

The nutritional carbohydrates are mostly polymers of hexoses. The principal breakdown product is glucose, which forms the most important sugar in the circulation. In contrast with other organs that utilize carbohydrates, proteins, and lipids as their sources of energy, the brain depends almost exclusively on carbohydrates. Even though some energy is released through the catabolism of amino acids and fatty acids in the structural turnover of nervous tissue, the normal energy requirement of the CNS is covered exclusively by glucose. Reserve stores of carbohydrates are sparse in the brain, and these are remarkably stable. Therefore, the brain depends exclusively on the steady supply of glucose by the

bloodstream. The concentration of glucose in the brain varies in accordance with the blood sugar level. The healthy brain removes from the bloodstream 5.5 mg of glucose per 100 g of tissue per minute. Translated into terms of 24-hour consumption, the brain utilizes around 115 g of glucose daily. This glucose consumption amounts to about 50% of the average intake of carbohydrates by a healthy individual and is enormously high, considering that the brain accounts for only 1.5–2% of the total body weight. In hypoglycemia, lactate becomes the most important source of energy besides glucose (Fernandes *et al.*, 1984).

Gluconeogenesis

The sensitivity of the brain to even minor fluctuations of the level of blood sugar necessitates the presence of an endogenous source of glucose when the nutritional intake of carbohydrate is inadequate. In the first place, the liver, but also the kidneys, is capable of forming glucose from other metabolites, such as amino acids, lactate, and glycerin. Gluconeogenesis thus utilizes the catabolites of other organs. The reactions necessary for gluconeogenesis are catalyzed by appropriate enzymes. If any of these are defective, they may give rise to enzymopathies. These, however, are far more common in defects of enzymes that control glucose catabolism.

Glucose Catabolism

When glucose enters a cell, it is normally phosphorylated to glucose 6-phosphate by the action of a hexokinase and is finally broken down into CO_2 and H_2O. The following pathways are available:

1. The Embden–Meyerhof pathway, in which cleavage into trioses forms pyruvic acid, subsequently transformed into acetyl coenzyme A (acetyl-CoA). In the absence of triose-phosphate isomerase, neurological symptoms appear, which tend to stabilize during adolescence, but commonly lead to death before the age of 5 years without demonstrable morphological changes. Lack of phosphoglycerate kinase may, in severe cases, cause neurological symptoms, which dominate the clinical picture.
2. The hexose monophosphate shunt or the direct oxidative pathway through oxidation and decarboxylation

The citric acid cycle (Krebs cycle or tricarbonic acid cycle) is a sequence of reactions by which acetyl-CoA is broken down into CO_2 and H_2. Acetyl-CoA reacts first with C_4 carbonic acid (oxaloacetic acid) to form citric acid and CoA. In seven consecutive reactions two molecules of CO_2 are split off and oxaloacetic acid is reconstituted. Four H_2 atom pairs are transferred to the flavoprotein cytochrome chain leading to the formation of 12 molecules of ATP and four of H_2O. Two molecules of H_2O are reutilized in the cycle. The Krebs cycle is the common pathway for the oxidation of carbohydrates, fats, and some amino acids to CO_2 and H_2O.

Hyperglycemias

Diabetes Mellitus

Hyperglycemia is the principal finding in diabetes mellitus, but also occurs as an epiphenomenon in other conditions, such as Down syndrome and Friedreich's ataxia. The neuropathology of diabetes mellitus and its complications has not revealed any characteristic lesions, in either type or localization. The formerly held view that glucose metabolism in the brain is normal in diabetic hyperglycemia, however, is erroneous.

Apart from the well-defined and extensively described diabetic neuropathy, which is not dealt with here, there are several neurological syndromes based on hyperglycemia, that have received little attention or have remained controversial. These include acute hyperglycemic edema as well as chronic encephalopathies and myelopathies. In addition, some syndromes deserve mention that represent primary metabolic disturbances in the context of the multifactorial hereditary forms of diabetes. Their pathogenesis has not been fully clarified and their morphology remains largely unreported.

Acute Diabetic Encephalopathy

Dillon *et al.* (1936) described the occurrence of acute cerebral edema with fatal outcome in patients with juvenile diabetes. Several cases were subsequently reported (Warren *et al.*, 1969).

Clinical Picture As a rule acute diabetic encephalopathy affects patients under 45 years of age who, apart from their diabetes, have remained well. During treatment for diabetic ketoacidosis and rapid correction of hyperglycemia and electrolytic imbalance, the patients develop hyperthermia, hypotonia, and rapidly deepening coma with signs of increased intracranial pressure. With rare exceptions the condition is uniformly fatal.

Neuropathology The brain shows flattening of convolutions and obliteration of sulci. The leptomeninges are congested and contain circumscribed hemorrhages. Herniations are prominent. Light microscopy reveals accentuation of edema around blood vessels, occasionally accompanied by granulocytic infiltration. The cerebral edema of ketoacidosis can be ascribed to hyperosmolarity of the plasma in relation to brain tissue. The pathogenesis is the same as in other forms of hyperosmolar edema (Cervós-Navarro *et al.*, 1983). In cases of nonketotic diabetic coma, the subjects are usually older patients in whom the encephalopathy presents with focal symptoms (Maccario, 1968). Presumably, ischemic changes are responsible for the syndrome. However, the observation that the syndrome commonly occurs during the treatment of diabetic coma suggests the operation of an iatrogenic factor. The rapid correction of hyperglycemia reduces the osmolarity of the plasma and causes a temporary osmolar imbalance between the blood and the tissues. This leads to a shift of water and electrolytes into the tissues, which, if severe enough, may cause fatal cerebral edema.

Chronic Diabetic Encephalopathy

The term *chronic diabetic encephalopathy* was coined by De Jong (1950) apropos of a case of chronic juvenile diabetes with severe clinical and histological abnormalities in the CNS. Reske-Nielsen and Lundbaek (1971) pointed out that while none of the lesions observed was specific for diabetic encephalopathy, the conjunction of these lesions did not occur in other conditions.

Clinical Picture All patients with neurological symptoms of this condition also suffer from diabetic retinopathy, and often also from nephropathy and coronary insufficiency. In about one half of the patients, mental changes are prominent and may be severe. Vertigo is a further symptom. The principal neurological signs are areflexia, transient ischemic attacks, dyspraxia, dysdiadochokinesia, dysarthria of the bulbar type, and episodes of orthostatic hypotension. In patients with long-term insulin-dependent diabetes mellitus, brain stem audiometry revealed abnormal responses in 40% (Parving, 1990). By magnetic resonance imaging (MRI) subcortical and/or brain stem lesions with abnormally high signals were seen in 69% of the patients with disease of long duration. Dejaard *et al.* (1991) considered these findings as signs but not symptoms of CNS affection or diabetic encephalopathy.

Neuropathology *Gross appearances.* The leptomeninges are thickened, and the cerebral cortex and the optic chiasm are atrophic. Atheromatous changes in the basal arteries are common. The incidence and extent of cerebral infarcts are increased in diabetes (Plum, 1981), and cerebral infarcts are found in one third of the cases. Preischemic hyperglycemia aggravates brain damage following transient ischemia and adds some special features to the damage incurred, notably a high frequency of postischemic seizures, cellular edema, and affection of additional brain structures, such as the substantia nigra pars reticulata (Lundgren *et al.*, 1991, Zhou *et al.*, 1994). This is thought to be due to lactic acid accumulation, the level of which is proportionate to the amount of available glucose. Other authors have found that hyperglycemia is not necessarily a disadvantage in acute cerebral ischemia (Ibayashi *et al.*, 1991). The results of some experimental studies suggest that cerebral ischemia and its outcome become more deleterious in hypoglycemic than in normoglycemic and hyperglycemic states (Nedergaard *et al.*, 1988).

Light microscopy. The thickened leptomeninges show fibrosis, and occasionally infiltration by lymphocytes and macrophages with periodic acid–Schiff (PAS) and Sudan-positive granules in their cytoplasm (Reske-Nielsen and Lundbaek, 1971). Foci of perivascular rarefaction are found in the cerebral cortex and the subcortical white matter (Fig. 10). Degenerative changes in axons and myelin sheaths are present in the optic chiasm, with gliomesenchymal scarring in blind patients. Atheromatous plaques are abundant in major arteries; hyalinosis is prominent in arterioles (Fig. 11). In more than 50% of the cases, there is conspicuous calcification of the blood vessels in the globus pallidus and the dentate nucleus of the cerebellum (Olsson *et al.*, 1968).

The tendency to deposition of lipopigments and sudanophil substances in the neurons of diabetic brains has frequently been noted. True storage phenomena are uncommon. The clinical picture resembles that of premature senescence; in certain areas of predilec-

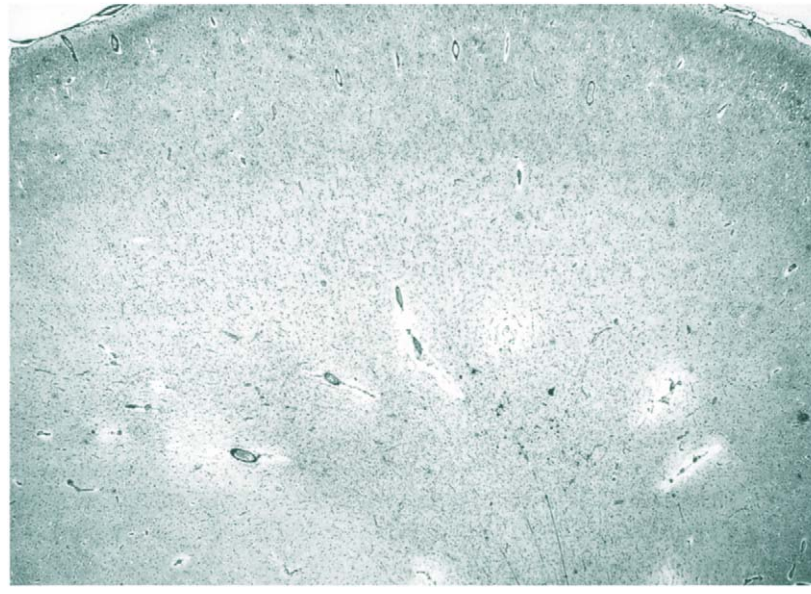


Fig. 10 Diabetic angiopathy. Foci of perivascular rarefaction in deeper layers of the cerebral cortex and the subcortical white matter. Nissl stain; ×12.

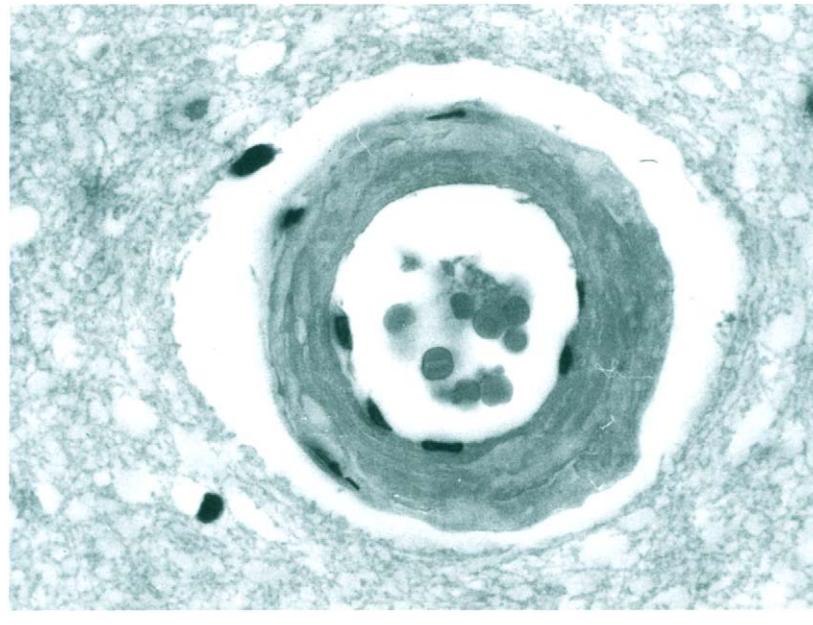


Fig. 11 Diabetic angiopathy. Prominent hyalinosis in a cortical arteriole. Hematoxylin–eosin stain; ×220.

tion, such as the globus pallidus and the inferior olive, one may observe premature cell loss, possibly secondary to the lipid deposition. The astrocytes appear naked, but the nuclei are not empty, as in hepatic failure. Under higher magnification traces of processes may be seen, often with a fine dusting with lipofuscin. Regressive changes in astrocytes are prominent in the pallidum, with an increase in the amount of normal pallidal pigment. In the cerebral cortex one may observe a proliferation of rod-shaped microglia, as well as foci of perivascular devastation (Fig. 10).

The diabetic microangiopathy (Fig. 11) does not display any specific features (Cervós-Navarro, 1980). On electron microscopy it does not differ from hypertensive hyalinosis.

Diabetic Myelopathy

The concept of diabetic pseudotabes is the result of the work of Althaus (1884). In the same year von Frerichs noted "myelitic foci" of vascular origin in his monograph on glucose, thus extending the range of lesions affecting the spinal cord in diabetes. However, only a few clinical reports have appeared in the past 10 years (Anderson *et. al.*, 1987; De Toffol *et al.*, 1990; Giladi *et al.*, 1991).

Clinical Picture The muscles of the lower extremities, and rarely those of the upper extremities, are atrophic. Fasciculations in the affected muscles are frequently observed. Disturbances of bowel and bladder function occur in some patients. The picture frequently merges with that of a peripheral diabetic neuropathy. De Jong (1950) estimated the incidence of a pseudotabetic syndrome, partially of spinal origin, in 26% of diabetics.

Neuropathology *Gross appearances.* According to Slager (1978), diabetic myelopathy occurred in 41% of 75 consecutive nonselected diabetic patients in an autopsy study. Edema of the spinal cord was observed in several instances.

Light microscopy. Discrete degeneration of posterior columns may be accompanied by myelin loss in the dorsal roots and their entry zones. Degenerative changes may also occur in anterior horn cells with or without involvement of the anterior roots (Bischoff, 1963).

Pathogenesis Up to now there has been no convincing evidence that changes in the cerebral cortex, spinal cord, or peripheral nervous system are caused directly by the diabetic metabolic abnormalities rather than by vascular insufficiency.

An important factor for the pathogenesis of diabetic microangiopathy may be the increased concentration of the specific glycosyltransferase, leading to enhanced synthesis of basement membranes (basal laminae). Glycosyltransferase is involved in the assembly of protein-bound carbohydrate units that form the basal laminae. Polyglucosan bodies (see p. 97) are found in the axons in alloxan-diabetic rats, and occasionally in human diabetics (Mancardi *et al.*, 1985), together with an increased concentration of glycogen. In the diabetic BB/W rats the changes in progressive axonal atrophy and axon glial dysfunction have been attributed to activation of the polyol pathway (Kamijo *et al.*, 1993).

Lipodystrophic Diabetes

Lipodystrophic diabetes, a rare disease, may be either congenital or acquired. The congenital form is inherited as an autosomal-recessive trait, and lack of adipose tissue is already apparent at birth. Diabetes appears at puberty. Further abnormalities are hepatomegaly, insulin resistance, excessive growth in length, and slight virilization beginning in childhood. Possible causes are hypothalamic dysfunction, with production of fat-mobilizing and diabetogenic factors, or a disturbance of insulin activity. Mental retardation is present in about half of the congenital cases. The acquired form has no familial incidence and seems to be precipitated by nonspecific illness such as a viral infection. Vogel and Horoupian (1990) reported on a 41-year-old man with lipodystrophic insulin-dependent diabetes mellitus who had developed severe atherosclerosis, lacunar infarcts, and hydrocephalus. Microscopically, gliotic aqueductal stenosis, swollen neurons due to accumulation of pigment, especially in cortical layers III and V, in pyramidal cells of the hippocampus, and in the nuclei pontis, inferior olives, and some cranial nerve nuclei, were seen. Meganeurite formation was clearly identified. Electron microscopy revealed numerous concentric or undulating paired parallel membranous profiles admixed with neuronal lipofuscin, which were similar to fingerprint bodies of ceroid lipofuscinosis.

DIDMOAD Syndrome (Wolfram Syndrome)

DIDMOAD is an acronym of a syndrome described by Wolfram (1938), which stands for diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. Dysarthria, seizures, anosmia, nystagmus, ataxia, and changes in the electroencephalograms (EEGs), electroretinograms, and evoked potentials may be present (Rando *et al.*, 1992). Familial incidence has been reported. Leiva-Santana *et al.* (1993) found an abnormal brain computerized tomographic (CT) scan with prominent atrophy of the brain stem; on MRI severe brain stem and cerebellar atrophy was detected. They concluded that Wolfram syndrome includes phenotypical manifestations of olivopontocerebellar atrophy, confirming the findings of Carson *et al.* (1977). The muscle mitochondrial oxidative phosphorylation displays a profound defect in all respiratory activities assayed (complexes I, I + III, II + III, III, and IV), which correlates with a defect in mitochondrial protein synthesis in cultured cells.

Neuropathology Cremers *et al.* (1977) stated that, apart from a single case in which an acidophil adenoma of the pituitary was found responsible for both diabetes mellitus and diabetes inspidus, no definite morphological changes had been found in the primary genetic DIDMOAD syndrome. However, Carson *et al.* (1977) found olivopontocerebellar atrophy in two sisters. In patients with lesions in the hypothalamo-hypophyseal axis, the diabetes is secondary and unaccompanied by optic atrophy. Kinsley and Firth (1992) found that most of the corpus callosum and the septum pellucidum were absent.

Pathogenesis Van den Ouweland *et al.* (1992) found a mutation in the mitochondrial $tRNA^{Leu(UUR)}$ gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Maternally inherited diabetes and deafness result from an mtDNA re-

arrangement that fused the 3′ end of the cytochrome *b* gene at nucleotide position 1482 to the $tRNA^{Gln}$ gene at nucleotide 4398 (Ballinger *et al.*, 1992). The symptoms of all maternal relatives appeared when these women were between the ages of 20 and 40 years.

Familial Hypogonadism with Mental Retardation (Sohval–Soffer Syndrome)

In two brothers with hypogonadism, skeletal abnormalities, and mental retardation, Sohval and Soffer (1953) found hyperglycemia and glucosuria. An aunt and three maternal cousins were also retarded. Bilateral testicular biopsies on both brothers showed narrow hyalinized seminal tubules and wider tubules with aplasia of germ cells. No autopsy has been reported.

Prader–Labhart–Willi Syndrome (Amyotonic Diabetes)

Prader *et al.* (1956) described a syndrome in which neonatal cerebral symptoms were followed by multiple disturbances in other organs.

Clinical Picture The typical clinical picture consists of muscle hypotonia, obesity, mental retardation, acromicria, hypogonadism, and an abnormal glucose tolerance test (Vischer *et al.*, 1971). Focal epilepsy has been reported rarely. Life expectation is reduced; most patients die in the first or second decade, but some reach as much as the fifth decade.

Pathology Hypoplasia of the endocrine part of the pancreas with fatty infiltration of the stroma and a reduction in the number of islets are the principal features of this syndrom (Oda *et al.*, 1972). Fatty changes in the liver and the myocardium were described in patients dying in the first decade.

Neuropathology *Gross appearances.* Both the basal and meningeal arteries contain atheromatous plaques. Fatty changes are also seen in the media of these arteries. Hypoplasia of the frontal lobes and polymicrogyria have been reported (Hattori *et al.*, 1985). Dilatation of the ventricular system has been mentioned repeatedly (Vischer *et al.*, 1971).

Light microscopy. Hattori *et al.*, (1985) found multiple heterotopias in the subcortical and deep white matter. Multiple small softenings of vascular origin in the caudate nucleus, internal capsule, and pons have been reported, as well as large fat granule cells distributed throughout the white matter. Oda *et al.* (1972) found, apart from a cerebral infarct, an intense fibrillary gliosis in the optic tract and the inferior olives as well as axonal swellings in the pyramids and the nucleus gracilis.

Pathogenesis The muscular hypotonia is presumably of central origin, as muscle biopsy showed no evidence of either myopathy or denervation (Vischer *et al.*, 1971). The lack of other neurological symptoms suggests a subcortical-supraspinal lesion (Zellweger and Schneider, 1968). In view of the early history of the patients, Tolis *et al.* (1974) discussed the possibility of early brain damage affecting particularly the hypothalamo-hypophyseal axis.

Diverse translocations were discovered on chromosome 15 (Emberger *et al.*, 1977; Mascarello *et al.*, 1983), and a deletion of the proximal chromosome 15q(11q13) has been found in a large percentage of cases (Anavi and Mintz, 1990). The same deletion was described in another distinct mental disorder: Angelman syndrome (Malzak *et al.*, 1993). In some cases, however, chromosome 15 does not show any cytogenetic or detectable molecular genetic abnormality (Orstavik *et al.*, 1992).

Hypoglycemias

In older children and adults blood glucose values below 40 mg/100 ml are considered hypoglycemic. The causes of hypoglycemia are multiple and have been classified differently by various authors. The primary hypoglycemias are disturbances of carbohydrate metabolism that lead directly to depression of the blood sugar level. Secondary, or reactive, hypoglycemias are those metabolic disorders that lead to an accumulation of metabolites in the bloodstream, which indirectly affects the glucose metabolism. Included in this group are conditions erroneously diagnosed as diabetes mellitus, in which administration of insulin leads to hypoglycemic shock. Röther *et al.* (1992) described a patient who had progressive brain stem symptoms due to a diet-induced hypoglycemia initially diagnosed as basilar artery thrombosis.

Primary Hypoglycemias

One can distinguish hyperinsulinemic and normoinsulinemic forms of primary hypoglycemia. The hyperinsulinemic conditions include endocrine disorders and tumors that lead to a pathological production of insulin. Needless to say, insulin shock can also be produced iatrogenically. The normoinsulinemic group comprises disturbances of the gastrointestinal tract with impaired glucose absorption, enzyme defects in the mucosa of the small intestine, and diseases associated with impaired glycolysis. We consider here only the pathology of hypoglycemic coma and some syndromes of unknown etiology that may be associated with changes in the CNS.

Hypoglycemic Coma

In contrast with hypoxia, which induces central vasodilation, hypoglycemia lacks this compensatory mechanism. Deep hypoglycemia may, nevertheless, be tolerated for prolonged periods without morphological lesions. Insulin shock used in the treatment of psychoses can be tolerated for 30–180 minutes without permanent damage. Mental retardation may occur in children with repeated hypoglycemic attacks (McQuarrie, 1954). Psychomotor retardation has been found in 50% of the patients who had suffered from hypoglycemia in childhood. Hypoglycemia, as a rare but important cause of acute brain stem dysfunction, must be considered in patients suspected to suffer from basilar artery thrombosis (Röther *et al.*, 1992).

From time to time, reports appear on neuropathological findings in patients who have survived hypoglycemic coma for prolonged periods (Cervós-Navarro, 1980). Children

with long survival after hypoglycemic coma exhibit microcephaly with atrophy of the cortex and the white matter, as well as lesions in the basal ganglia (Rubinstein, 1967). In contrast with the case of anoxic lesions, the cerebellum is often spared, or only slightly affected.

Histologically, the lesions consist of diffuse atrophy, or extensive necrosis of the cerebral cortex, basal ganglia, and hippocampus. An unusual case with subcortical necrosis was reported by Schmid *et al.* (1982). This lesion, as well as necrosis of the caudate nucleus, is indistinguishable from the lesions of ischemia. Necrosis of the granule cells of the dentate fascia has been claimed as a characteristic lesion of hypoglycemic damage (Auer *et al.*, 1989). To account for the cerebral lesions following insulin poisoning, additional local circulatory disturbances may be discovered to be responsible. However, Auer (1992) postulated that in hypoglycemic brain damage a metabolically derived aspartate accumulates in the cerebrospinal fluid (CSF) and acts as an excitotoxin.

In experimental hypoglycemia induced by insulin, early stages of ischemic nerve cell change have been demonstrated by electron microscopy. Myers and Kahn (1971) found necrosis of the cortex, basal ganglia, and hippocampus in long-term animal experiments; the most severe lesions were in the striatum.

Earlier writers emphasized glial proliferation in the white matter independent of neuronal loss and interpreted this as a sequela of cerebral edema. Myers and Kahn (1971) were unable to confirm this hypothesis in their animal experiments.

Idiopathic Infantile (McQuarrie) Hypoglycemia

In 1954 McQuarrie isolated a group of cases of "idiopathic, spontaneously occurring hypoglycaemia of infants." About 30% of the idiopathic forms turned out to be leucine sensitive and to form a separate entity (see page 28). Furthermore, some of the apparently idiopathic hypoglycemias of newborns may have a definite cause, such as congenital islet cell adenomas or systemic carnitine deficiency (Slonim *et al.*, 1983). A common characteristic of the so-called "idiopathic forms" is increased insulin sensitivity without evidence of lack of an antagonistic regulatory hormone and a therapeutic response to cortisone or corticotropin. Neonatal hypoglycemia constitutes a different situation from that in the adult with regard to hypoglycemic brain damage. Metabolically, the immature brain has the capability to oxidize lactate for fuel, apparently a protective response to neonatal hypoglycemia (Hellmann *et al.*, 1982).

Apart from transient hypoglycemia without neurological sequelae, observed in about 10% of neonates, there is also a severe form that produces permanent neurological damage. This manifests itself during the first 6 months of life, not infrequently before the end of the neonatal period, often with uncharacteristic symptomatology. Two thirds of the children suffer permanent cerebral damage. This is preventable by early diagnosis and treatment of hypoglycemia.

The pathogenesis of the truly idiopathic (McQuarrie) hypoglycemias remains unknown. Cornblath and Schwartz (1976) emphasized that the neurological sequelae were independent of birth weight and demonstrated that the degree of damage depended directly on the severity and duration of hypoglycemia. It may be added that neonatal hypoglycemia shows a stepwise, not a continuous, progression, and in many cases leads to

spontaneous recovery after some years. This leads to the tendency to interpret these episodes as "transient neonatal hypoglycemia." There are, however, certain idiopathic hypoglycemias that form separate well-defined disease entities.

Ketotic Hypoglycemia

Children with so-called cyclical acetonemia present in the early phases of an episode with hypoglycemia, an increased level of ketones in the blood, and acetonuria. Colle and Ulstrom (1964) defined the diagnostic criteria of the condition. The syndrome appears predominantly in boys after the first year of life and is the most common form of hypoglycemia in childhood. It is still open to doubt whether it constitutes a specific entity. It is, among others, a typical feature of Reye's syndrome (see page 154). The combination of hypoglycemia and ketosis may also occur in families and twins without a definite pattern of inheritance. One may presume that it is a primary disturbance of the neurovegetative system, which leads to hypoglycemia with secondary ketosis.

Leucine-Sensitive Hypoglycemia

In an analysis of a group of children with idiopathic hypoglycemia, Cochrane *et al.* (1956) were struck by the observation that some of these children had a marked increase in the number and severity both of seizures and of hypoglycemia when kept on a high-protein, low-carbohydrate diet.

The attacks were mainly postprandial and could be produced by oral administration of L-leucine, which caused a dramatic fall in blood sugar. Ingestions of both L-leucine and casein hydrolysate produced marked irritability, accompanied by pallor and disturbances of consciousness. Children with insulinomas or β cell hyperplasias may react in a similar fashion. An identical response was obtained in some apparently normal children. The leucine-sensitive hypoglycemia belongs to the hyperinsulinemic group, but its exact biochemical mechanism is still unknown. It is assumed that leucine has a stimulating effect on β cells.

Characteristically, the symptoms of hypoglycemia appear after meals, but attacks may also occur in fasting children. In contrast with insulinomas, the condition is not progressive and shows no predilection for underweight children. Although familial cases have been recorded, there is no firm evidence of a genetic component. An inhibition of growth is observed occasionally. In untreated cases cerebral atrophy and microcephaly have been repeatedly mentioned, and the prognosis of this condition must be considered serious (Cornblath and Schwartz, 1976).

Beckwith–Wiedemann Syndrome

The clinical picture of this syndrome was described independently by Beckwith (1963) and Wiedemann (1964). The predisposition to Wilms' tumor and other malignancies in the patients led to the interpretation of the condition as premalignant.

The constant features are macroglossia and hypoglycemia. Umbilical hernia, visceromegaly, and gigantism are frequently present. Microcephaly is uncommon. Severe

hypoglycemia, if untreated, leads to death a few days after birth. All organs and tissues contain abundant glycogen. Survivors develop a variety of tumors. In the context of visceromegaly, hyperplasia of the pancreas, with an increase in the number of islets, is particularly striking. Among the tumors a case of ganglioneuroma has been reported (Perez Lafuente *et al.*, 1981).

The majority of cases are sporadic, but several families with an autosomal-dominant mode of inheritance with variable expression and reduced penetrance have been described. In such families Beckwith–Wiedemann syndrome has been linked to DNA markers for the insulin gene and H-*ras* on chromosome band 11p15 (Nordenskjold *et al.*, 1993). A high-resolution radiation hybrid map of the distal short arm of human chromosome 11 has provided precise order information for several 11p15 genes (Richard *et al.*, 1993). Insulin-like growth factor II overexpression plays an important role in somatic overgrowth and in the development of embryonal tumors (Weksberg *et al.*, 1993). In the development of tumors that arise in association with the syndrome, three separate 11p loci may be significant (Byrne *et al.*, 1993). The association with 11p15 duplications of paternal origin and of balanced translocations and inversions within 11p15.5 of maternal origin and the demonstration of uniparental paternal 11p15 isodisomy in some sporadic cases point toward the involvement of genomic imprinting (Tommerup *et al.*, 1993).

Glucose-6-phosphate Dehydrogenase Deficiency

Deficiency of the enzyme glucose-6-phosphate dehydrogenase is probably the most common genetic disorder, with 100 million carriers of the gene. The geographic distribution of the defect corresponds roughly with that of malaria. It has been suggested that carriers of this gene have a better chance of surviving malarial infections. The condition is X chromosome linked and is characterized by a reduction in enzyme activity.

The main clinical manifestation is an acute—or, less commonly, chronic—hemolytic anemia precipitated by certain drugs and foods. This enzyme deficiency may lead to kernicterus in 5% of the affected neonates. Neurological symptoms have been repeatedly recorded (Westring and Pisciotta, 1966).

Secondary Hypoglycemias

Over 100 diseases can be accompanied by fasting hypoglycemia (reactive hypoglycemia). Included among these are metabolic errors associated with a raised level of carbohydrates in the blood. These may be erroneously diagnosed as diabetes and treated with insulin, with resulting severe hypoglycemia. Hypoglycemia is only a secondary feature of glycogenosis, galactosemia, and fructose intolerance, but may be the presenting symptom in other disorders of carbohydrate metabolism. In all cases it is responsible for the ensuing cerebral damage. The neuropathology of these cases has rarely been reported and deserves the attention of pathologists.

Pentosurias

Apart from nutritional pentosuria, which may occur after excessive consumption of some varieties of fruit (e.g., plums, cherries, berries, and grapes) or their juices, there exists an essential pentosuria with excretion of L-xylose. It has hitherto been reported only

in those of eastern European descent and occurs only in homozygotes. The metabolic disorder is due to a block in the oxidation of glucuronic acid, presumably caused by a deficiency of L-xylose reductase, which reduces xylose to xylite. These patients often suffer from mental lability, but no pathological changes have been described either in the CNS or in other organs. Misguided treatment with insulin due to an erroneous diagnosis of diabetes may induce severe hypoglycemia.

Galactosemias

The galactosemias represent a group of inborn metabolic disorders in which children are incapable of converting galactose into glucose. The first case was described by Reuss (1908). Up to now three enzymatic defects have been identified: (1) lack of galactose-1-phosphate uridylytransferase, (2) lack of galactokinase, and (3) lack of UDP galactose 4-epimerase. In the diagnosis of galactosemia, the appropriate enzyme defect should always be specified.

Galactosemia with Transferase Deficiency (Galactose-1-phosphate Uridylytransferase Deficiency)

Some authors recognize this syndrome as the only true galactosemia. This is the only form in which pathological and neuropathological abnormalities have so far been demonstrated.

Clinical Picture The clinical manifestations of this type of galactosemia depend largely on the remaining residual activity of the enzyme. In severe cases symptoms appear in infants as soon as milk feeding begins, particularly with human milk. Refusal to drink, vomiting, diarrhea, weight loss, jaundice, and hepatomegaly develop (Kaloud and Sitzmann, 1975). These infants die in the first few weeks of life if untreated. In the subacute group symptoms develop insidiously in the first few months after birth. These children are brought to the physician because of failure to thrive, loss of appetite with refusal to eat, episodes of vomiting, and diarrhea. Microcephaly is conspicuous (Haberland *et al.*, 1971). Cataracts may already be present at that time. In a third group children develop mental retardation, cerebellar dysfunction, and tremor in spite of early dietary treatment with lactose-free food. Lo *et al.* (1983) separated this group from the remaining forms of transferase galactosemia. Finally, there is a chronic group with minimal symptoms, consisting mainly of refusal of milk and milk products. Only detailed clinical and biochemical investigations reveal the nature of the enzyme defect in this group.

In half of the cases, mental development is subnormal. Severe retardation with intelligence quotients (IQs) under 50, however, is uncommon. In most cases the mental state takes the form of debility or remains at the lower limit of normality. It is worth remembering that children who reach the age at which their intelligence can be tested suffer from a milder form of the disorder.

Pathology On light microscopy the main changes are in the liver, starting with fatty changes, proceeding to pseudoglandular remodeling of the trabeculae with intralobular cholestasis, and ending in a micronodular cirrhosis. The changes are largely reversible

when the patient is placed on a milk-free diet. Signs of tubular damage may be present in the kidneys. An earlier claim of a deficiency of UDP galactose in the erythrocytes of galactosemia patients has not been confirmed (Kirkman, 1992).

Neuropathology *Gross appearances.* Haberland *et al.* (1971) found cortical atrophy and reduced size of the white matter with internal hydrocephalus. The left Ammon's horn was severely atrophic and sclerotic.

Histology The larger neurons contained an excess of lipofuscin for the patient's age. The white matter showed diffuse pallor of myelin, foci of necrosis, and reactive fibrillary gliosis. There was considerable loss of Purkinje cells in the cerebellum, the remaining cells being chromatolytic or pyknotic. The changes reported by Haberland *et al.* (1971) were more conspicuous and consisted of a moderate decrease in nerve cells in the cortex. Pallidonigral pigmentary degeneration with deposition of coarse pigmented granules was found in the thickened wall of the vessels. In the pallidum the neurons showed pigmentary atrophy and a moderate reduction in number. Hypertrophied astrocytes were abundant and Alzheimer's type II neuroglial cells were often seen, but no conspicuous fiber production was present. The ganglion cell losses were severe in the anterior and medial nuclear groups. In the thalamus a characteristic feature on hematoxylin–eosin (H&E) staining was the presence of bright pink, hyalinlike structures ranging in size from 30 to 150 μm as well as disseminated Alzheimer's type I neuroglia.

Pathogenesis The cerebral damage is ascribed to a reduction in cellular respiration due to cellular accumulation of galactose-1-phosphate. Lott *et al.* (1982) drew attention to the reduction of lipid-bound inositol in the brains of patients with acute galactosemia as a possible factor in the pathogenesis of cerebral damage. This is supported by experimental results in rats fed a diet rich in galactose (Berry *et al.*, 1981).

The fact that impairment of intelligence often cannot be reversed by prompt treatment points to prenatal maldevelopment. The theory that high levels of galactose may already operate *in utero* is supported by the fact that some neonates may exhibit liver damage and cataracts. Children treated within 1 week of birth still grow to have IQs 10% below average at the age at 4 years (Thalhammer *et al.*, 1980).

Galactosemia Due to Galactokinase Deficiency

Gitzelmann (1967) described the second form of galactosemia caused by deficiency of the enzyme galactokinase. In contrast with the transferase galactosemia, these patients have no symptoms in early childhood. Cataracts develop later and remain the only abnormality. In two sisters operated on for cataracts at the ages of $5\frac{1}{2}$ and $7\frac{1}{2}$ years, the impression of mild mental retardation was not confirmed in later years. Pickering and Howell (1972) reported the case of a girl who, apart from a cataract diagnosed at the age of 4, remained well until the age of 17, when she experienced epileptic seizures that lasted a few minutes and recurred at intervals of 5–10 minutes. She also had generalized muscular weakness. The authors left open the question as to a connection between the galactosemia

and the neurological deficit. There are no neuropathological observations in either the epimerase or galactokinase form of galactosemia.

Wolfrom *et al.* (1993) observed, in the skin fibroblasts of patients presenting with galactosemia, from either galactose-1-phosphate uridylylransferase or galactokinase deficiency, a deficit in extracellular glucose utilization. If expressed in many cell types, this impaired glucose uptake would be expected to seriously damage highly glucose-dependent tissues such as the CNS. This might be of relevance to the persistent neurological damage observed in many galactosemic patients, in spite of their compliance with an early strict galactose-free diet.

Fructosurias

There are three forms of fructosuria: (1) essential benign fructosuria, (2) hereditary fructose intolerance [L-fructose-bisphosphate aldolase ("aldolase B") deficiency], and (3), fructose-1,6-bisphosphatase deficiency. The first of these is harmless and causes no clinical symptoms.

Hereditary Fructose Intolerance

The first cases of fructose intolerance were described by Chambers and Pratt (1956) as "idiosyncrasy to fructose." Froesch *et al.* (1957) established the hereditary nature of the disorder and concluded from the biochemical changes in the blood after a fructose load that it was due to L-fructose-bisphosphate aldolase deficiency. This was confirmed by enzyme estimations from a needle biopsy of the liver. Analysis of the literature on the fatalities following parenteral fructose administration established that all patients had hereditary fructose intolerance (Sachs *et al.*, 1993). The severe hypoglycemia associated with the condition after fructose intake is not due to hyperinsulinism, but to a reduction of intracellular phosphate that remains bound in the blocked fructose l-phosphate. As neurons do not contain L-fructose-bisphosphate aldolase, there is, as a rule, no impairment of psychomotor development.

The patients remain symptom free as long as their diet contains no fructose or saccharose. The first symptoms appear with feeds of cow's milk fortified with cane sugar and with addition of fruit and vegetables to the diet. The symptoms may be acute, with vomiting and manifestations of hypoglycemia, such as sweating, pallor, tremor, nausea, loss of consciousness, and seizures. Occasionally, one may observe a hemorrhagic tendency. In a case reported by Levin *et al.*, (1968), the first manifestation was a subarachnoid hemorrhage.

There is also a chronic form of the condition, presenting as failure to thrive, vomiting, hepatomegaly with ascites, and edema; recurrent attacks of hypoglycemia may be responsible for the occasional cases of mental retardation. Fructose intolerance leads to diffuse fatty changes in the liver and the jejunal mucosa. No neuropathological observations are available.

Fructose-1,6-bisphosphatase Deficiency (Hexose Bisphosphatase Deficiency)

This anomaly was first described by Baker and Winegrad (1970). It is inherited as an autosomal-recessive trait. The lack of hexose bisphosphatase (fructose-1,6-bisphosphatase) blocks gluconeogenesis and leads to neurological disturbances. A simultaneous deficiency of fructose-1,6-bisphosphate aldolase has been described.

The course of the disease is punctuated by episodes of hypoglycemia with lactic acidosis and seizures, which may be fatal within a few hours. The crises are provoked by fasting, oral intake of fructose, or intravenous administration of fructose or sorbitol for treatment of cerebral edema. They may resemble the features of Reye's syndrome (Nakai *et al.*, 1993). Hepatomegaly and muscular hypotonia may also be present.

In a 7-month-old child Servidei *et al.* (1986) found the typical features of neuroaxonal dystrophy (see p. 507) in the CNS.

Disorders of the Respiratory Chain

The manifold subentities of enzyme complexes involved in the respiratory chain and the fact that some of these enzymes are encoded by mtDNA while others are encoded by nuclear DNA render the unraveling of these genetic enzymopathies difficult. The complexity of the processes in the orderly agglomeration of enzymes on the inner mitochondrial membrane adds to the difficulty. In an attempt to classify the largely overlapping disease entities, we separate the disorders of pyruvate metabolism from the large field of mitochondrial encephalopathies. The primary genetic lactic acidosis includes various enzymopathies of the pyruvate hydrogenase complex. Moreover, lactic acidosis also occurs in disorders of amino acid metabolism and of the redox system (Robinson *et al.*, 1983). Other genetic causes of lactic acidosis include the fructose-1,6-bisphosphatase deficiencies. The not fully pathogenetically elucidated disease complex known as subacute necrotizing encephalomyelopathy (SNE), or Leigh disease, is based in part on the disorders of pyruvate metabolism. However, the results of Paulus and Peiffer (1990), using a monoclonal antibody to an inner mitochondrial membrane antigen, substantiate its classification among the mitochondrial encephalopathies and it is therefore considered among them.

Pyruvate Dehydrogenase Deficiency (Pyruvate Decarboxylase Deficiency; L-Decarboxylase Deficiency)

Pyruvate dehydrogenase (PDH) deficiency has long been recognized as the most common defined cause of primary lactic acidosis in infancy and early childhood. It has also been described in patients with subacute or chronic neurodegenerative diseases without significant metabolic acidosis (Brown, 1992). Different clinical syndromes may arise, depending on the severity of the enzyme deficiency. Residual PDH activity of less than 20% leads to a severe lactic acidosis in infancy. Reduced activity (between 20% and 75%) causes different clinical manifestations, the severity of which is not always correlated with the level of residual activity (Marsac *et al.*, 1993).

Malignant Congenital Pyruvate Dehydrogenase Deficiency

Clinical Picture Severe acidosis develops during the first few days of life, with a high level of lactate in the blood, urine, and CSF. This leads to death from respiratory failure after a few weeks in untreated cases. Exceptionally, some patients survive for a few months or even years. These patients suffer from intractable seizures and spasticity

(Riviello *et al.*, 1985). Hypotonia is a prominent feature in patients who die in later infancy (Marsac *et al.*, 1993).

Neuropathology *Gross appearances.* Severe cortical atrophy and hydrocephalus, absence of corpus callosum (Robinson and Sherwood, 1984), and cystic changes in the cortex and the brain stem (Reynolds and Blass, 1976) have been observed.

Light microscopy. Hypomyelinization and vacuolation, cyst formation, and gliosis in the cerebral and cerebellar white matter are prominent features. Loss of nerve cells is particularly prominent in the putamen. Heterotopia of the inferior olives and cerebellar dysplasia have been mentioned by De Meirleir *et al.* (1992). Proliferation of the astroglia in the basal ganglia and the cerebral cortex has received an occasional mention, and focal overgrowth into the meninges has been reported (Chow *et al.*, 1987; Michotte *et al.*, 1993). Endothelial proliferation and gliosis have been noted in the putamen, mamillary bodies, and dentate nucleus. Marked vascular proliferation with thin-walled congestive vessels in the cerebral and cerebellar white matter, and to a lesser extent in the striatum, has been mentioned by Michotte *et al.* (1993).

Incomplete Deficiency of Pyruvate Dehydrogenase (Spinocerebellar Degeneration with Pyruvate Dehydrogenase Deficiency)

In about 40% of the patients with various spinocerebellar degenerations, the activity of PDH is reduced to 25–40% of normal values (Melancon *et al.*, 1984). In the majority of the cases, the activity of α-ketoglutaric dehydrogenase is also reduced.

The main clinical features are ataxia and choreoathetosis. The spectra of the condition include mild to moderate mental retardation and seizures in adults. Chabrol *et al.*, (1994) reported on a boy who presented with peripheral neuropathy, severe limb hypotonia, absent deep-tendon reflexes, and reduced motor nerve conduction velocities at 8 months of age.

Due to a differential distribution of the PDH complex in the CNS, the anterior cerebellar vermis is the most vulnerable structure, even in mild reduction of enzyme activity, which may not affect other regions of the brain (Reynolds and Blass, 1976).

Cerebral Lactic Acidosis

Brown *et al.* (1988) described in six patients a combination of defects in pyruvate metabolism with profound brain damage and minimal systemic acidosis. They proposed for this condition the term *cerebral lactic acidosis.*

Clinical Picture The patients with this disorder were of low birth weight (below the third percentile). In the neonatal period hypotonia and feeding difficulties were pronounced and all patients required prolonged gavage feeding. Two children whose disease was managed without gavage feeds died soon after birth. The infants diagnosed at a few months of age displayed mildly dysmorphic faces that may have resulted from the effect of disordered brain growth on development of the facial skeleton and the cranial fault.

The other children had made no developmental progress and were microcephalic and blind, with spastic quadriplegia. None has had clinically apparent episodes of acidosis. Seizures developed in three of these patients in later childhood. The blood lactate concentration never exceeded 5 m*M* in any of the patients, and this is generally lower than the levels found in the series of patients with PDH deficiency. By contrast, grossly elevated levels of lactate and pyruvate were found in the CSF.

Pathogenesis In the majority of the encephalomyelopathies caused by deficiencies in the PDH complex, a defect has been detected in its $E1_{\alpha}$ subunit (Shanske, 1992) in the human X chromosome. This mutation led to a C-to-T substitution in a CpG dinucleotide in amino acid codon 302, resulting in the replacement of arginine by cysteine at this position. Dahl *et al.* (1992) have tabulated a total of 20 different mutations in the $E1_{\alpha}$ gene, including deletions, insertions, and point mutations. Most of the mutations are found in exons 10 and 11. Chun *et al.* (1993) found missense mutations, resulting in a changed amino acid residue at positions 148, 170, 202, 234, and 263 of the mature protein. Some patients had one normal $E1_{\alpha}$ gene and one with a deletion at the sites of tandem repeats. Others also had one normal $E1_{\alpha}$ gene and one with an insertion. Robinson *et al.* (1990) and Marsac *et al.* (1993) described one defect in the dihydrolipoamide acetyltransferase (E2) subunit and two abnormalities of the lipoyl-bearing protein X component in patients with lactic acidemia and PDH deficiency. The patients were clinically indistinguishable from those with E1 PDH complex deficiencies.

Pyruvate Decarboxylase Deficiency In biotin-dependent deficiency of multiple decarboxylases, intermittent ataxia has been reported in several siblings (Sander *et al.*, 1980). Apart from the combined biotin-dependent deficiency, a pure form of pyruvate decarboxylase deficiency occurs that manifests itself soon after birth with hypotonia, metabolic acidosis, and mental retardation (Haworth *et al.*, 1981). Affected children survive for only a few years.

Neuropathological examination revealed a loss of neurons in the cerebral cortex, rarefaction of white matter with hypomyelinization, disturbances of migration, gliosis, and aggregation of perivascular macrophages (Atkin *et al.*, 1979). A loss of Purkinje cells and necrotizing myelopathy have also been reported (Sander *et al.*, 1980).

Mitochondrial Encephalomyopathies

The concept of mitochondrial myopathies, first formulated by Luft *et al.* (1962), was expanded by Shapira *et al.* (1977) to include that of encephalomyopathies, in order to define a subgroup of these disorders. This includes a number of mostly progressive, not uncommonly hereditary, diseases, characterized by involvement of the CNS and sometimes also the peripheral nervous system as well as the skeletal musculature. Nosologically, they are disturbances of mitochondrial metabolism. The recognition and elucidation of the biochemistry of the mitochondrial myopathies have thrown new light on the involvement of the CNS. Most investigations have been carried out on striated muscle and cul-

tured fibroblasts, with a few also on liver cells and heart muscle. The cerebral manifestations may overshadow the muscle involvement; it is therefore important to perform muscle biopsies on patients with obscure encephalopathies, even in the absence of muscular symptoms (Morgan-Hughes *et al.*, 1982).

The mitochondrial encephalopathies were first divided into those involving the cerebrum and the brain stem, on the one hand, and those belonging to the complex of spinocerebellar degenerations, on the other, while in some cases the allocation to either group presents difficulties. The clinical evidence rests on the demonstration of impaired mitochondrial activity in fibroblast cultures, leukocytes, and striated muscle.

The allocation of specific syndromes to identifiable mitochondrial enzyme deficiencies is rendered difficult by the fact that different enzyme deficiencies may result in the same phenotype, while the same defects may occur in different clinical syndromes elsewhere. In some cases we may be dealing with epiphenomena of no primary significance in the pathogenesis of the disorders. A system of classification based on specific enzymopathies is therefore impossible at present. There have been numerous reports of an overlap pattern between mitochondriopathies. The link between the defect in oxidative phosphorylation in the brain and the specific neuropathological pattern is unclear.

Molecular genetic studies are now bringing a new classification and new insights into already recognized mitochondrial encephalomyopathies. A better knowledge of nuclear mutations in mitochondriopathies and of the interactions between nuclear and mitochondrial genomes will probably allow new developments. However, although particular mtDNA mutations are usually associated with specific phenotypes, overlaps and atypical presentations are not rare and relatives of affected patients may have few symptoms, if any. Therefore, for the time being, a classification based on the clinical symptomatology in concordance with the localization of lesions appears to be the most useful system.

Mitochondrial Respiratory Chain

The 13 polypeptides encoded by the mtDNA are all components of oxidative phosphorylation that generates energy in the form of ATP by oxidizing hydrogen transferred from carbohydrates and fats via NAD^+ and the flavins. Reduced NADH + H^+ is oxidized to NAD^+ by NADH dehydrogenase, or complex I. Electrons are transferred from complex I (NADH dehydrogenase) to coenzyme Q (CoQ), then to complex III cytochrome *c* oxidoreductase, next to cytochrome *c*, then to complex IV (cytochrome *c* oxidase), and finally to oxygen to give water. The energy released is used to pump protons across the mitochondrial inner membrane through complexes I, III, and IV, creating an electrochemical gradient. This gradient is used by complex V (ATP synthase) as a source of potential energy to condense ADP and inorganic phosphate to make ATP, and the ATP is exported to the cytoplasm by the translocator (Wallace, 1994).

Seven of the 13 mtDNA gene products (ND1, 2, 3, 4L, 4, 5, and 6) are subunits of complex I: one (cytochrome *b*) of complex III, three (COI, II, and III) of complex IV, and two (ATP6 and 8) of complex V. Therefore, all deleterious mutations of the mtDNA affect energy metabolism. Mutations in mtDNA protein genes inhibit specific respiratory complexes, whereas mutations in the mtDNA tRNAs affect the assembly of all the respiratory complexes.

Relevant for the understanding of mtDNA-related diseases is the fact that, in contrast with nuclear genes, which are represented by two alleles, multiple mitochondria are present in every cell, and each mitochondrion contains multiple genomes. At the time of cell division, mitochondria (and mtDNAs) distribute haphazardly between daughter cells (polyplasmy) (Di Mauro and Moraes, 1993).

mtDNA mutations result in cells having a mixture of mutant and normal wild-type mtDNAs (heteroplasmy). When such cells divide, the mutant mtDNAs are distributed randomly into the daughter cells by cytokinesis. With repeated cell divisions the proportion of mutant mtDNAs drifts, and may ultimately give rise to cells with either pure mutant or pure normal molecules (homoplasmy). Different tissues and organs rely on mitochondrial energy to different extents, with the brain being the organ most dependent on mitochondrial energy, followed by the heart, muscle, kidneys, endocrine glands, and liver. The overall proportion of mtDNAs carrying the mutation is primarily determined by segregation during oogenesis or early embryological development, and this random replicative (mitotic) segregation, subsequent to the establishment of primary germ layers, is responsible for the variation between tissues.

Uneven distribution of mutant mitochondria between cells and tissues occurs and could give rise to less characteristic clinical syndromes. In elderly patients such variants are difficult to differentiate from more familiar forms of late-onset neurological disease, unless the diagnosis of mitochondrial cytopathy is kept actively in mind (Lennox *et al.*, 1989).

Although particular mtDNA mutations are usually associated with specific phenotypes, overlaps and atypical presentations are not rare and relatives of affected patients may have few symptoms or none at all.

Classification of Mitochondrial Encephalomyopathies

Pathological mtDNA mutations can be divided into genomic rearrangements and nucleotide substitutions (Wallace, 1994). Genomic rearrangements can involve deletions, insertions, or a combination of the two and commonly are found in the array of clinical symptoms encompassed by chronic progressive external ophthalmoplegia (PEO) (see p. 47) and Kearns–Sayre syndrome (KSS) (see p. 24) and also have been associated with adult-onset diabetes and deafness (see p. 652). Single mtDNA large-scale deletions (Holt *et al.*, 1988; Lestienne and Ponsot, 1988; Zeviani *et al.*, 1988) or, more rarely, insertions (Poulton *et al.*, 1989) were found in about 50% of the cases of sporadic adult-onset chronic PEO with ragged red fibers (RRFs), and in nearly 100% of the cases of KSS.

Deleterious nucleotide substitutions can alter either a conserved amino acid in a protein (missense mutation) or a tRNA (protein synthesis mutation). Missense mutations that affect the electron transport chain (complexes I, III and IV) frequently present with Leber's hereditary optic neuropathy (LHON) (De Vivo, 1993). Point mutations were identified in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (see p. 51) and myoclonic epilepsy with RRFs (see p. 54).

In this group of disorders, Di Mauro *et al.* (1985) also included SNE (see p. 38), progressive infantile poliodystrophy (see p. 479), and trichopoliodystrophy (see p. 413), and Morgan-Hughes (1986) added the cerebrohepatorenal syndrome (see p. 337), since a mitochondrial myopathy has been shown to be present in this syndrome. Disorders of mito-

chondrial metabolism have also been presumed to underlie the van Bogaert–Bertrand and Canavan diseases (see p. 524), Reye's syndrome (see p. 154), and some still unclassified complex encephalomyopathic syndromes.

Although the overall correspondence between clinical phenotypes and specific molecular lesions is remarkably good, the occurrence of these "exceptions" must be considered in setting up a diagnostic protocol for mtDNA mutations. Furthermore, not all MERRF (myoclonic epilepsy with RRFs) or MELAS (syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokes) pedigrees are associated with the corresponding known mtDNA mutations (Zeviani *et al.*, 1991; Hammans *et al.*, 1991, Bindoff *et al.*, 1991), implying that other, still unidentified, mutations can also determine the clinical phenotypes.

Some of the mitochondrial diseases are primary, while others are secondary to other metabolic disorders (Goebel *et al.*, 1989). In this chapter we deal only with those conditions in which a primary disturbance in the respiratory chain leads to well-established morphological findings. Paulus *et al.* (1990) recommended the monoclonal antibody M-II 68, which recognizes the inner mitochondrial membrane in routinely processed tissue by light microscopic immunohistochemistry to detect accumulations of mitochondria and increases in mitochondrial cristae density.

Subacute Necrotizing Encephalomyelopathy (Leigh Disease; Leigh's Encephalomyelopathy; Infantile Form of Wernicke's Encephalopathy)

This condition was first described by Leigh (1951) in an 8-month-old child. The lack of well-defined characteristic localization of lesions, on the one hand, and the largely nonspecific tissue changes, on the other, allow one to surmise that the large number of diagnosed and reported cases do not constitute a homogeneous entity. The demonstration of different metabolic disturbances, as well as the variable clinical course has led investigators to attempt to differentiate SNE in the strict sense from Leigh syndrome (Walter *et al.*, 1986). The common denominator remains a disturbance of the respiratory chain based on a variety of enzymopathies. PDH and cytochrome-*c* oxidase deficiency are common metabolic disturbances in Leigh syndrome. Complex I or II deficiency has also been claimed. These results indicate that the underlying defect in Leigh's encephalomyelopathy is heterogeneous and only 30% of the patients had enzyme defects demonstrable in muscle biopsy material (Nagai *et al.*, 1992). Brain lesions of the SNE-type distribution associated with a mitochondriopathy of Pearson's syndrome were reported in one case (Yamadori *et al.*, 1992).

The results of Paulus and Peiffer (1990), using a monoclonal antibody to an inner mitochondrial membrane antigen, substantiate the classification of SNE disease as primary mitochondrial encephalopathy.

The occasional appearance of the disorder in older children, adolescents, or adults justifies a separation of juvenile and adult variants from the common infantile form, which affects children under 2 years of age.

1. The **infantile form** of SNE often appears in siblings as an autosomal-recessive genetic disorder. There are possible combinations with posterior column degeneration or a Friedreich-like complex.

Clinical Picture The disease manifests itself in the course of the first or second year of life with loss of appetite, vomiting, difficulties in sucking and swallowing, and muscular hypotonia. Later symptoms include nystagmus, strabismus, deafness, disturbances of gait, optic atrophy, and a characteristic weak cry. Van Coster *et al.* (1991) identified three clinical stages. Most patients have normal neurological development during the first 8–12 months (stage I). Somatic complaints are common, including chronic diarrhea, recurrent vomiting, anorexia, and decelerating body and head growth. The second stage evolves during late infancy and early childhood, when motor regression becomes evident. Eye signs, altered breathing patterns, and pyramidal, extrapyramidal, and cerebellar signs merge and sudden clinical deterioration occurs during intercurrent infectious or metabolic stress. The last stage may extend from 2 to 10 years and is manifested by extreme hypotonia, swallowing difficulties, and undernutrition. Feeding assistance is necessary and seizures may occur. A neonatal variant presenting soon after birth with apnea and hypotonia was reported by Seitz *et al.* (1984). Parental consanguinity has been found in several families; the hereditary pattern is recessive and males are more commonly affected (2:1).

Raised blood levels of lactate, pyruvate, and α-ketoglutarate are common, but nonspecific. The CSF lactate concentration is consistently elevated. The uncompensated metabolic acidosis can stimulate hyperventilation, which in turn leads to respiratory alkalosis. A raised level of endorphins in the CSF has been linked with the occurrence of episodic apnea (Brandt *et al.*, 1980).

Brain stem auditory evoked potentials are always abnormal in these patients (Davis *et al.*, 1985). Ultrasonography revealed hyperechoic lesions in the putamen and the caudate nucleus during the preclinical stage (Yamagata *et al.*, 1990b). CT and MRI scans have shown symmetrical lesions in the basal ganglia (Martin *et al.*, 1988), most frequently in the putamen. Lesions are also commonly found in the globus pallidus and the caudate nucleus, but never in the absence of putaminal abnormalities. In patients who present with lactic acidosis and whose MR findings show symmetrical abnormalities in the brain, but with sparing of the putamen, the diagnosis of SNE is in doubt (Medina *et al.*, 1990). However, the absence of focal lesions detected by either modality in one patient does not exclude the diagnosis of SNE, since focal lesions were reported in a case at autopsy 1 month following negative CT and MRI (Greenberg *et al.*, 1990).

Death from respiratory failure follows after 1–4 years, or in the neonatal form after only a few days or weeks. An intermittent course with remissions and relapses is distinctly rare. The clustering of cases in some families suggests an autosomal-recessive inheritance.

Pathology RRFs with subsarcolemmal accumulation of enlarged mitochondria (Seitz *et al.*, 1984) were observed in skeletal muscles (Walter *et al.*, 1986), as well as in the myocardium. Hypertrophic cardiomyopathy has also been reported (Pastores *et al.*, 1994).

Neuropathology *Gross appearances.* Frequently one can detect a dark brown discoloration of the floor of the fourth ventricle, around the aqueduct, in the inferior olives, the corpora quadrigemina, and the pontine tegmentum (Fig.12A–C). Multilocular cystic foci

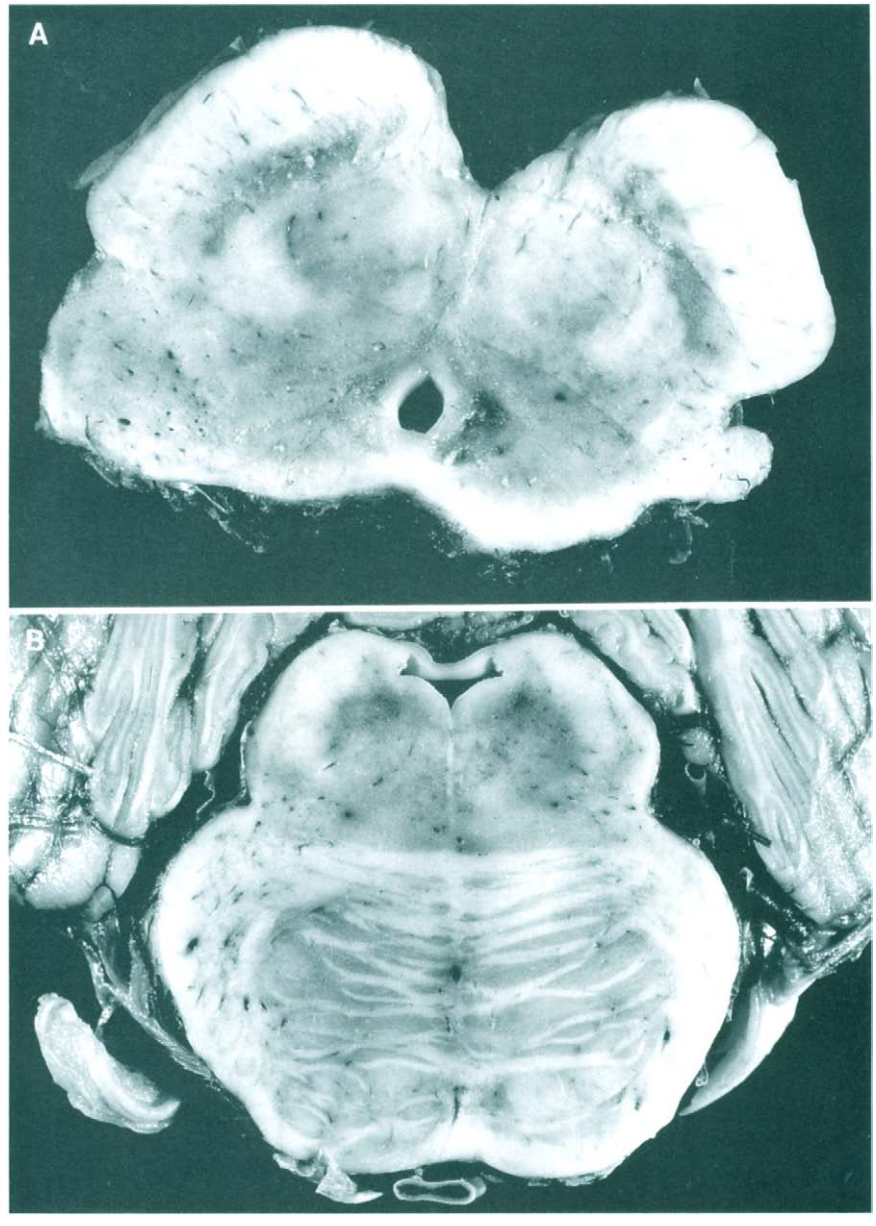


Fig. 12 Infantile form of subacute necrotizing encephalomyelopathy. Bilateral discoloration of the necrotic spongy foci in (A) the midbrain, (B) the pontine tegmentum, and (C) the medulla oblongata.

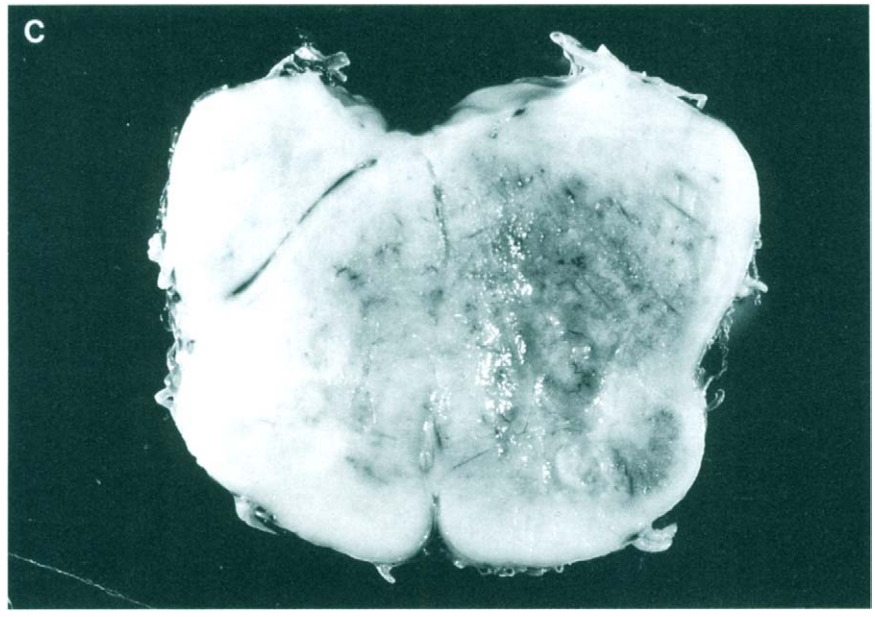


Fig. 12 Continued.

as well as involvement of the cerebral cortex has been reported. The thalamus, the striatum (Fig.13A and B), and the central gray of the medulla oblongata and of the cervical cord may show discoloration. Agenesis of the corpus callosum has been recorded occasionally (Carleton *et al.*, 1976). A panencephalopathy that may also involve the spinal cord has been described in the congenital form of this condition (Seitz *et al.*, 1984).

Light microscopy. Loss of myelin (Fig.14A and B), and frequently also status spongiosus and microcysts, are present in the macroscopically affected areas (Tsai *et al.*, 1990). Prominent features are thickening of the capillaries with plump endothelia, and astrocytic gliosis with relative sparing of the neurons (Fig. 15). Multinucleated neurons are found occasionally. Only rarely have sparse perivascular lymphocytic infiltrates been observed.

The process may extend onto the white matter of the cerebellum, the cerebral peduncles, the basal ganglia, and the white matter of the cerebral hemispheres. Multilocular cystic changes and involvement of the cerebral cortex have been described. In rare instances the corpus callosum and the optic nerves may also be affected (Dooling and Richardson, 1977). In general, the lesions resemble those of Wernicke's encephalopathy, but with minor differences in distribution. The mamillary bodies tend to be spared, but not always (Kamoshita *et al.*, 1968). On the other hand, involvement of the substantia nigra is common in SNE, but rare in Wernicke's encephalopathy.

Ultrastructurally, axonal swellings and splitting of myelin sheaths (Carleton *et al.*, 1976) are present, and myelin splitting plays an important role in the formation of the spongy lesions (Kimura *et al.*, 1991).

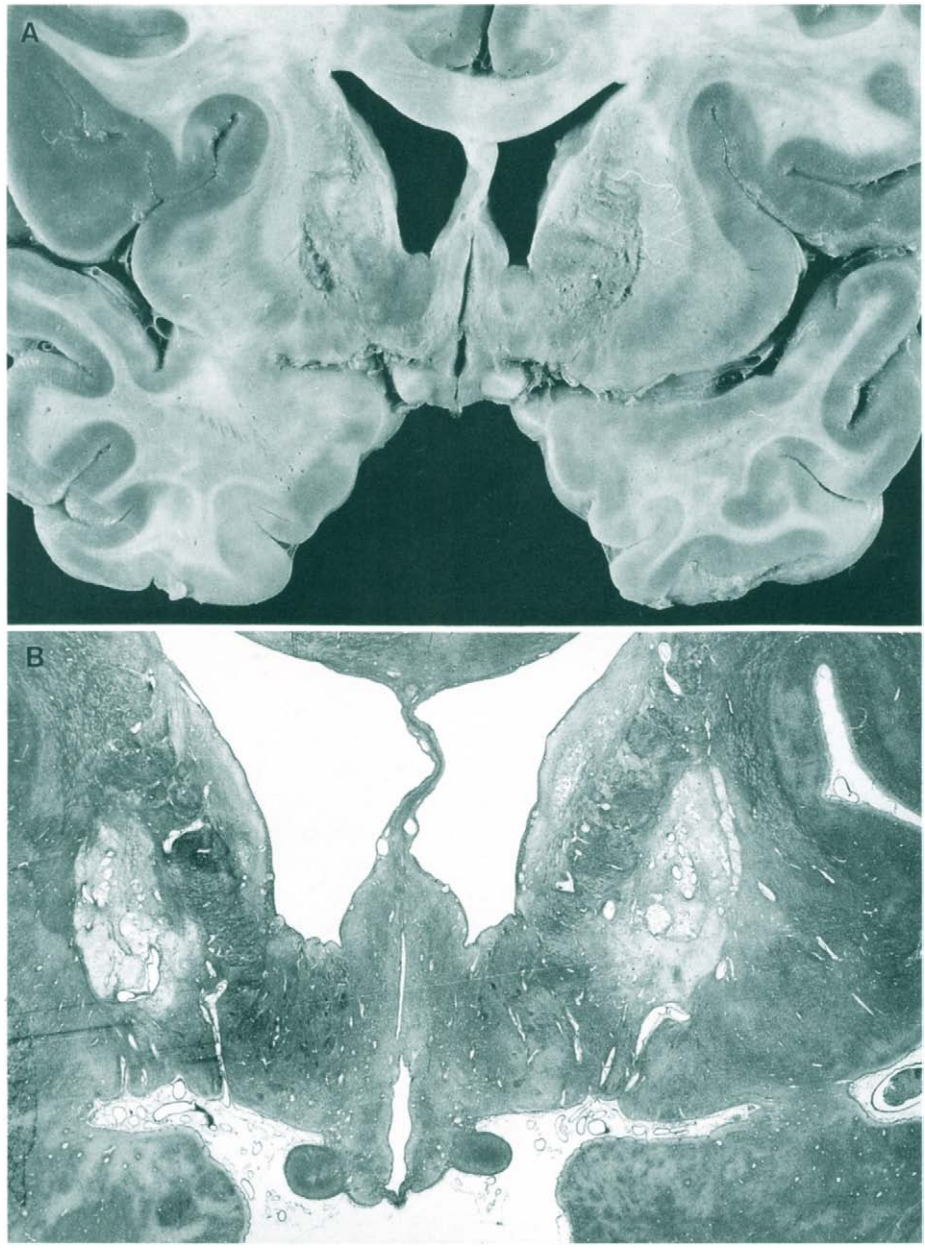


Fig. 13 Infantile form of subacute necrotizing encephalomyelopathy. Bilateral symmetrical foci with microcystic changes in the striatum.

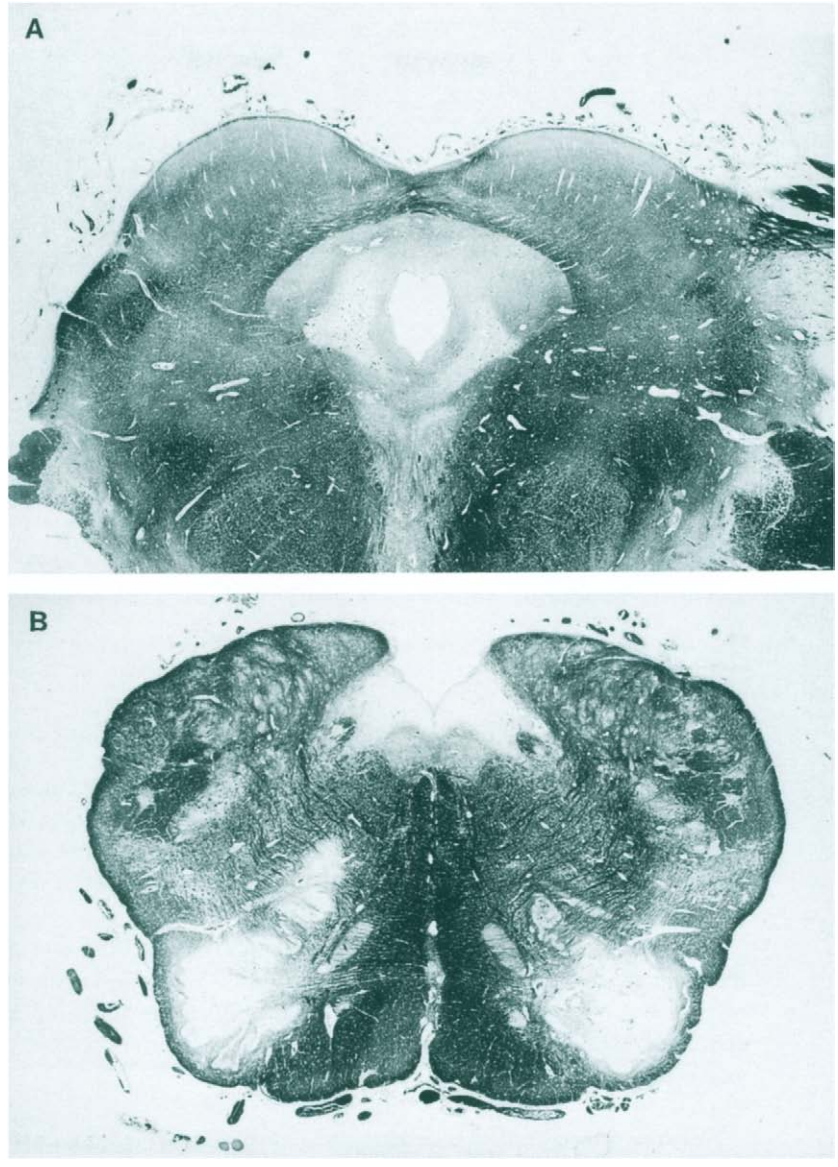


Fig. 14 Infantile form of subacute necrotizing encephalomyelopathy. Foci of demyelination (A) around the aqueduct at the level of the corpora quadrigemina and (B) in the floor of the fourth ventricle. Hematoxylin–eosin stain; ×120.

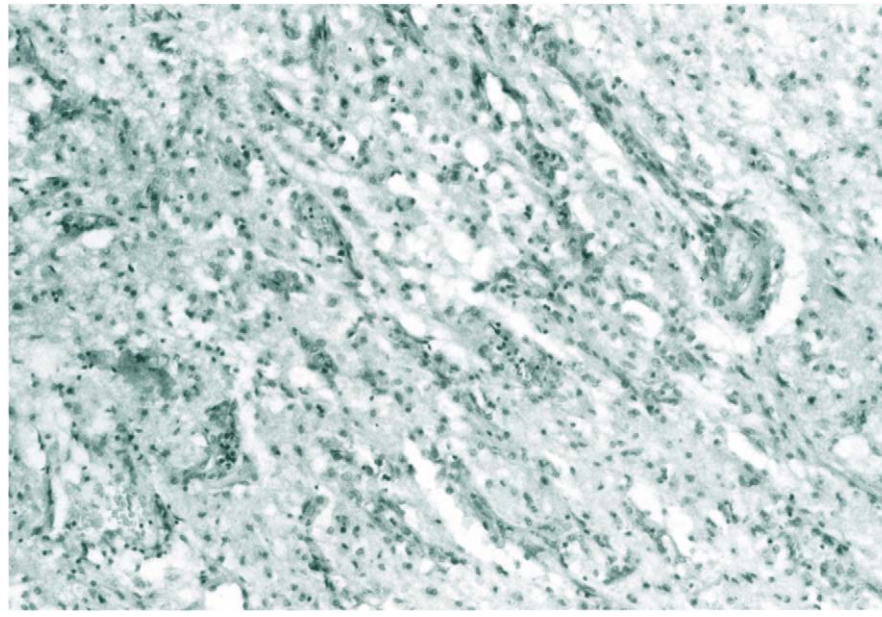


Fig. 15 Infantile form of subacute necrotizing encephalomyelopathy. Proliferation of glia and blood vessels in the floor of the fourth ventricle. Hematoxylin–eosin stain, ×120.

2. The separation of a **juvenile form** from the infantile form was first postulated by Peterson and Alvord (1964). Guazzi *et al.* (1968) doubted the validity of such a separation, as the disease runs a prolonged course in some patients with presentation in infancy. Nevertheless, the concept of juvenile SNE has now been widely accepted.

Clinical Picture The first symptoms appear toward the end of the first decade in the form of transient visual disturbances (Lahl, 1981). These are followed by disorders of gait and coordination, as well as by difficulties in breathing and swallowing. The course of the disease is slowly progressive, with a duration from a few years up to 15 years (Montpetit *et al.*, 1971).

Neuropathology The character and distribution of lesions correspond roughly with those seen in the infantile form. In addition, there is involvement of structures rarely affected in infancy (Montpetit *et al.*, 1971; Lahl, 1981), such as the cerebral and cerebellar cortices (Fig. 16), among others.

Electron microscopy showed hypertrophic mitochondria with bizarre disorganized cristae in astrocytes (Fig. 17). Hypomyelinization of peripheral nerves leads eventually to demyelination (Jacobs *et al.*, 1990), and rarely to severe peripheral neuropathy (Federico *et al.*, 1990), and chronic demyelinating neuropathy can be an important initial presentation of the disease (Grunnet *et al.*, 1991).

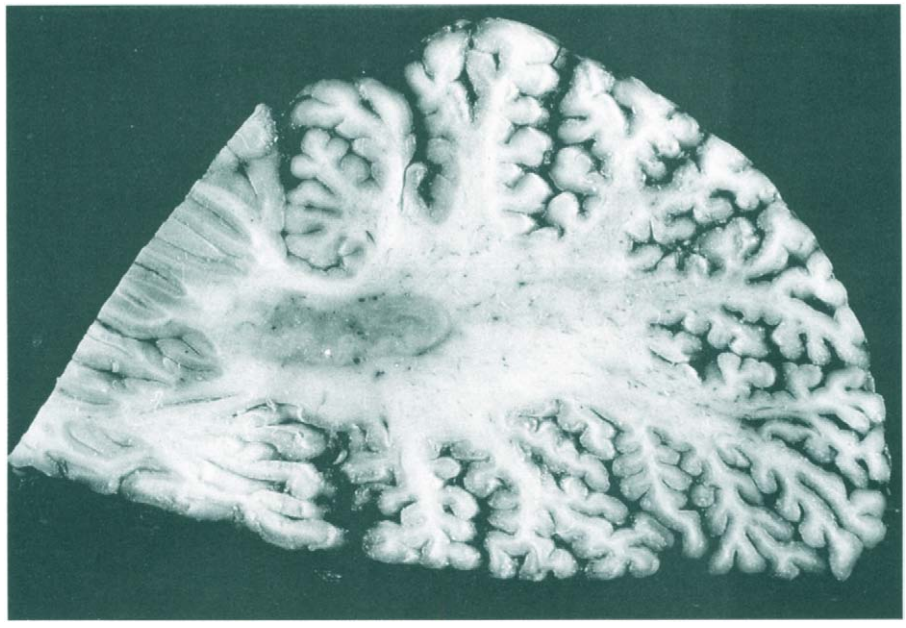


Fig. 16 Juvenile form of subacute necrotizing encephalomyelopathy. Pronounced atrophy of the cerebellum.

3. The first case of an **adult form** of SNE, reported by Feigin & Goebel (1969), was followed by several others, some of which were diagnosed only at autopsy. The inclusion of some of these cases under *Leigh syndrome* does not appear to have been fully justified (Lahl, 1981) as the corpora mamillare were frequently involved (Anzil *et al.*, 1981), leading to possible confusion with chronic Wernicke's syndrome.

Clinical Picture Neurological symptoms usually appear between the second and fifth decades. Some authors include cases presenting in the first to fifth year of life among the adult cases, if the patient survived beyond the age of 20. The first symptom is often a slowly progressive optic atrophy. Lesions in the basal ganglia and the midbrain may be detected by CT (Gray *et al.*, 1984; Bianco *et al.*, 1987) and, more clearly, by MRI (Kissel *et al.*, 1987). Similar changes, however, can be seen in striatonigral degeneration (see p. 563). The duration of the illness may exceed 30 years. Most cases are sporadic, but familial cases have been reported.

Neuropathology The optic nerves and chiasm are affected more frequently than in the other forms of the disease. The mamillary bodies were spared in only a few cases. The presence of intact neurons surrounded by necrotic tissue in association with optic nerve atrophy have led, in some cases, to the diagnosis of Leigh's SNE in patients without ganglial involvement.

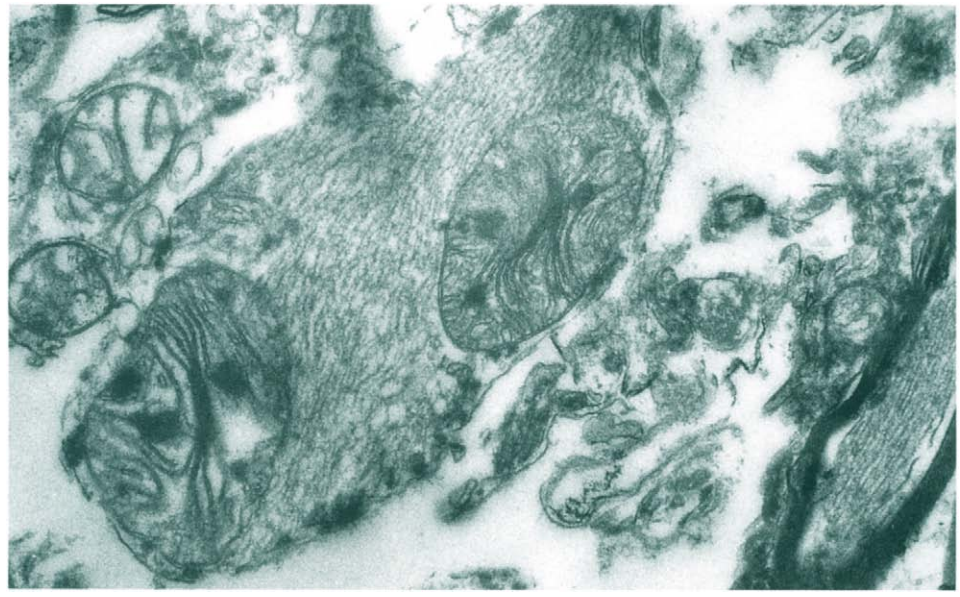


Fig. 17 Juvenile form of subacute necrotizing encephalomyelopathy. A neuronal process with hypertrophied mitochondria in the parietal cortex, ×25,000.

Pathogenesis The lack of thiamine triphosphate in the brains of patients with SNE was explained by a factor inhibiting the enzyme thiamine-pyrophosphate-ATP-phosphoryltransferase. This inhibitor was detected in the CSF, among other sites. It was also discovered in the patient's unaffected relatives (Plaitakis *et al.*, 1980). In any event it is important to distinguish patients with infantile Wernicke's encephalopathy due to nutritional thiamine deficiency from those with SNE.

Patients with SNE have been described with different biochemical defects, all affecting cerebral energy metabolism. The disturbance of oxidative decarboxylation of pyruvate, detected by several authors (Van Biervliet *et al.*, 1979), was not corroborated in all cases (Hansen *et al.*, 1982). Vice versa, no evidence of SNE was formed in established cases of pyruvate decarboxylase deficiency. There is thus no obligatory connection between SNE and pyruvate decarboxylase deficiency, even though this has been demonstrated in the fibroblast cultures of some patients (Hinman *et al.*, 1984). This enzyme deficiency may be responsible for different cerebral lesions (see p. 33). A disturbance of cytochrome *c* oxidase and cytochrome *c* reductase in skeletal and cardiac muscle was discovered in many cases of SNE, both infantile (Willems *et al.*, 1977) and adult (Martin *et al.*, 1988), and established an abnormality in the mitochondrial respiratory chain in at least a subgroup of this disorder. The biomolecular abnormality was thought to implicate a nuclear-encoded protein affecting the structure or stability of the holoenzyme complex (Van Coster *et al.*, 1991). In SNE associated with a deficiency of PDH complex activity, an A-

to-C transversion in the PDH complex E1$^{\alpha}$ subunit gene has been found (Matthews *et al.*, 1993). As the E1$^{\alpha}$ subunit is encoded on the X chromosome, this observation confirms that some patients with the SNE syndrome may exhibit X-linked inheritance.

In addition to the phenotype of ataxia and retinitis pigmentosa (RP) described by Holt *et al.* (1990), the mutation at nucleotide 8993 can produce the clinical phenotype of SNE (Shoffner *et al.*, 1992; Tatuch *et al.*, 1992). This results in the substitution of an arginine residue for a leucine. It is maternally inherited and heteroplasmic, it produces marked clinical and biochemical heterogeneity between pedigree members, and its level varies along the maternal lineage.

Kearns–Sayre Syndrome (Ophthalmoplegia Plus; Oculocraniosomatic Neuromuscular Syndrome; Ophthalmoplegia with Retinopathy and Cerebral Symptoms; Spongiform Encephalopathy with Ophthalmoplegia)

KSS was first described by Kearns and Sayre in 1958. Schmitt (1982) included KSS among the mitochondrial encephalomyelopathies.

Clinical Picture The classical picture consists of retinitis pigmentosa (RP), external ophthalmoplegia, and disorders of the myocardial conduction system. Further symptoms include ataxia, deafness, raised protein in the CSF, and occasionally mental retardation. Proximal myopathy, optic atrophy, small stature, hypogonadism, endocrine disturbances, and hypersomnia have been reported as additional clinical manifestations (Kotagal *et al.*, 1985). There are patients who present almost exclusively with muscular symptoms but without significant neurological ones and who can initially be misdiagnosed as having psychosomatic disorder (Norby *et al.*, 1994). Others display simultaneous involvement of both systems; in still others the neurological symptoms overshadow the myopathic manifestation, which may become apparent only after a course of several years (Menger *et al.*, 1986). Most cases appear to be sporadic, but autosomal-dominant inheritance has also been reported (Bastiansen *et al.*, 1982). KSS has also been associated with a variety of endocrine and metabolic disorders, particularly short stature, gonadal failure, diabetes mellitus, and others (Harvey and Barnett, 1992). Children who survive the initial phase of Pearson's syndrome may develop KSS (Simonsz *et al.*, 1992).

Pathology *Light microscopy.* There are circumscribed degenerative foci in skeletal muscles, which, in transverse section, reveal RRFs with reddish granules in the sarcoplasm (Fig. 18). Hammerstein *et al.* (1983) found a type I fiber predominance with hypotrophy of type II fibers. After a follow-up of 10 years, a 50% reduction in the number of RRFs has been reported (Reichmann *et al.*, 1993).

Electron microscopy. The salient feature of this condition is the subsarcolemmal proliferation of abnormal or giant mitochondria (Fig. 19A and B) with disorganized cristae, electron-dense paracrystalline inclusions in the RRFs (Ketelsen *et al.*, 1982), and hypertrophic concentric lamellae. These abnormalities have been found not only in type I, but also in type II fibers (Farrants *et al.*, 1988). Excessive accumulation of glycogen in hyper-

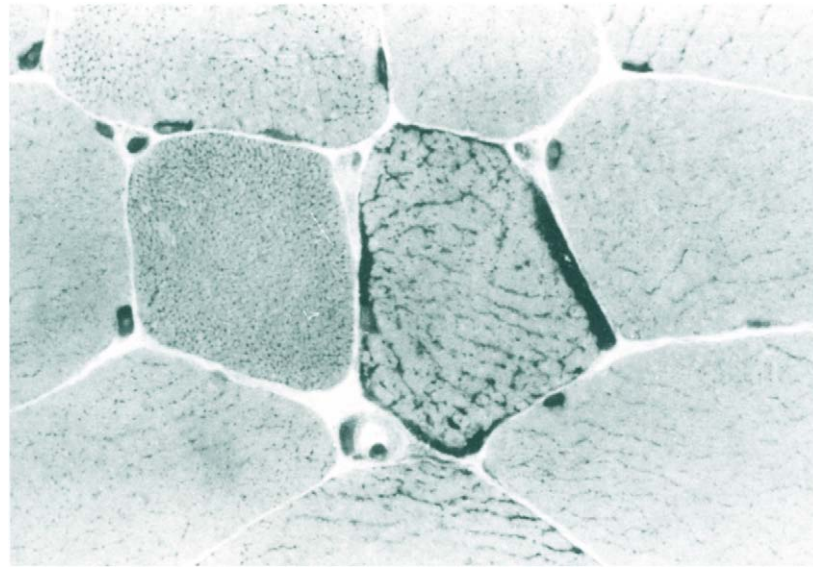


Fig. 18 Kearns–Sayre syndrome. Transverse section of muscle with ragged fiber. Hematoxylin–eosin stain; ×600.

trophic fibers has been observed occasionally. Similar mitochondrial changes have been found in the liver and in the sweat glands. Both in the myocardium and in skeletal muscles aggregations of mitochondria without paracrystalline inclusions may also be present.

Neuropathology *Gross appearances.* On coronal sections of the brain, large, confluent, unsharply limited changes in the white matter, which appears grayish and softer than the normal white matter, can be found in the frontal parietal, temporal, and occipital lobes of both hemispheres. The putamen and the globus pallidus are affected and the caudate nuclei of both sides are very thin with a concave surface against the ventricles, which are moderate and symmetrically enlarged. Occasionally, atrophy of the folia of vermis has been reported (Oldfors *et al.*, 1990). Severe cerebellar atrophy is rare. Groothuis *et al.* (1980) observed atrophy of the optic nerves.

Light microscopy. The striking feature is a coarse status spongiosus of the white matter, most striking in the occipital lobes. It may be particularly prominent in the brain stem and tends to be moderately severe in the pallidum and the thalamus and only slight in the striatum, cerebellum, and anterior and lateral columns of the spinal cord (Kornfeld, 1978). Demyelination of the motor roots of the cranial and spinal nerves was reported by Groothuis *et al.* (1980). In the macroscopically discolored areas of the putamen and the globus pallidus, a complete loss of nerve cells with gliosis and capillary proliferation can be detected. The globus pallidus displays large deposits of intracellular iron, and the caudate nuclei are shrunken with a severe loss of nerve cells, marked astrogliosis, and nu-

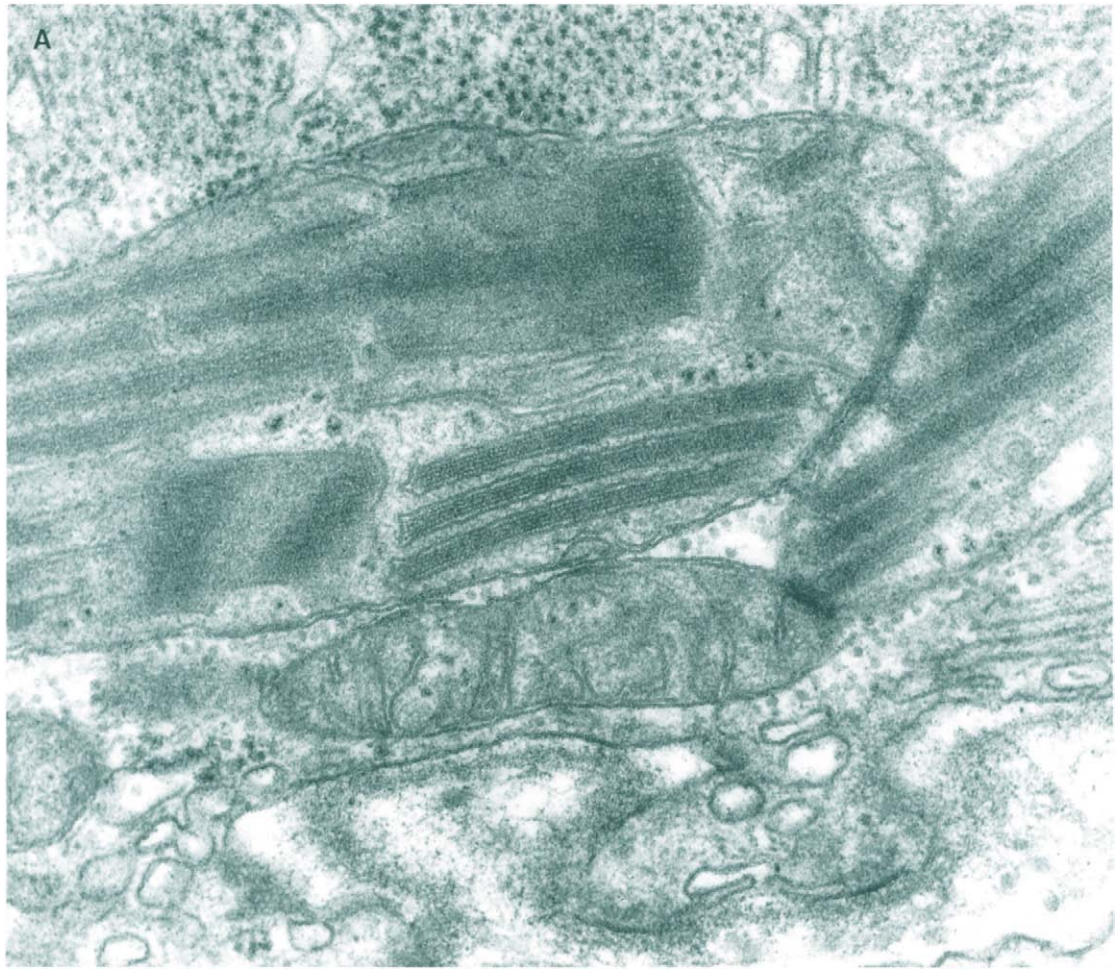


Fig. 19 Kearns–Sayre syndrome. Giant subsarcolemmal mitochondria with paracrystalline inclusions. (A) Longitudinal section, ×64,000. (B) Transverse section, ×80,000.

merous capillary vessels. A loss of neurons has also been recorded in the oculomotor nuclei (Castaigne *et al.*, 1971) and the locus coeruleus and minimally in the paraventricular nucleus. The cerebellum is rarely affected, but a loss of Purkinje cells was observed by Castaigne *et al.* (1977).

Electron microscopy. Mitochondrial abnormalities were seen in the cerebellum (Schneck *et al.*, 1973) and in the retina (Newell and Polascik, 1979). Cellular inclusions of the globus pallidus appear as lipofuscin mixed with extremely electron-dense spherical bodies (Oldfors *et al.*, 1990).

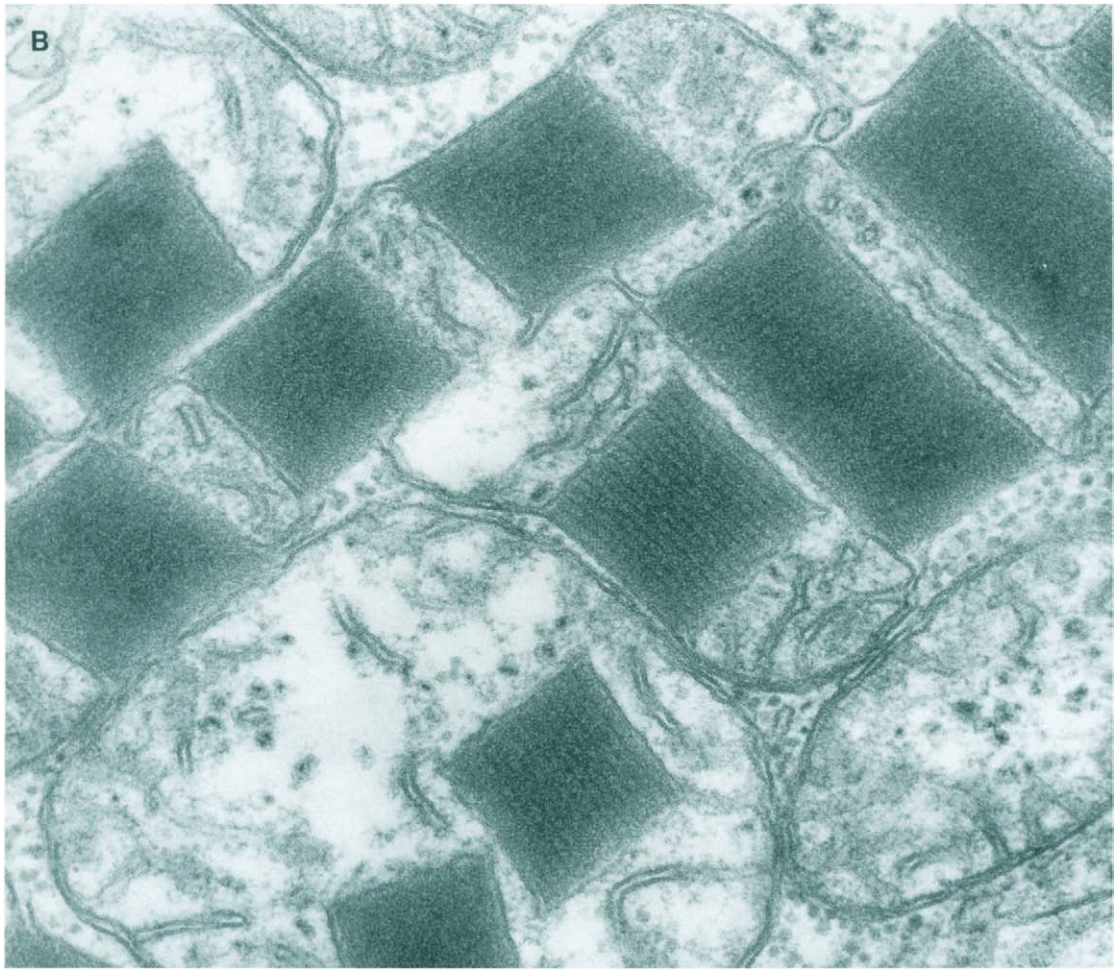


Fig. 19 Continued.

Pathogenesis The mitochondrial abnormalities are of paramount significance for understanding the clinical symptomatology. In contrast with the striking morphological appearances, the results of investigations of mitochondrial function were equivocal. Di Mauro *et al.* (1973) found a lack of control of mitochondrial metabolism in the presence of α-glycerophosphate, while the substrates glutamate and succinate were normally oxidized. These findings were questioned by other authors (Hammerstein *et al.*, 1983), who failed to find any abnormalities in mitochondrial phosphorylation or calcium uptake.

Shanske *et al.* (1990) found in mtDNA a single deletion of 4.9 kb in all tissues. Most patients exhibit a heteroplasmy of the mtDNA in the skeletal muscle mitochondria, consisting of a partially deleted and a normal-length mtDNA species. The deletion of mtDNA includes the *ND4*, *ND5*, and *ND6* genes coding for subunits of the respiratory

complex. The percentage of deleted mtDNAs varied widely between tissues, from only 4% in smooth muscle to approximately 50% in skeletal muscle. Biochemical analysis showed no clear correlation between mitochondrial enzyme activity and deleted mtDNAs. In a case of KSS, a deletion was described, bracketed by direct repeats, one of them located 11–13 nucleotides from the deletion seam (Remes *et al.*, 1993).

The proportion of mtDNAs carrying the $tRNA^{Leu(3243)}$ mutation was not uniform in members of a pedigree reported by MacMillan *et al.* (1993) and did not undergo rapid mitotic segregation along germ layer divisions. These findings are consistent with the hypothesis of a random replicative segregation (see p. 37).

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokes

This condition was first described by Askanas *et al.* (1978). Pavlakis *et al.* (1984) introduced the acronym *MELAS* and drew attention to other cases in the literature.

Clinical Picture This condition manifests itself between ages 3 and 11. The characteristic, constantly present, features consist of stunted growth, focal or generalized epileptic seizures, episodic paralyses, intermittent vomiting, migraine, cortical blindness or hemianopia, and occasionally ophthalmoplegia (Fang *et al.*, 1993). Motor disturbances may present as hemiparesis or paraparesis, alternating from side to side.

Impairment or loss of hearing, ataxia (Mukoyama *et al.*, 1986), dysarthria, and aphasia as well as hallucinations are additional symptoms. A positive family history can be elicited in about one third of the patients. After initially normal mental development, dementia frequently supervenes in later stages of the disease. Further investigations may reveal generalized or focal abnormalities on the EEG, including epileptic activity. CT scanning may show areas of hypodensity or calcification in the basal ganglia (Stefan, 1987).

Hirano *et al.* (1992) found incomplete syndromes in relatives of patients with the full syndrome, and incomplete syndromes might also be encountered in sporadic cases. Some MELAS patients have features of KSS or MERRF, but none had full KSS. More rare combinations, for example, with Friedreich's ataxia, have been described by Nakano *et al.* (1982).

Nicoll *et al.* (1993) described two patients who experienced recurrent headache with vomiting and strokelike episodes, but MELAS without RRFs or lactic acidosis was diagnosed by the presence of the A-to-G mutation in the $tRNA^{Leu(UUR)}$. At the time of autopsy, skeletal muscle showed the characteristic features of mitochondrial cytopathy.

Pathology Light microscopy of muscle biopsies reveals RRFs in preparations stained with Gomori's trichrome. In addition, hypertrophy of the myocardium, fatty changes of the liver, focal sclerosis of the glomeruli and dilatation of the tubules of the kidneys, and hyaline degeneration of the Langerhans' islets of the pancreas were observed (Ban *et al.*, 1992).

Electron microscopy demonstrates aggregates of enlarged and morphologically abnormal mitochondria. Swelling of the vascular endothelia and thickening of the basement membranes as well as generalized mitochondrial microangiopathy (Förster *et al.*, 1991; Müller-Hocker *et al.*, 1993) have also been reported. The duodenal biopsy of a case re-

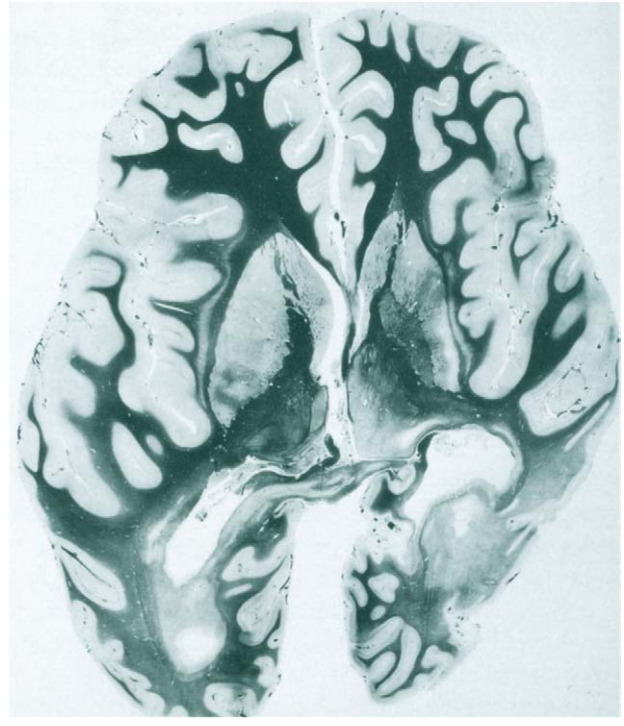


Fig. 20 Syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokes (MELAS) stained for myelin, showing an area of infarction.

ported by Nicoll *et al.* (1993) showed marked accumulation of enlarged structurally abnormal mitochondria in smooth muscle cells of the muscularis externa.

Neuropathology The calcification in the basal ganglia seen on CT is verified morphologically (Kuriyama *et al.*, 1984). Status spongiosus of the cerebral cortex white matter, optic nerve, and pons has been seen in several cases (Hart *et al.*, 1977; Peiffer *et al.*, 1988; Ihara *et al.*, 1989). Minor and major infarcts (Fig. 20) of variable extent and distribution have been demonstrated in the brain and the cerebellum (Kuriyama *et al.*, 1984), mainly in the crest of the cerebral gyri and in the subcortical white matter. They showed liquefaction, cystic degeneration, laminar necrosis, and incomplete necrosis. A severe loss of neurons and an increased number of astrocytes in the dentate nucleus (Ihara *et al.*, 1989) as well as moderate changes in the red nuclei (McKelvie *et al.*, 1991) have been reported.

Electron microscopy reveals an increase in the number of mitochondria in the neurons of the cerebral cortex, Purkinje cells, granular cells, astrocytes, oligodendroglia, capillary endothelium, and walls of the arterioles (Ohama *et al.*, 1987; Ihara *et al.*, 1989). In the choroidal epithelial cells (Fig. 21) a loss of microvilli, collapsed or attenuated apical

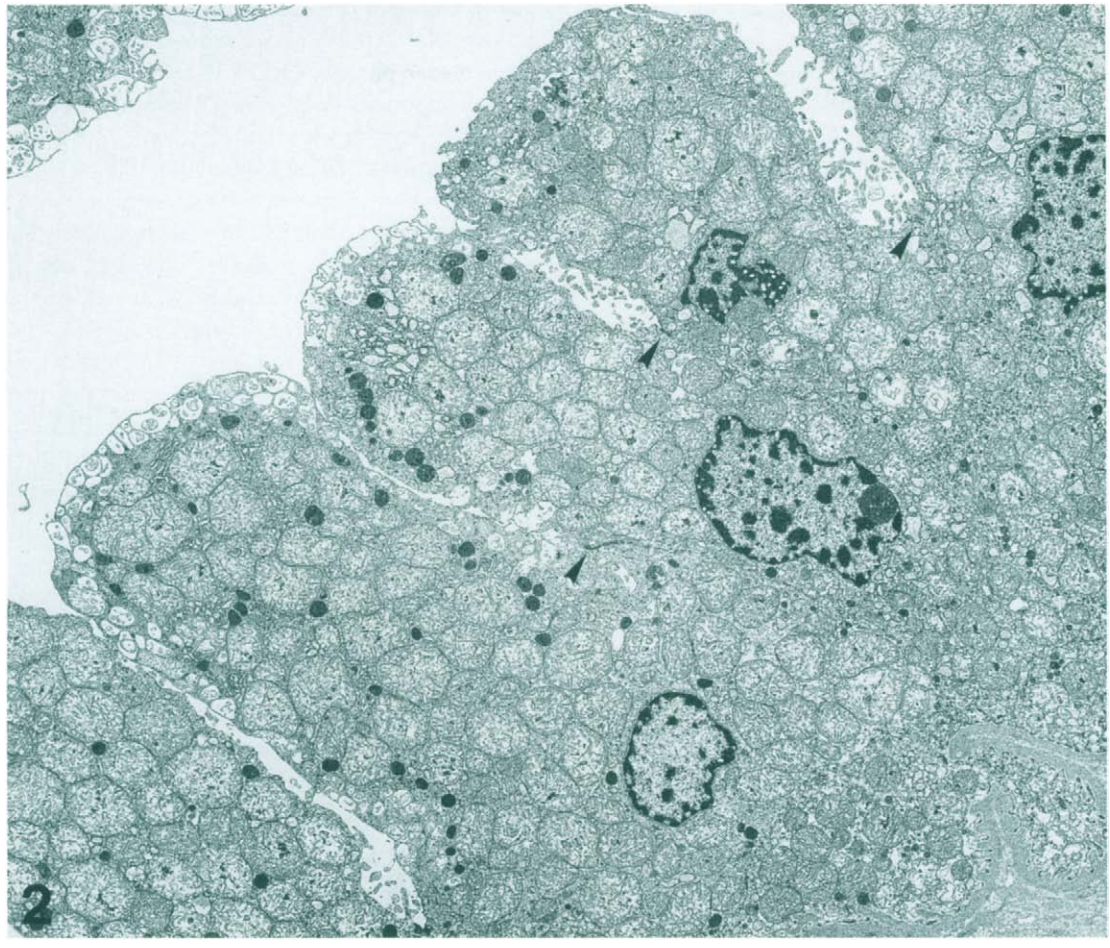


Fig. 21 A choroid plexus from the lateral ventricle, showing the epithelial cells tightly packed with mitochondria. The apical cytoplasm shows attenuated cytoplasmic processes permeated by infoldings. Arrowheads indicate intercellular tight junctions, ×3,560. (Reproduced from Ohama and Ikuta, 1987.)

cytoplasmic processes, an increased number of mitochondria, and lysosome-like dense bodies were found by Ohama and Ikuta (1987).

The amount of wild-type as well as mutant mtDNA was increased in the RRFs (Tokunaga *et al.*, 1994). The nucleotide 3243 A-to-G mtDNA mutation associated with the MELAS syndrome has been measured in different heteroplasmic tissues of adults (Matthews *et al.*, 1994).

Pathogenesis Müller-Hocker *et al.* (1993) illustrated heterogeneous tissue expression of respiratory chain defects in the MELAS syndrome, indicating that vascular cy-

tochrome *c* oxidase deficiency may be involved in the cerebral manifestation of the disease, whereas in other organs a similar pathogenetic importance of the microangiopathy cannot be verified. The percentage of mutant mtDNA at nucleotide 3243 in each tissue ranges between 22% and 95% (Shiraiwa *et al.*, 1993). The content of mutant mtDNA was highest (95%) in the hypophysis and higher in the cerebral cortex than in the white matter. This shows a possible correlation of tissue dysfunction with accumulation of mutant mtDNA in the brain. The proportion of mutant mtDNA is higher in the strongly succinate dehydrogenase-reactive blood vessels than in non–succinate dehydrogenase-reactive blood vessels. It seems likely that systemic vascular abnormalities involving cerebral vessels lead to the evolution of strokelike episodes in MELAS. Patients with the 3243 mutation frequently have PEO. Clinical features did not distinguish PEO patients with the 3243 mutation from those with large-scale deletions of mtDNA. However, most cases with single large-scale mtDNA deletions are sporadic, whereas most patients with the 3243 mutation had maternal relatives who were affected (Moraes *et al.*, 1993).

Myoclonic Epilepsy with Ragged Red Fibers (Ramsay Hunt Syndrome; Dyssynergia Cerebellaris Myoclonica)

After the original report on some patients by Tsairis *et al.* (1973), Fukuhara *et al.* (1980) defined these cases as a subgroup of the complex class of progressive myoclonic epilepsies. Some authors (e.g., Feit *et al.*, 1983) consider the condition identical to the dyssynergia cerebellaris myoclonica (see p. 613) described by Ramsay Hunt in 1921. A degenerative form of Ramsay Hunt syndrome with a lack of RRFs has been stressed by different authors (see p. 613). A transitional form, combining the features of MELAS and MERRF, has been reported (Kuriyama *et al.*, 1984; Peiffer *et al.*, 1988; Pou-Serradell *et al.*, 1991).

Clinical Picture There is considerable heterogeneity in the age of onset, severity, and associated clinical features of this condition. The symptoms appear in a wide age range, from 5 to 42 years, most commonly in the second decade. Myoclonus and ataxia are constant features. Muscular weakness is usually slight or not appreciable, but is sometimes prominent. Other symptoms, including seizures, gait and speech disturbances, cerebellar ataxia, dementia (70%), optic atrophy (50%), stunted growth, and impairment of hearing (37%), may be present in various combinations. A positive family history is obtained from two thirds of the patients (Rosing *et al.*, 1984). Chen *et al.* (1993) documented the fluctuating CT changes in a patient. Berkovic *et al.* (1989) suggested, after an analysis of the literature, that many cases previously described as Ramsay Hunt syndrome, as well as other hitherto unclassified system degenerations associated with myoclonus epilepsy, are actually examples of MERRF.

A clinically and biochemically atypical variant was described by Riggs *et al.* (1984) in two patients. Meanwhile, atypical forms are increasing in number, and the wide variation of clinical symptoms should be considered (Moraes *et al.*, 1993; Nomura *et al.*, 1993). MERRF patients with the same mtDNA mutation can display different

symptoms and all three adult forms of mitochondrial encephalomyelopathies can be expressed within a single kindred (Crimmins *et al.*, 1993). Brain CT reveals findings ranging from a low-density area in the right occipital lobe to moderate atrophy of the pons and the cerebellum, gait and speech disturbances, cerebellar ataxia, myoclonus in the extremities, and mild muscular weakness.

Pathology The usual method to diagnose MERRF is by demonstrating RRFs in skeletal muscle (Di Mauro *et al.*, 1985). However, the absence of RRFs, especially when only one muscle is sampled, does not exclude MERRF. When clinical suspicion of MERRF is high, evidence for mitochondrial disease should be sought from biochemical studies of muscle, morphological examination of the skin, and even a second muscle biopsy.

Neuropathology *Gross appearances.* Cerebellar atrophy (Fukuhara, 1983) as well as a slightly shrunken upper brain stem and brachium conjunctivum (Berkovic *et al.*, 1989) has been detected.

Light microscopy. Status spongiosus is present in the cerebral cortex, and occasionally also in subcortical structures (Peiffer *et al.*, 1988). All cases show a loss of neurons in the dentate nucleus and the inferior olivary nucleus. A mild loss of neurons in the red nucleus and a loss of Purkinje cells have also been reported (Berkovic *et al.*, 1989). Astrocytic gliosis is present throughout the cerebellar white matter, to a lesser extent in the molecular layer of the cerebellum but particularly dense around and within the dentate nucleus. The brain stem also shows diffuse gliosis, with accentuation in the red nucleus and the brachium conjunctivum. Degeneration of the posterior columns and the spinocerebellar tracts has been found in the spinal cord.

Pathogenesis The MERRF pattern of selective neuronal degeneration underlying a chronic progressive neurological syndrome has traditionally been known as an "abiotrophy" or a "system degeneration" (Gowers, 1902). Recognition of mitochondrial disease as a cause of this type of system degeneration allows clarification of a complex and confusing group of patients and families with progressive myoclonus epilepsy. However, there are two major difficulties in integrating the current concept of MERRF with the pathological data. First, there is no pathological evidence for cerebral cortical lesions, yet three of the cardinal features of MERRF (myoclonus, seizures, and dementia) are usually attributed to cortical dysfunction, although generalized myoclonus may also be generated in the lower brain stem. Second, there is no morphological evidence of mitochondrial encephalopathy (Di Mauro *et al.*, 1985). This may relate to factors including differences in the morphological reactions of brain and muscle mitochondria, and the difficulty of obtaining fresh brain tissue for electron microscopy.

A defect in succinate–cytochrome *c* reductase (complex II) was also found in some cases (Riggs *et al.*, 1984). A lack of activity of both cytochrome *c* oxidase and NADH–cytochrome *c* reductase has been established by Angelini *et al.* (1988). The reduced aerobic metabolism demonstrated in PEO by Berkovic *et al.* (1989) could be a di-

rect reflection of the basic cerebral enzymatic defect, rather than a secondary effect due to progressive cellular dysfunction. Half of the intramuscular blood vessels in muscle biopsies from MERRF patients were darkly stained with succinate dehydrogenase but had no activity, and electron cytochemistry also failed to show any activity in the mitochondria. The cytochrome-*c* oxidase deficiency in arteriolar smooth muscle cells is probably related to the pathophysiology of MERRF (Hasegawa *et al.*, 1993).

The condition is inherited through the maternal line by mtDNA. The mutation, which is present in most of the MERRF patients, is an A to G transition at nucleotide 8344 in the pseudouridyl loop of the $tRNA^{Lys}$ gene. The same mutation has been identified in multiple symmetrical lipomatosis with myoclonus epilepsy and occasionally in PEO with or without myoclonus epilepsy (Suomalainen *et al.*, 1992).

The variability and severity of the clinical features of MERRF patients vary markedly among different members of the same family, suggesting that the degree, tissue distribution, and segregation of mtDNA heteroplasmy in different subjects contribute to the clinical expression of the MERRF phenotype, and the relative amount of mutated mtDNA in blood samples is not indicative of its clinical expression (Piccolo *et al.*, 1993). Although the mutation has been considered to be probably the primary cause of the disease, Houshmand *et al.* (1994) detected only mutations, homoplasmic and nucleotides conserved between species, suggesting that none of the tRNA mutations identified was pathogenic. Houshmand *et al.* concluded that mitochondrial tRNA mutations and mtDNA deletions are probably an infrequent cause of mitochondrial disorders in infants. Patients with MERRF and chronic PEO may lack both pathogenic point mutations of tRNA genes and deletions of mtDNA.

Leber's Hereditary Optic Neuropathy

Leber (1871) described a rapidly progressive failure of vision affecting predominantly, but not exclusively, young males. The disease occurred in several generations of one family, but its mode of inheritance did not conform to mendelian patterns. It can be autosomal dominant, autosomal recessive, and X linked (Huber, 1994). The diagnosis of LHON remained unknown in six female patients with bilateral optic neuropathies until molecular analysis revealed the 11778 mtDNA mutation (Weiner *et al.*, 1993). Definite maternal inheritance was established by Nikokelainen *et al.* (1987) and was soon followed by the discovery of mutations in mtDNA (Howell *et al.*, 1991).

Clinical Picture The onset of visual disturbances is usually sudden, commonly in adolescence or early adult life, but cases of early and late onset are also on record. The disease progresses rapidly over a few weeks or months and then stabilizes at a variable degree of severity, ranging from a central scotoma to total blindness. Cases associated with the 144β4 mtDNA mutation have a better prognosis for visual recovery (Johns *et al.*, 1993). It may remain in the pure form or may be associated with a variety of neurological symptoms, such as ataxia, dysarthria, spastic paraparesis, or loss of posterior column sensation. Unusual associations are with infantile encephalopathy, dystonia

(Novotny *et al.*, 1986; Bruyn *et al.*, 1992; Leuzzi *et al.*, 1992), and Charcot–Marie–Tooth disease (McLeod *et al.*, 1978). Cases of dystonia occurred either in patients with optic atrophy or in otherwise unaffected siblings. In all cases CT and MRI showed bilateral putaminal lesions, interpreted as striatal necrosis.

In all of these pedigrees, the ophthalmological and neurological abnormalities appeared in different members of the families, and occasionally in the same member, but all were inherited through the same maternal pathway. Another common association is with abnormalities in the conduction system of the heart, as demonstrated by abnormal electrocardiograms (Oritz *et al.*, 1992). The life span is generally normal.

Pathology A muscle biopsy showed considerable variation in fiber size and an abnormal number of central nuclei (Novotny *et al.*, 1986). The appearance of mitochondria was not recorded.

Neuropathology The optic atrophy may be confined to the maculopapillary bundle or may involve a total fiber loss in the optic nerves, chiasm, and tracts. The lateral geniculate bodies may be normal, or may show transneuronal atrophy or, as in one case, a total loss of neurons and myelinated fibers. Degeneration of the posterior columns is not uncommon in the spinal cord (Bruyn *et al.*, 1992), and that of the pyramidal tracts is occasional. Bruyn *et al.* (1992) showed a marked depletion of myelinated nerve fibers in the corticopontine tracts and the striatum as well as practically complete neuronal depletion in the putamen and the lateral part of the caudate.

Pathogenesis Analysis of the sequence of mtDNA revealed a mutation at point 11778 with a G-to-A transition at the mtDNA nucleotide. This converts the 340th amino acid in NADH subunit 4 from arginine to histidine (Singh *et al.*, 1989). This mutation has been found in 40–60% of the examined pedigrees. An extremely high prevalence of approximately 90% was found in a Japanese LHON pedigree (Nakamura, 1993). It may be present in all mitochondria or only in a proportion, and may vary from tissue to tissue (Newman and Wallace, 1990). The disease is genetically heterogeneous (Huber, 1994), and other mutations have been found. Among them were a G-to-A transition at nucleotide 3460 in the *ND1* gene (Huoponen *et al.*, 1991; Howell *et al.*, 1991), a G-to-A transition at nucleotide 15257 (Brown *et al.*, 1991), and point mutations at nucleotides 4160 and 14484 of the *ND1* gene (Heher and Johns, 1993). Mutations at nucleotide 9438 as well as at position 9804 were found by Johns and Neufeld (1993).

While genetic linkage studies unequivocally indicate that the presence of one of the LHON mutations is a necessary condition to produce the clinical symptomatology, additional factors, either genetic or environmental, are required for phenotypic expression of the mitochondrial defect. Whether the mutation is homo- or heteroplasmic, or whether secondary mutations additionally exist, did not explain intra- or interfamilial phenotypic variations. Two monozygous twin brothers remained discordant for the development of optic neuropathy for 6 years, despite harboring the identical homoplasmic 4216, 13708, and 11778 mtDNA mutations. Epigenetic factors were important determinants of visual loss in LHON in these brothers (Johns *et al.*, 1993). A role as "modulators" of the pheno-

typic expression of LHON could be provided by the additional mtDNA mutations that have been described in association with the disease. Segregation analysis showed that both mtDNA and an abnormal X-linked gene are necessary for the development of optic atrophy (Nakamura and Yamamoto, 1994). Howell *et al.* (1991) postulated the existence of mitochondrial gene mutations that might protect the patient from development of the disease, acting as intragenic suppressor mutations.

Familial Adult-Onset Muscular Dystrophy with Leukoencephalopathy

Van Engelen *et al.* (1992) reported on three siblings with an adult-onset muscular dystrophy with predominantly distal muscle weakness. In the female index patient this was associated with epilepsy and a progressive spastic ataxic gait, while the other two siblings had no appreciable clinical nervous system involvement. Additional investigations revealed muscular dystrophy and leukoencephalopathy in all three siblings. Congenital muscular atrophy of the Fukuyama type (see p. 683) is the only clinical syndrome comparable to that in the reported patients. The syndromes show remarkable similarities. Dizygotic twins with myopathy and leukoencephalopathy were described by Degoul *et al.* (1994). The female twin had an incomplete form of MELAS with the point mutation MELAS-3243, but this was not found in any of the tissues tested in the male twin. The familial occurrence of asymptomatic periventricular leukoencephalopathy, with myopathy starting in early childhood, was reported by Cole *et al.* (1988). However, changes resembling inclusion body myositis were observed. As in the Fukuyama syndrome and in reported akin cases, the mode of inheritance is most likely autosomal recessive, with variable expression. The syndrome might be due to allelic mutation at the putative congenital muscular dystrophy locus.

Ataxia–Retinitis Pigmentosa–Dementia Complex

The ataxia–RP–dementia complex is a rare maternally inherited disease associated with a mtDNA point mutation. The disorder is characterized by the combination of RP and blindness, seizures, ataxia, proximal neurogenic muscle weakness, sensory neuropathy, and dementia (Holt *et al.*, 1990), resembling the syndrome described by Furukawa *et al.*, (1968) in a Japanese family (see p. 632). Tatuch and Robinson (1991) reported on a female infant who died at 7 months of age with lesions in the basal ganglia and the brain stem typical of Leigh disease. Her maternal aunt and a maternal uncle were affected by an early-onset fatal syndrome characterized by lactic acidemia, hypotonia, and multisystemic degeneration of the CNS, while a second maternal uncle was a 37-year-old man suffering from the syndrome originally described by Holt *et al.* (1991). An Italian pedigree mtDNA showed the presence of a heteroplasmic 8993 point mutation in subunit 6 of the ATPase gene. A correlation between the amount of mutated genome inducing ophthalmic defects and the associated mental retardation have been confirmed (Puddu *et al.*, 1993). mtDNA mutations at 8993 can produce the clinical phenotype of Leigh disease in addition to the phenotype of ataxia and RP (Pastores *et al.*, 1994).

Rotig *et al.* (1992) described a case with diabetes mellitus, skin abnormalities, mitochondrial myopathy with RRFs, and cerebellar ataxia. They found complex III deficiency with a heteroplasmic partial duplication of the mtDNA (26 kb), involving one full-length and one partially deleted mitochondrial genome, and with one single abnormal junction between the genes for ATPase 6 and cytochrome *b*.

Mitochondrial Encephalomyelopathy with Degeneration in the Olivopontocerebellar Systems

Kageyama *et al.* (1991) reported on a case of a previously healthy woman who developed a neurological illness at the age of 40 years and died 10 years later. The disease presented with bilateral hearing loss, followed by slowly progressive dysarthria and gait disturbance. There was mild to moderate muscular weakness with some wasting. Muscle biopsy revealed RRFs with accumulation of abnormal mitochondria with paracrystalline inclusions. An assay of the mitochondrial respiratory chain enzymes showed decreased activity of complex I (NADH-CoQ reductase).

Autopsy revealed a cardiomyopathy with accumulation of abnormal mitochondria, chronic pancreatitis with similar mitochondrial abnormalities, fatty changes of the liver, and bilateral adrenal atrophy. In the CNS the hindbrain was most severely affected, with almost total neuronal loss and gliosis in the nuclei pontis and the inferior olives. The cerebellar cortex showed a loss of Purkinje and granule cells. Lesions in the cerebrum were less pronounced, with mild cortical atrophy, dilatation of the lateral ventricles, and some neuronal loss, with gliosis in the globus pallidus, periaqueductal gray, and red nuclei.

Glycoproteinoses (Oligosaccharidoses)

Glycoproteins, or the partial products of their splitting, oligosaccharides, are ubiquitous in their distribution. As a result of disturbances on their predominantly lysosomal breakdown, oligosaccharides accumulate and are either excreted in the urine in large quantities or deposited in various organs. For this reason, the corresponding disease entities have been called oligosaccharidoses. Beaudet (1983) prefers to call them *glycoproteinoses*.

In the autosomal-recessive glycoproteinoses caused by various enzyme defects, different oligosaccharides or glycopeptides are stored in lysosomes. The following conditions belong to this group: aspartylglycosaminuria, Hancock's monosaccharidosis, mannosidosis and fucosidosis, sialuria, Salla disease, and sialidosis (Wolfburg-Buchholz and Schlote, 1985). Some aspects of GM_1 gangliosidosis (see p. 302) and Sandhoff GM_2 gangliosidosis (see p. 325) permit their inclusion in this group. They are considered, however, with the disorders of lipid metabolism.

β-Aspartyl-*N*-glucosaminidase Deficiency (Aspartylglycosaminuria)

In a chromatographic examination of urinary amino acids of mentally retarded Finns, Palo (1967) found, in one patient, large amounts of a substance that was subsequently

identified by Jenner and Pollitt (1967) in two English patients as 2-acetamido-1(β-aspartamido)-1,2-didesoxy-β-D-glucose (aspartylglucosamine). Further cases were recorded in American families of Italian extraction, in Norwegian families of Finnish origin, and in a Puerto Rican family (Chitayat *et al.*, 1988).

Clinical Picture Psychomotor retardation is already apparent in childhood in those with this deficiency. Coarse facial features and recurrent infections are the main features of the condition. Psychotic symptoms are common. Gastrointestinal disturbances, hepatomegaly, and signs of cardiac involvement are present in some patients. The course of the disease is progressive and most patients die before the age of 40 (Pollitt, 1981). Some stationary or mild cases in a higher age group have also been reported. One patient with angiokeratoma has been described by Gehler *et al.* (1981).

Pathology *Gross appearances.* Enlargement and pallor of the liver have been noted. Nodular expansions are found in the mitral valve.

Light microscopy. Almost all hepatocytes contain large central vacuoles surrounded by a rim of cytoplasm and a flattened nucleus. Vacuolation also affects the mesenchymal elements. Except for a few lipofuscin granules, the vacuoles appear empty.

Electron microscopy. The vacuoles appear membrane bound. Their diameter ranges from 0.5 to 10 μm. They contain fine granular material with isolated electron-dense lipid drops, and frequently also concentric membranous structures and lipofuscin conglomerates, usually at the margin of the vacuoles. These may convey the impression of invagination of the vacuole membrane.

Neuropathology *Gross appearances.* Atrophy of cerebral convolutions contrasts with the normal brain stem and cerebellum.

Light microscopy. Ballooning of almost all neurons is conspicuous in the cerebral cortex. The cytoplasm contains empty vacuoles, resembling those of "watery change" (Haltia *et al.*, 1975), and a few lipofuscin granules. In some circumscribed areas, particularly in the visual cortex, there is a severe loss of neurons with status spongiosus. Figures of neuronophagia are encountered occasionally, as well as phagocytic cells with droplets of lipid and granules of lipofuscin in their cytoplasm. The astrocytic reaction is slight. Neuronal changes in the basal ganglia and the thalamus resemble those seen in the cerebral cortex. The globus pallidus is severely affected, with a loss of neurons. The cerebellum shows a diffuse loss of Purkinje cells, the surviving cells containing abundant lipofuscin in their cytoplasm.

Electron microscopy. The intraneuronal vacuoles are smaller and less numerous than those seen in hepatocytes. Electron-dense cytosomes, consisting of membrane-bound conglomerates of granular material and lipid, are prominent in some neurons. These inclusions also appear in the cytoplasm of macrophages. Vacuoles are also seen in the capillary endothelia and the pericytes (Haltia *et al.*, 1975).

Pathogenesis The accumulation of glycoasparagines in the liver suggests a disturbance of the breakdown of proteoglycans.

Mannosidoses

Öckermann (1967) described a new disease that superficially resembled Hurler syndrome, but with a different enzymatic defect and nature of the stored substance. The latter could be identified as mannose in a lipid-free extract from the cerebral gray matter. The disease was therefore called mannosidosis. Apart from the usual form, based on a deficiency of α-D-mannosidase, a β-mannosidase deficiency has been described in goats.

Mannosidosis I (α-Mannosidase Deficiency)

The phenotype of affected children superficially resembles that of the Sanfilippo type of mucopolysaccharidosis (see p. 124). In contrast with the latter, the urinary excretion of mucopolysaccharides is normal. On the other hand, large amounts of mannose-containing oligosaccharides, and occasionally also glucosamines, are demonstrable in the urine.

Clinical Picture Cases generally fall into a severe infantile type or a milder juvenile or adult type. The disease manifests itself in the infantile type at the age of 1–3 years with psychomotor retardation, particularly with a delay of speech development. Upon examination one is struck by the coarseness of facial features, which increases with age and comes to resemble that of Hurler syndrome. Audiometry reveals a combined hearing defect. Cataracts have been mentioned occasionally. Other features include hepatomegaly, hernia, and, less commonly, macrocephaly, partial cranial synostoses, gingival hypertrophy, and recurrent respiratory infection. X-rays reveal slight to moderate skeletal abnormalities reminiscent of dysostosis multiplex (Spranger *et al.*, 1976). Some patients die before the age of 5.

The juvenile type shows the symptoms to a lesser extent and the patients acquire some speech and may benefit from special schooling. The condition is barely progressive. Growth and joint function remain normal, and prolonged survival is common, with the oldest patients reaching the age of 30 or more.

The α-mannosidase can be estimated in cultured amniotic cells (Petushkova *et al.*, 1987). The defect in enzyme activity is measurable in the serum at pH 4. Mannosidosis is inherited as an autosomal-recessive trait. Heterozygotes show a moderate reduction in enzyme activity.

Pathology *Light microscopy.* The hepatocytes and Kupffer's cells contain fine vacuoles, the contents of which cannot be stained with H&E, PAS, or alcian blue. Large storage cells, coarsely vacuolated and speckled with abnormal granules, are found in the bone marrow. The cytoplasm of lymphocytes is coarsely vacuolated. α–Mannosidase activity is absent in leukocytes and fibroblasts.

Electron microscopy. The vacuoles are membrane bound. Their contents consist of both electron-lucent and electron-dense material. Loosely arranged, reticular, and granular material is often associated with one or more spherical electron-dense structures, usually situated just inside the enveloping membrane. The vacuoles in the hepatocytes range in size from 1.5 to 9 μm; those in the Kupffer's cells, from 0.3 μm to a few microns. The contents of both cell types are identical (Autio *et al.*, 1973). Similar inclusions were also found in the duodenal mucosa, conjunctiva, and gingiva.

Neuropathology *Gross appearances.* There are few abnormalities in the brain other than some increase in weight. The medulla oblongata is also expanded, while the cerebellum, particularly the vermis, is atrophic. The consistency of the white matter is generally firm, and the ventricular system is dilated.

Light microscopy. The striking feature is ballooning of the cytoplasm of all neurons in the cerebral cortex, brain stem, and spinal cord. There is a diffuse loss of neurons in the cerebral and cerebellar cortices accompanied by gliosis (Öckermann, 1973). In the basal ganglia the large neurons are severely affected, as opposed to the small ones (Sung *et al.*, 1977). The cerebellar and retinal neurons are free from storage, which is present in neurons of both the brain stem and the autonomic nervous system. With conventional staining methods, including PAS and fat stains, the vacuoles remain un-

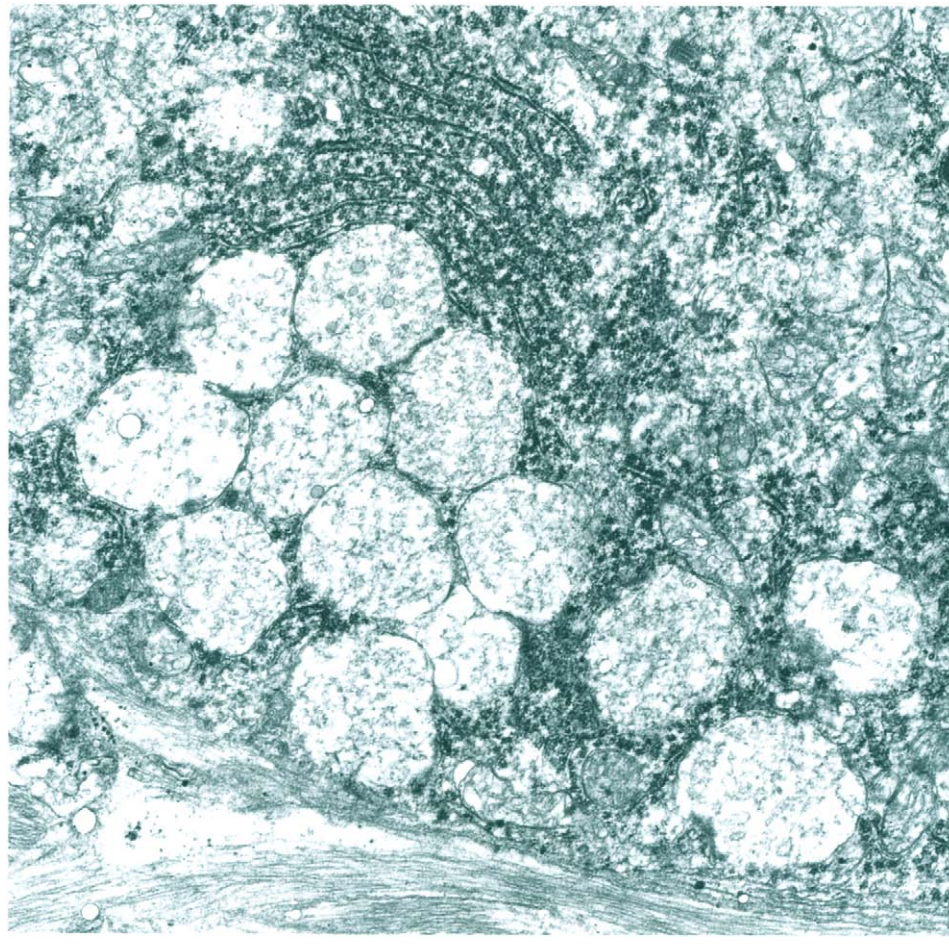


Fig. 22 Mannosidosis. Intracytoplasmic vacuoles in neurons of the inferior olive, ×17,000. (Reproduced from Sung *et al.*, 1977.)

stained and appear empty. In unfixed tissue part of the stored material can be visualized by Kjellmann modification of the PAS technique.

Electron microscopy. In the cerebral cortex, hippocampus, and inferior olives electron-lucent vacuoles are present both in neurons (Fig. 22) and in astrocytes. In the white matter only astrocytes contain vacuoles (Fig. 23), while oligodendrocytes are unaffected. In the neurons the vacuoles reach a size of up to 2 μm. They contain a finely reticular material and occasionally lipid droplets (Sung *et al.*, 1977). In the cerebellum vacuoles are present only in granule cells. The anterior horn cells in the spinal cord are particularly rich in vacuoles, which may contain circumscribed stacks of fine fibrils (Fig. 24). The neurons of the spinal and autonomic ganglia show the same structure.

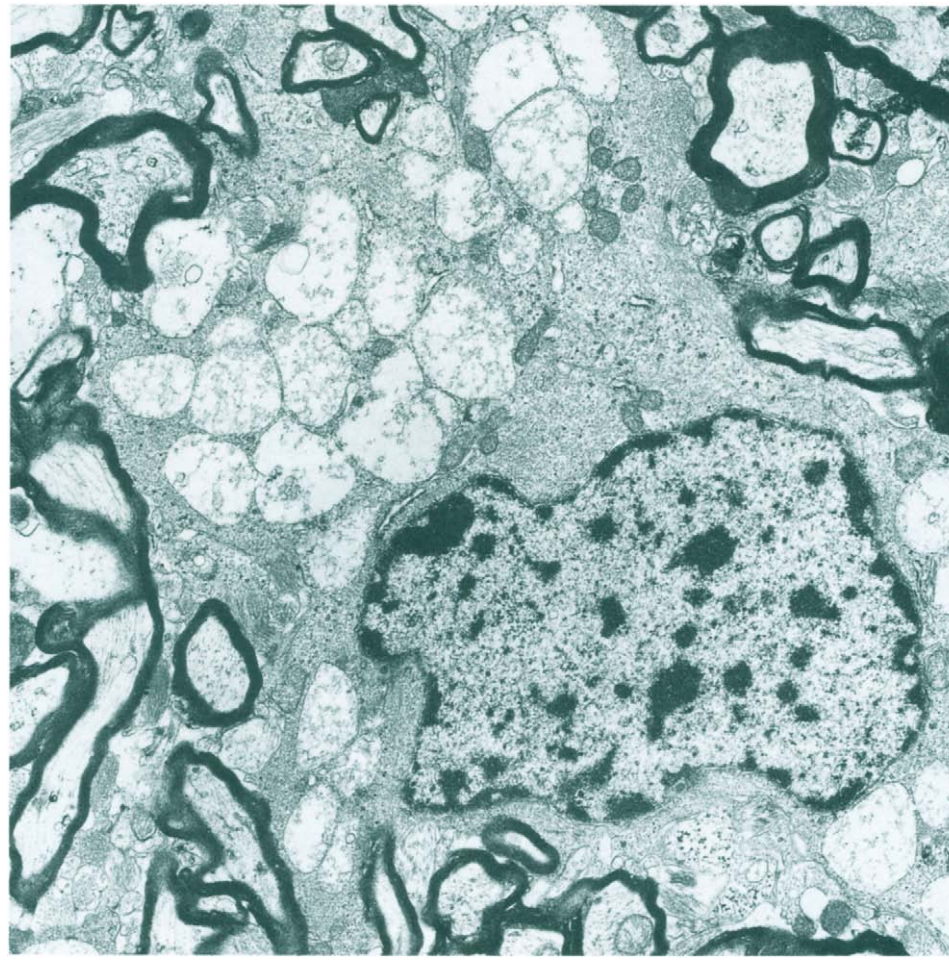


Fig. 23 Same case shown in Fig. 22. An astrocyte in the cerebral white matter with electron-lucent vacuoles, ×12,000.

Pathogenesis The degradation of the carbohydrate moiety of glycoproteins proceeds in a stepwise fashion through the action of exoglycosidases, possibly also with the support of endoglycosidases. If the carbohydrate chain contains mannose, α-D-mannosidase is indispensable for its breakdown. In the absence of activity of this enzyme, oligosaccharides accumulate in the lysosomes, principally mannose and N-acetylglucosamine. The degradation of the peptide moiety of the glycoprotein is unimpaired. The large quantities of mannose in the urine, compared with its low concentration in the serum, point to a strong clearance activity for mannose in the renal tubules (Lott and Daniel, 1981). This explains the relatively low levels of mannose in the brains of patients with mannosidosis compared with the large amounts of fucose in the brains of those with fucosidosis (see p. 65) as well as the stationary course of the disease and its relatively good prognosis.

α-Mannosidosis in Animals A disease entity similar to that in humans has been observed in cattle (Healy *et al.*, 1981). Vacuolar inclusions are found in neurons,

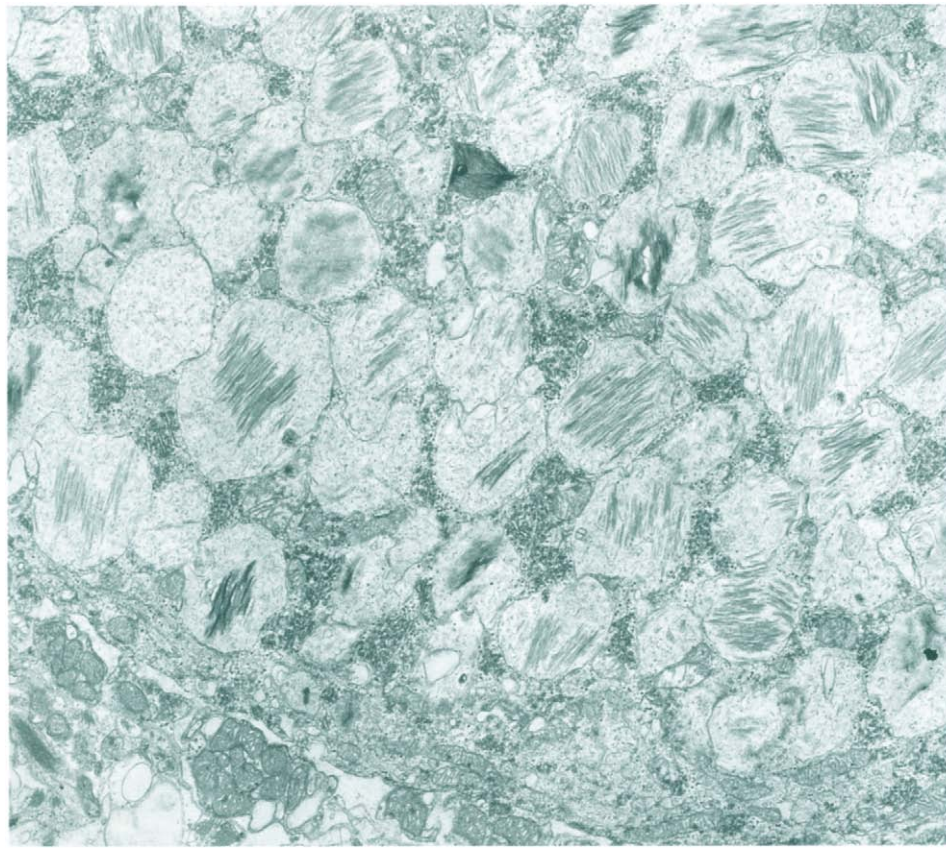


Fig. 24 Same case shown in Fig. 22. An anterior horn cell of the lumbar cord, with vacuoles containing stacks of fine fibrils, ×8,400.

macrophages, reticuloendothelial cells, and epithelial cells of the exocrine glands (Jolly and Thomson, 1978). In cats with α-mannosidase deficiency, cytoplasmic vacuoles in the neurons are present (Vandervelde *et al.*, 1982) as well as numerous axonal swellings. In the pyramidal cells of the cerebral cortex, meganeurites, secondary neurites, and various disorders of the dendritic tree are conspicuous.

Experimentally, mannosidosis can be produced in mice by feeding them beans of the *Swainsonia genus* (Huxtable *et al.*, 1982). The activity of α-mannosidase is apparently zinc dependent. A deficiency of zinc leads to a depression of α-mannosidase activity in rats.

Mannosidosis II (β-Mannosidase Deficiency)

Mannosidosis II was first described only in goats that showed neurological symptoms at birth, as well as abnormalities of the facial bones and joint contractures (Hartley and Blakemore, 1973). The condition has also been diagnosed in cattle (Patterson *et al.*, 1991). Meanwhile, human β-mannosidosis has been described as an inherited lysosomal storage disorder in few families (Kleijer *et al.*, 1990, Levade *et al.*, 1994).

Almost all cells, with the exception of muscle cells, show vacuolation of the cytoplasm.

Gross appearances. The brain shows appreciable hydrocephalus. Light microscopy reveals hypomyelinization of the white matter that demonstrates regional variation (Lovell *et al.*, 1994) and granular eosinophilic, PAS-positive deposits in axonal spheroids. Both fine and coarse vacuoles are found in the neurons, oligodendroglia, and macrophages, ranging in diameter from 0.2 to 0.8 μm. Their contents are PAS negative in both paraffin and frozen sections.

Electron microscopy. In electron microscopy the vacuoles appear membrane bound and contain electron-lucent or floccular material. Occasional irregularly distributed membranes are also encountered, particularly in the pericytes (Jones *et al.*, 1983). In peripheral nerves, apart from vacuoles in Schwann cells, there are also accumulations of electron-dense inclusions in the nerve endings.

Pathogenesis Considerable amounts of oligosaccharides with high mannose content were found in both the brain and the kidneys. These were also excreted in the urine. Reduced activity of β-mannosidase could be demonstrated in sick goats. In humans this enzyme deficiency was found in three patients between ages 19 and 44 years by Wenger *et al.* (1986) and Cooper *et al.* (1986).

Fucosidosis

Durand (1966) described a new form of oligosaccharide storage disease. The high content of fucose, discovered in all tissues, led to adoption of the term *fucosidosis* (Durand *et al.* 1968).

Clinical Picture The severe form (type I) of fucosidosis is a rapidly progressive neurodegenerative process, starting in infancy and progressing to complete psychomotor dis-

integration within a few years. Symptoms appear between the ages of 4 to 12 months and consist of psychomotor retardation, hypotonia, and recurrent respiratory infections. The further course of the illness leads to developmental arrest, with a loss of already acquired skills. During the second year a spastic quadriplegia supervenes, associated with a coarse tremor. The facial features undergo gradual coarsening and resemble those seen in mucopolysaccharidosis. The children die at the age of 5 or 6 years in a state of decerebrate rigidity complicated by intercurrent infections. Some patients run a more acute course and die before the age of 2 years (Larbrisseau *et al.*, 1980). Patients with the milder form (type II) present with some psychomotor retardation during the second year of life, or occasionally earlier (Lamarche and Lemieux, 1986). A later onset, at the age of 7, was reported in one case (Troost *et al.*, 1977a). These children do not acquire speech and are clumsy. After a gradual loss of acquired skills, they develop a progressive dementia and spastic quadriparesis at about the age of 6 years. Seizures or myoclonic jerks may appear.

Small stature, kyphoscoliosis, and a heavy coarse facies are typical features. Ophthalmoscopy sometimes reveals moniliform dilatation of the retinal veins. A characteristic feature of fucosidosis type II is skin lesions, consisting of pinhead-sized reddish papules of the character of angiokeratoma diffusum (Patel *et al.*, 1972; Soshama and Graham Brown, 1994). The course of the disease is relatively slow, and patients survive well into the third decade (Svik *et al.*, 1981).

The excretion of fucose or fucose-containing oligosaccharides is increased. The diagnosis can be made on the basis of the clinical picture and confirmed by estimation of α-L-fucosidase in leukocytes, cultured fibroblasts, or other tissues. This enzyme can also be absent in saliva. The defect in α-fucosidase activity shows heterogeneity at the molecular level (Guazzi *et al.*, 1989).

Pathology *Light microscopy.* Evidence of intracytoplasmic storage can be formed in most tissues, particularly in hepatocytes, Kupffer's cells, vascular endothelia, epithelia of the sweat glands, and cells of the bone marrow. The cytoplasm of liver cells appears blown up and stains weakly with PAS. Myocardial cells and the epithelial cells of renal glomeruli are also expanded with storage material.

Electron microscopy. Large clear vacuoles, up to 10 μm in diameter, are present in the cytoplasm of the liver cells. They contain sparse granular material and occasionally concentric lamellar structures (Troost *et al.*, 1977; Larbrisseau *et al.*, 1980). Kupffer's cells contain similar vesicles, which do not exceed 2 μm in diameter.

Neuropathology *Light microscopy.* A loss of neurons is seen in the cerebral cortex, neostriatum, thalamus, and hypothalamus. The cerebellum shows a loss of Purkinje cells (Durand *et al.*, 1969). In the remaining neurons the cytoplasm is ballooned and the nucleus is displaced to the periphery. The cytoplasm appears optically empty (Fig. 25A and B), with the occasional presence of fine, weakly basophilic, PAS-positive granules. Oligodendrocytes and endothelial cells are also involved in the storage (Troost *et al.*, 1977). There is a considerable loss of myelin in the white matter, with status spongiosus and dense gliosis with Rosenthal fibers (Larbrisseau *et al.*, 1980). In peripheral nerves

granular inclusions are present in Schwann cells and occasionally in the endoneurium.

Electron microscopy. Membranous cytoplasmic bodies and pleomorphic inclusions are found in the neurons, astrocytes, and vascular endothelia. Moderate demyelination is present in peripheral nerves. Schwann cells in the gut, as well as axons and Schwann cells in the cutaneous nerves (Fig. 26), contain clear vacuoles and inclusions of a dense lamellar structure (Troost *et al.*, 1977; Lamarche and Lemieux, 1986).

Pathogenesis Van Hoof and Hers (1968) have established the total absence of α-L-fucosidase in their patients. Fucose is an essential component of glycosphingolipids and glycoproteins and may also appear bound to keratan sulfate. A lack of α-L-fucosidase blocks the breakdown of these substances. Accordingly, increased quantities of fucose-containing oligosaccharides, fucopeptides, and glycosphingolipids accumulate in tissues and body fluids. The clinical symptoms are due to these accumulations. It is not clear what constitutes the difference between type I and type II. Residual activity of one or

Fig. 25 Fucosidosis. Severe vacuolation of the neurons and the glia. Luxol fast blue stain; (A) ×35 and (B) ×210. (Courtesy of J. B. Lamarche, Sherbrook, Quebec, Canada.)

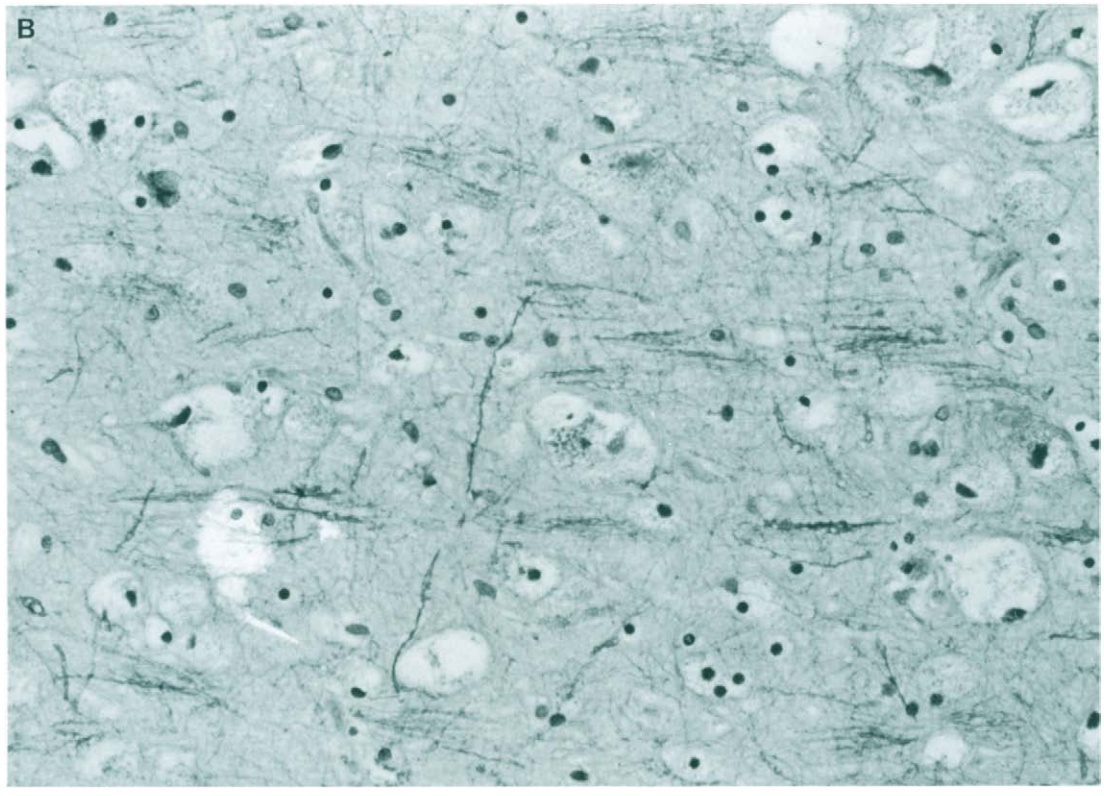


Fig. 25 Continued.

more isoenzymes, at least against naturally occurring substances, may be open to discussion. These are at least three isoenzymes of α-L-fucosidase, which can appear in three different combinations. These patterns are apparently determined by mutations of two alleles (*fuc1*, *fuc2*, and *fuc1,2*). By incorporation of neuraminic acid into the isoenzymes, further proteins are formed with fucosidase activity. One assumes that there are different genes and loci with variable expressivity for these isoenzymes.

Different types of single-base changes have been found, resulting in either a nonsense or frameshift mutation (Soo *et al.*, 1993; Williamson *et al.*, 1993). In addition, a large deletion at the 3′ end of the gene may cause the disease (Williamson *et al.*, 1993). Different types of point mutations may be present in one family. Only heterozygosity for the described genetic changes causes phenotypic disease (Yang *et al.*, 1993).

Sialidosis (Sialooligosaccharidosis with α-Neuraminidase Deficiency; Mucolipidosis I; Myoclonic Syndrome with Cherry-Red Spot)

Spranger and Wiedemann (1979) defined mucolipidosis I clinically. In all cases excretion of sialooligosaccharides in the urine could be demonstrated, in the absence of

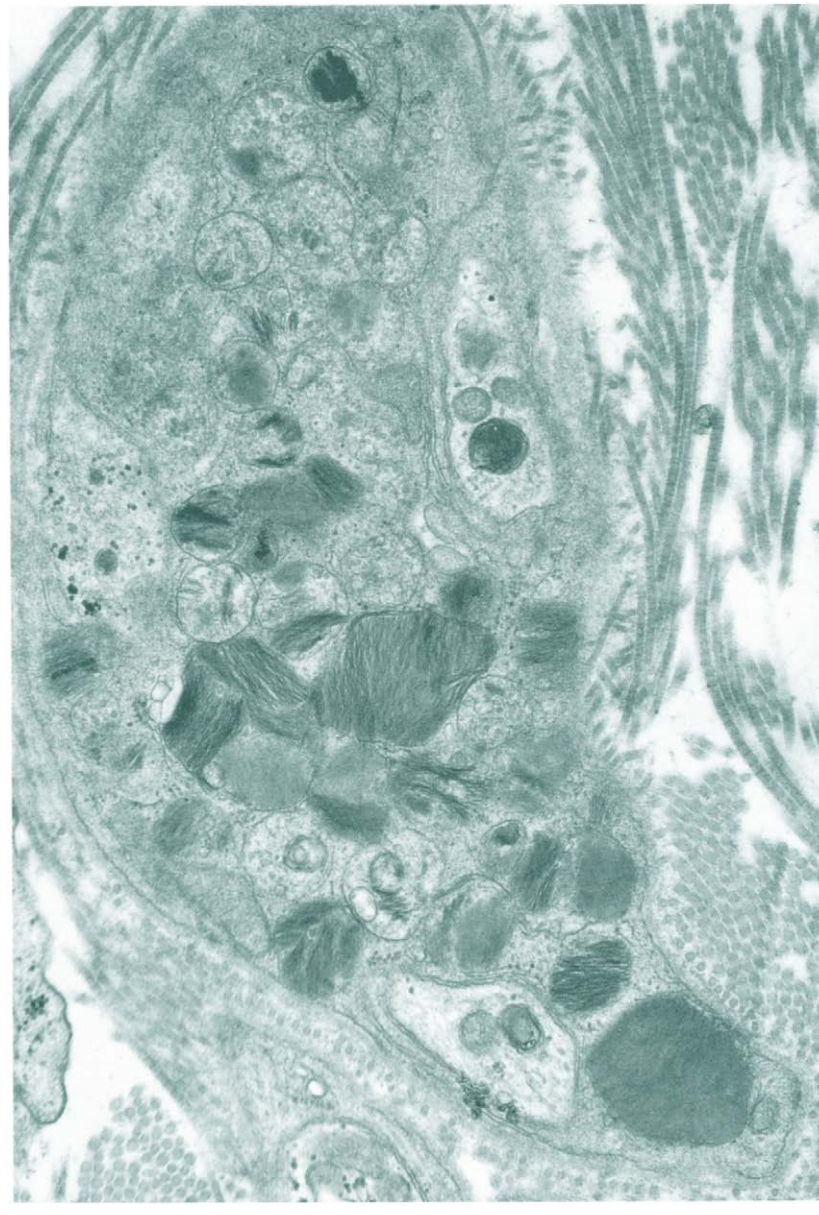


Fig. 26 Same case shown in Fig. 25. A Schwann cell of the cutaneous nerve with multivesicular bodies and lamellar inclusions, ×15,250.

excretion of mucopolysaccharides. Durand *et al.* (1977) reported on two siblings with cherry-red spot and punctate lens opacities without any neurological signs due to a defect of sialidase and coined the term *sialidosis*. We include in this group all diseases characterized by the excretion or storage of sialooligosaccharides and by the absence of neuraminidase. Cases with similar enzyme deficiency and associated with kidney pathology are grouped under *nephrosialidosis*.

Genetically, a group can be differentiated with both β-galactosidase and neuraminidase deficiencies (Palmeri *et al.*, 1986). The patients present with a variable phenotypic expression but have been grouped together as having galactosialidosis on the strength of their enzymatic pathology and biochemical abnormalities.

Inclusion among the sialidoses depends on the demonstration of sialooligosaccharide storage or excretion and the proof of appropriate enzyme deficiency. Therefore, cases that probably belong to this group, such as those described as adult forms of amaurotic idiocy, as Niemann–Pick disease, or as juvenile lipidosis, and finally those diagnosed as "mucolipidosis with β-galactosidase deficiency" cannot be included with any degree of certainty. The hitherto accepted cases fall into two groups.

Type I (Normosomatic Group, No Dysmorphic Features)

Clinical Picture This group includes patients with cherry-red spots and myoclonus without further neurological symptoms and without dementia (Rapin *et al.*, 1978). Sensorimotor peripheral neuropathy was rarely observed (Steinmann *et al.*, 1980). The symptoms appear, as a rule, toward the end of the second decade or the beginning of the third. The cherry-red spot may be obvious earlier, even in the first decade, and may fade by the time of onset of myoclonus. The disappearance of the cherry-red spot is not associated with loss of vision, as it is in the GM_1 gangliosidosis. The visual defect can be accentuated if lens or corneal opacity is present. These ocular signs may be associated with ataxia, myoclonus, and generalized seizures at a second stage (Federico *et al.*, 1991). The course of the disease is slow and patients survive to the age of 30 years and beyond.

Pathology A wide range of lesions were recorded at autopsy, which reflects, in part, the incompleteness of the clinical examination. The liver cells, and in some patients also cells of the bone marrow, showed vacuolation of the cytoplasm. The contents of the vacuoles stain with PAS and Sudan black (Durand *et al.*, 1977).

On electron microscopy the liver cells contain abundant lipofuscin as well as vacuolar inclusions with clear homogeneous contents (Durand *et al.*, 1977). The Kupffer's cells are grossly expanded, with vacuoles up to 5 μm in diameter, and resemble the "clear cells" of the mucopolysaccharidoses (Rapin *et al.*, 1978).

Neuropathology *Light microscopy.* An atrophic cerebral cortex retains its normal lamination. Endo *et al.* (1977) found lipid-laden neurons in the cerebrum, in the cerebellum, and in the motor nuclei of the brain stem and the spinal cord in a 22-year-old patient after illness of 7 years' duration.

The neurons of the sympathetic ganglia can show considerable swelling and can contain globular inclusions (Rapin *et al.*, 1978). These stain positively with Sudan black and Sudan IV, and weakly or not at all with Diezel's ganglioside stain or glycolipid stains, but re-

act positively with the mercuric nitrate phospholipid stain of Okamoto. They show a slight metachromasia with toluidine blue and alcian blue, and give a positive reaction with Bial's reagent for neuraminic acid and with PAS. In peripheral nerves Steinmann *et al.* (1980) found vacuolation of Schwann cells in both myelinated and unmyelinated fibers.

Electron microscopy. An excessive amount of lipofuscin is found in the neurons of the cerebral cortex as well as abundant lamellar cytoplasmic bodies. Moreover, Rapin *et al.*, (1978) found in all neurons inclusions of granular material with transitions to the lamellar structures. Glial cells are not involved in the storage, in contrast with the mesenchymal microglia, which was laden with inclusions. Lamellar cytoplasmic bodies and, in places, zebra bodies were present in the neurons of the sympathetic ganglia. The Schwann cells contain membrane-bound inclusions with fine granular material and curved as well as straight membrane complexes (Steinmann *et al.*, 1980).

Type II (Dysmorphic Group)

Clinical Picture Depending on the age of the patient at onset, it is possible to distinguish infantile and juvenile or adult forms. In the infantile group symptoms are present from birth (Beck *et al.*, 1984). In the juvenile form symptoms appear later, in some cases as late as 18 years (Kobayashi *et al.*, 1979). More than two thirds of the patients were Japanese. Aside from the cherry-red spot and myoclonic epilepsy, the symptoms included cerebellar ataxia and a variable degree of chondrodystrophy and dementia (Tsuji *et al.*, 1982). Pyramidal symptoms may be present. Characteristic changes have been observed on the EEG (Doose *et al.*, 1978). In a few cases angiokeratomas were present (Miyatake *et al.*, 1979).

Pathology *Light microscopy.* The heart valves appear slightly thickened. In the vertebral column the intervertebral disks are thin, while the lateral bony trabeculae are thickened. In the heart valves, the skin, and occasionally in the cornea (Cibis *et al.*, 1983) fibroblasts contain PAS-positive granules, which stain metachromatically with toluidine blue. Foamy macrophages, which stain partially with Sudan black, are present in the lymph nodes, bone marrow, liver, and spleen. Inclusions resembling the clear vacuoles of mucopolysaccharidosis may be found in the blood lymphocytes and the cells of the bone marrow (Kobayashi *et al.*, 1979).

Electron microscopy. Fibroblasts and macrophages contain numerous inclusions of a loosely arranged granulofibrillar material. Beck *et al.* (1984) found large inclusions in the liver cells surrounded by a thick membrane and containing granulofibrillary material, which they likened to Lafora's bodies.

Neuropathology *Gross appearances.* The leptomeninges are slightly thickened, and the cerebrum and the cerebellum are moderately atrophic.

Light microscopy. The striking feature is an almost ubiquitous ballooning of the neuronal perikaryon. The most extreme swelling is found in the motor neurons of the brain stem and the anterior horns of the spinal cord. The cells of the cerebral cortex and the Purkinje cells of the cerebellum are less severely affected. Amano *et al.* (1983) found a

severe loss of neurons in the cerebral cortex, particularly in the calcarine fissure, in a patient with adult onset of the disease. The neurons of the substantia nigra, the red nucleus, and the granular layer of the cerebellum are free of stored material. Astrocytes and microglia are involved in storage in the same areas as the neurons. In these areas a mild gliosis corresponds to the degree of neuronal loss. Storage is also prominent in neurons of the intestinal plexuses (Itoyama *et al.*, 1978).

Electron microscopy. Numerous pleomorphic inclusions 1–2 μm in diameter as well as lamellar and zebra bodies are seen in the cytoplasm of neurons in the CNS. Similar inclusions (Fig. 27) are frequently present in the neurons of the intestinal plexuses (Itoyama *et al.*, 1978) and of the sympathetic ganglia (Miyatake *et al.*, 1979). In peripheral nerves clear vacuoles are frequent in Schwann cells (Fig. 28A) and pleomorphic inclusions are present in unmyelinated axons (Fig. 28B).

Pathogenesis Cantz *et al.* (1977) and Spranger *et al.* (1977) found a deficiency of α-D-*N*-acetylneuraminidase in cultured fibroblasts of a patient with mucolipidosis I type I. In contrast with mucolipidoses II and III, the activity of other hydrolases was normal. O'Brien (1977) found a deficiency of neuraminidase in two patients of type II and assumed that the disease could be attributed to a lack of activity of lysosomal neuraminidase. This was supported by the finding that the parents of two patients with neuraminidase and β-galactosidase deficiencies showed reduced activity of the neuraminidase, but not of β-galactosidase. Apart from an excess of sialooligosaccharides and of sialoglycoproteins in the tissues, there may also be an increase in the amount of gangliosides.

The differences in the manifestations of the disease and of the residual activity in various tissues (Suzuki and Fukuoda, 1979) can be ascribed to the availability of isoenzymes of neuraminidase (Tsuji *et al.*, 1982).

In cases of type II—insofar as they have been examined—no deficiency of β-galactosidase, or only a minimal one, has been established. In group I there are cases with pronounced or partial deficiency of β-galactosidase (Miyatake *et al.*, 1979; Tsuji *et al.*, 1982). This may be caused by insufficient protection of the endogenous and exogenous β-galactosidases from lysosomal degradation (Van Diggelen *et al.*, 1982).

The cherry-red spot as an expression of storage in the retinal neurons—mainly of sphingolipids—appears in diseases that lead rapidly to dementia. This is the case in neuraminidase deficiency only in type I. The differences in neurological symptomatology may be ascribed to the difference in severity of the storage phenomenon in the two types. In type II neuronal swelling is absent or minimal, and the storage can only be demonstrated by electron microscopy, while in type I neuronal swelling is gross. The autopsy findings also suggest the involvement of a greater number of neurons. For a discussion of myoclonic epilepsy, see the section on Lafora's disease (p. 102).

Nephrosialidosis

The term nephrosialidosis was coined by Maroteaux *et al.* (1978) to designate an oligosaccharidosis associated with glomerular nephropathy.

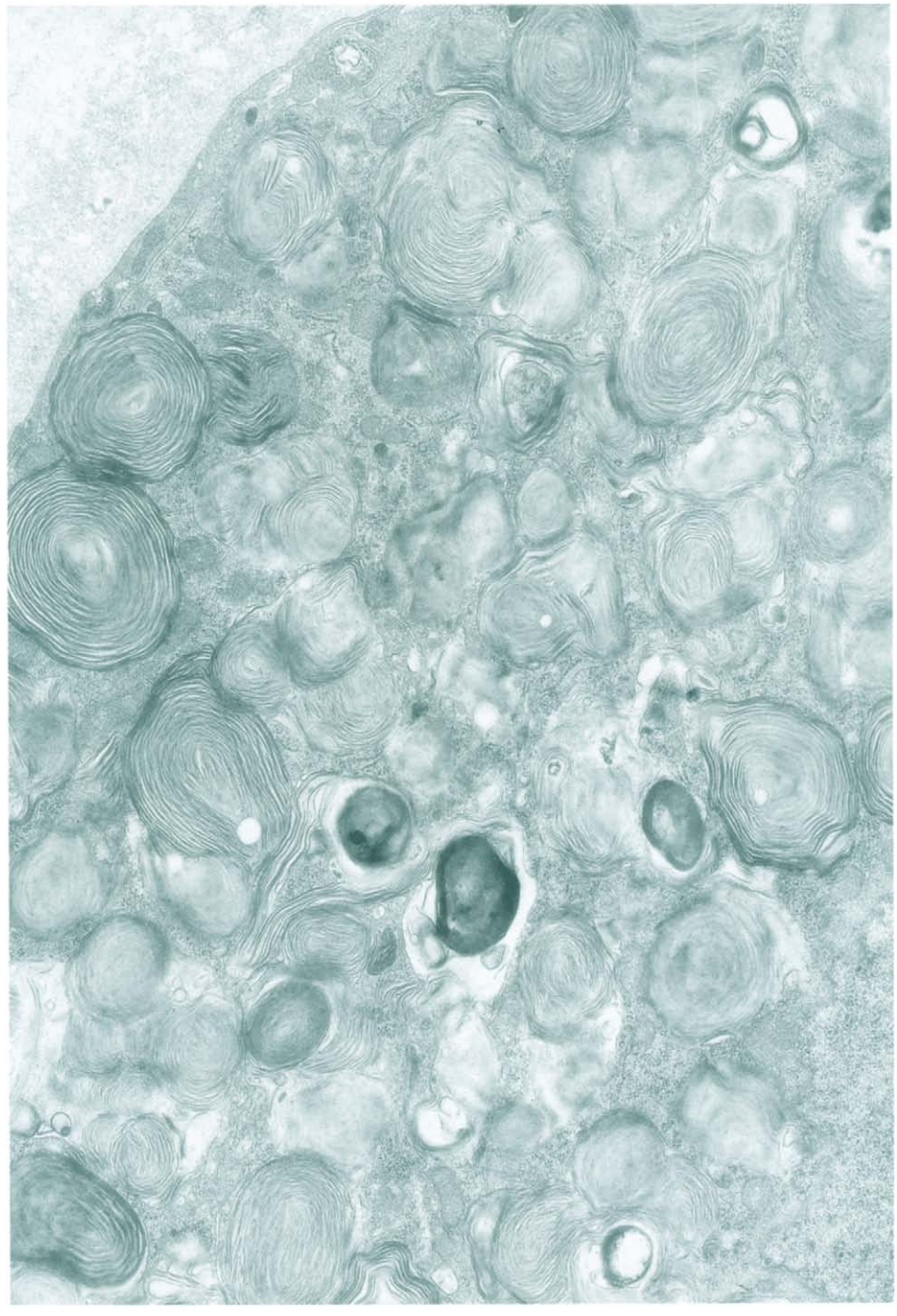


Fig. 27 Juvenile form of neuraminidase (sialidase) deficiency. Concentric and parallel laminar inclusions in the cytoplasm of a neuron in the myenteric plexus, ×14,000. (Reproduced from Miyatake *et al.*, 1979.)

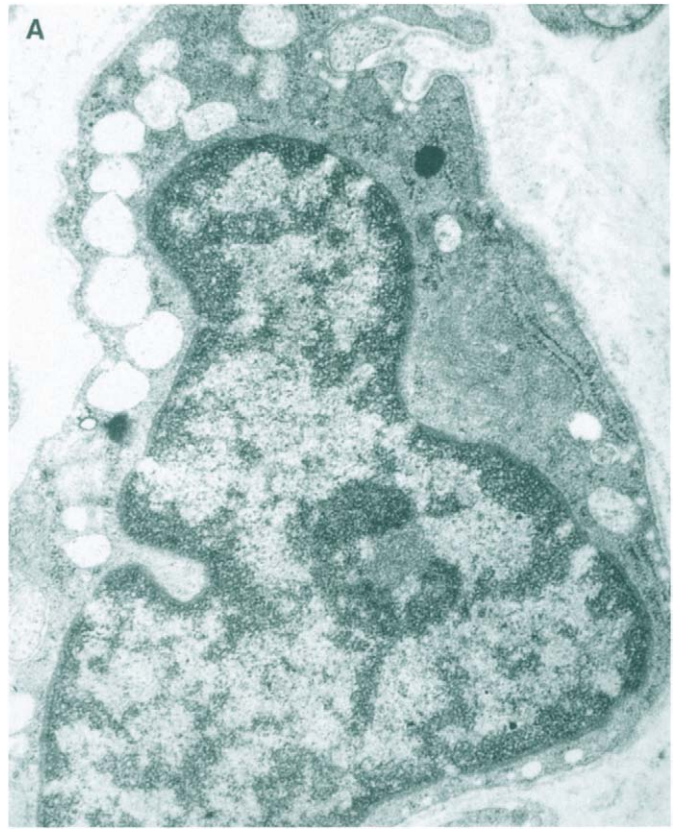


Fig. 28 Sialooligosaccharidosis in neuraminidase (sialidase) deficiency in the skin. (a) Multiple vacuoles in a Schwann cell, ×22,000. (b) Dense amorphous inclusions in an unmyelinated nerve fiber, ×60,000. (Reproduced from Cervós-Navarro and Goebel, 1989.)

Clinical Picture Hepatosplenomegaly, coarse face, dysostosis multiplex, and psychomotor retardation become apparent soon after birth or within the first few months. In the patient of Aylsworth *et al.* (1980), ascites was present at birth; in those of Maroteaux et al. (1978), it developed after some years. Large quantities of sialooligosaccharides are present in the serum. Clinical evidence of renal failure was not detected in one patient with a severely damaged kidney (Okada *et al.*, 1983). As the disease progresses a nephrotic syndrome with proteinuria supervenes. These children die between the ages of 2 and 8 years.

Pathology Lymphocytes, hepatocytes, glomerular and tubular cells of the kidneys (Roth *et al.*, 1988), and Kupffer's cells show pronounced vacuolation. Numerous foam cells are found in the bone marrow.

On electron microscopy the vacuoles are seen to contain fine reticulogranular material,

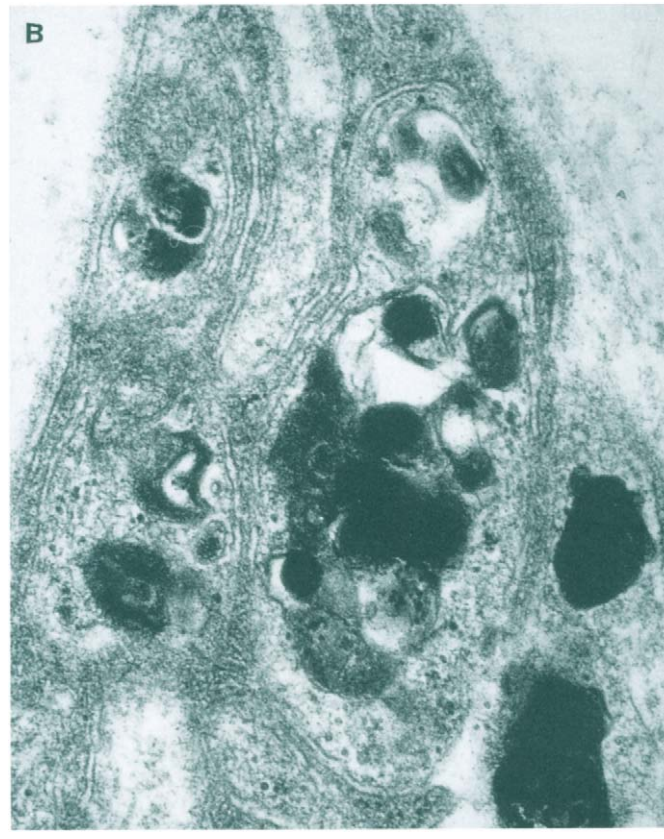


Fig. 28 Continued.

which may also be found lying free in the cytoplasm, particularly in hepatocytes (Aylsworth *et al.*, 1980). Similar changes are seen in the cultured fibroblasts.

Neuropathology Toyooka *et al.* (1993) found severe neuronal storage in the lower motor neurons of the brain stem and the spinal anterior horn cells, as well as neurons in the basal nucleus of Meynert. Sympathetic ganglia were severely affected. These investigators found little or no neuronal storage in the basal ganglia, cerebral cortex, or cerebellum, nor demyelination. Lectin histochemistry was positive for wheat germ agglutinin, *Ricinus communis* agglutinin 1, and peanut agglutinin in distended neurons. Electron microscopic examination showed fine, wavy, multilamellar structures in the spinal anterior horn cells or zebra body-like structures in the neurons of Meynert's nucleus basalis.

Pathogenesis The disease is caused by neuraminidase deficiency. Maroteaux *et al.* (1978) found only lack of activity of the α-2,6-neuraminidase, while Aylsworth *et al.* (1980) found the activity of both the α-2,6 and α-2,3-neuraminidases reduced to 5% of the normal values.

Galactosialidosis (Neuraminidase/β-Galactosidase Deficiency)

Galactosialidosis is a lysosomal storage disease in which inactivity was demonstrated both for β-galactosidase and for neuraminidase. Apart from a juvenile form (Loonen *et al.*, 1984) and a late infantile form (Andria *et al.*, 1981), some patients develop the disease in early infancy, at birth, or even prenatally (Sewell and Pontz, 1988).

Clinical Picture Myoclonus, cerebellar ataxia, epilepsy, visual disturbance, macular cherry-red spots, mental retardation, and gargoyle-like facial features and skeletal dysplasia are common symptoms. A patient with Kayser–Fleischer ring was reported by Mongalgi *et al.* (1992). Urinary excretion of sialololigosaccharides is elevated and the diagnosis can be confirmed on cultured fibroblasts which, in this instance, appear to be more reliable than leukocytes (Okada *et al.*, 1983; Loonen *et al.*, 1984). The infantile form occurs in all races. All adult patients have angiokeratomas, and most reports relate to Japanese patients (Kobayashi *et al.*, 1979).

Pathology All forms of galactosialidosis have vacuolated lymphocytes in fibroblasts, Schwann cells, endothelial cells, hepatocytes, histiocytes, and renal tubular and glomerular cells. All forms have vacuolated lymphocytes. Usui *et al.* (1993) observed granulofibrillary content frequently and occasionally lamellar structures in the vacuoles. Lysosomal storage in the form of optically empty vacuoles is found.

Neuropathology In the severe infantile form (Yamano *et al.*, 1985) the brain is atrophic with some loss of cortical neurons. Lipofuscin accumulation was prominent, particularly in the third, fifth, and sixth cortical layers. Almost complete loss of neurons and sponginess was found in the calcarine cortex. The white matter is partly demyelinated without gliosis. Neuronal ballooning and storage can be found in the oculomotor, hypoglossal, cerebellar dentate, and lateral geniculate nuclei. The stored material stains as for the gangliosidoses and ultrastructurally resembles membranous cytoplasmic bodies.

In the case of the late infantile form, Oyanagi *et al.* (1991a) observed a severe loss of neurons in the thalamus, globus pallidus, lateral geniculate body, gracile nucleus, and Purkinje and retinal ganglion cells. Marked ballooning was seen in Betz's cells and the neurons in the basal forebrain, in the motor neurons in the cranial nerve nuclei and the spinal cord, and in the trigeminal and spinal ganglia. Electron microscopic investigation revealed a variety of intracytoplasmic and intranuclear inclusions: membranous cytoplasmic bodies; parallel, wavy–lamellar, or tortuous tubular structures; lipofuscin-like irregularly-shaped pleomorphic bodies; and cytoplasmic vacuoles with fine granules and lamellar materials (Figs. 29–31).

Pathogenesis Additional β-galactosidase deficiency in galactosialidosis did not influence the nature of the excreted material and the sialidase deficiency determined completely the defective catabolism of glycoproteins in both sialidosis and galactosialidosis (Van Pelt *et al.*, 1991).

The primary defect is the absence of a "protecting protein," which normally protects some lysosomal hydrolases from a proteolytic degradation during the stage of enzyme

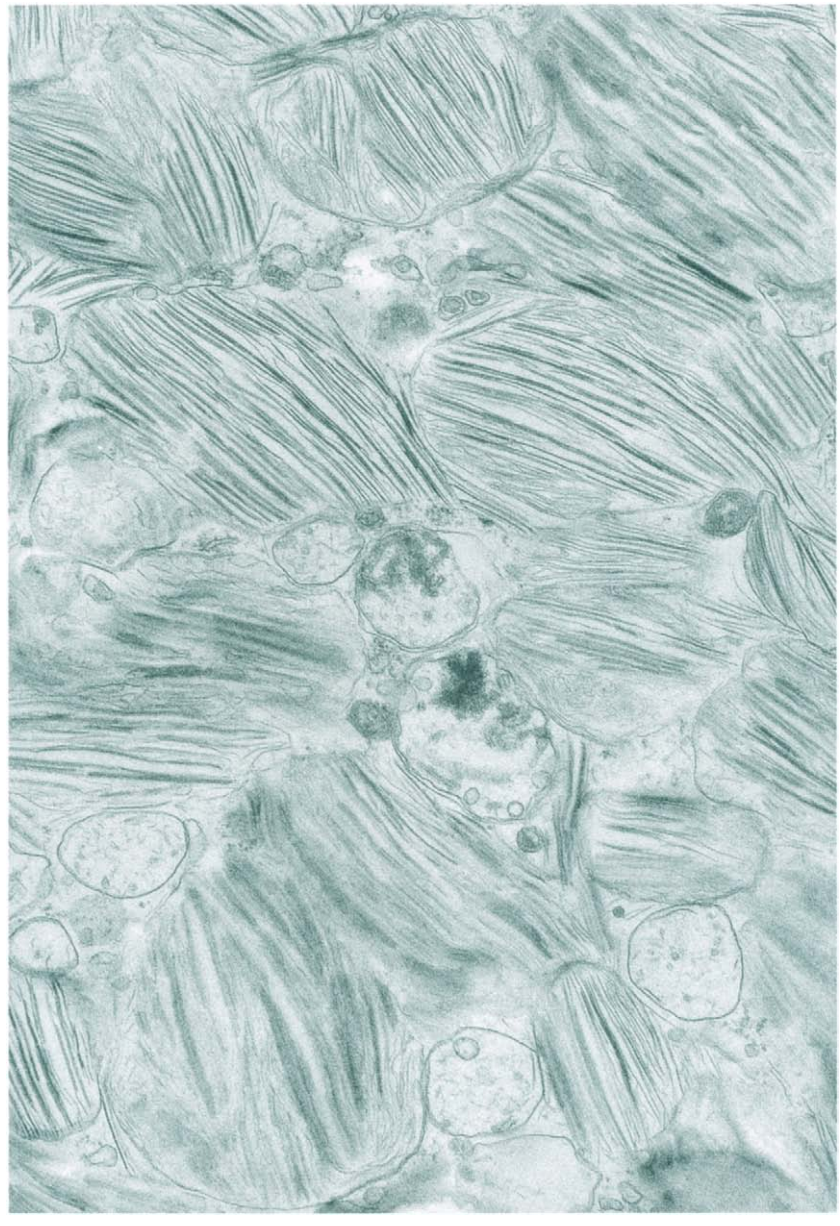


Fig. 29 Membrane-bound parallel lamellar inclusions and tiny cytoplasmic vacuoles with fine granules in an anterior horn cell. Uranyl lead stain, ×15,000. (Reproduced from Oyanagi *et al.*, 1991a.)

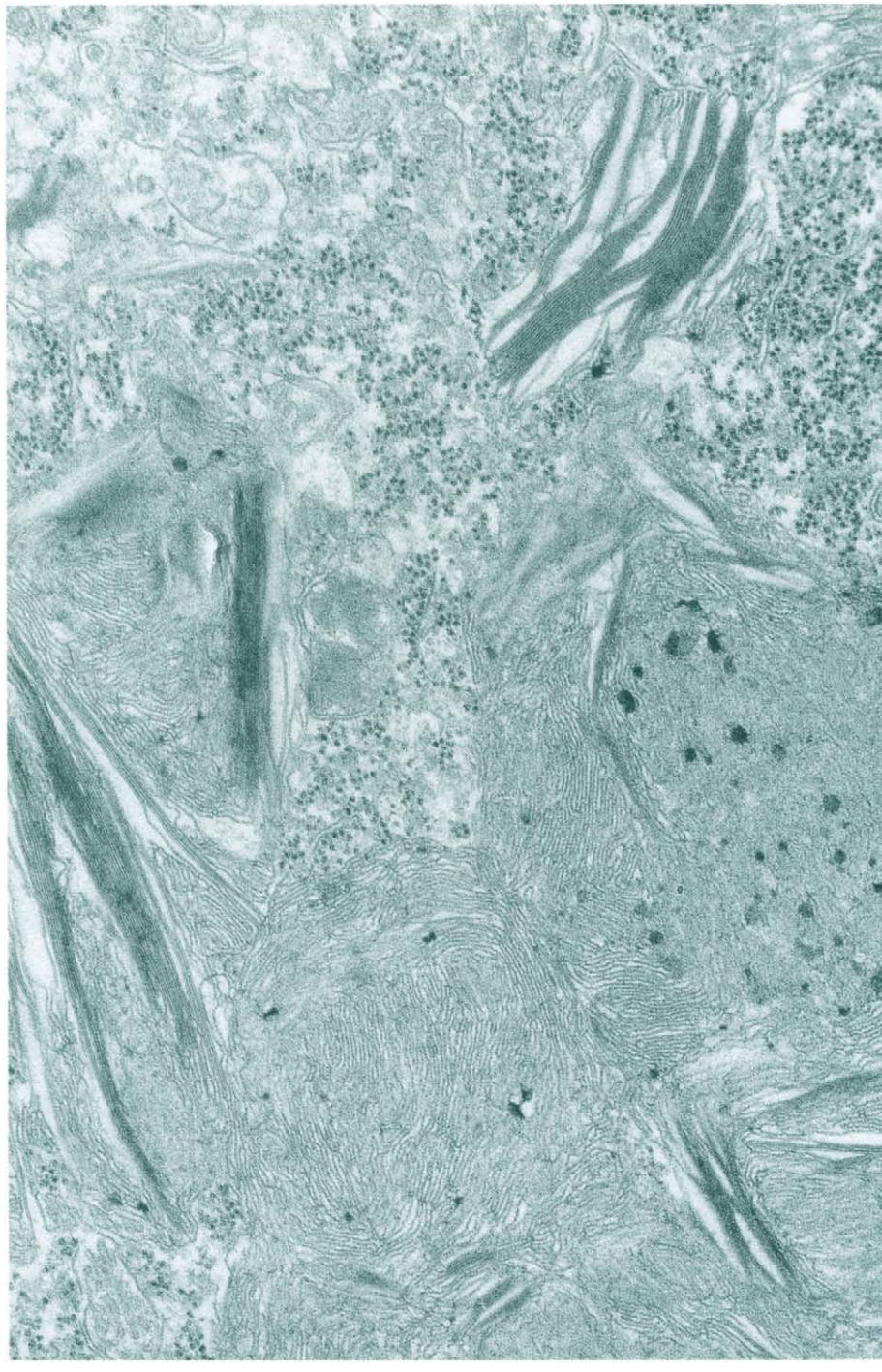


Fig. 30 A tortuous and parallel lamellar inclusion in continuity in a neuron of the dentate nucleus. Uranyl lead stain, ×40,000. (Reproduced from Oyanagi *et al.*, 1991a.)

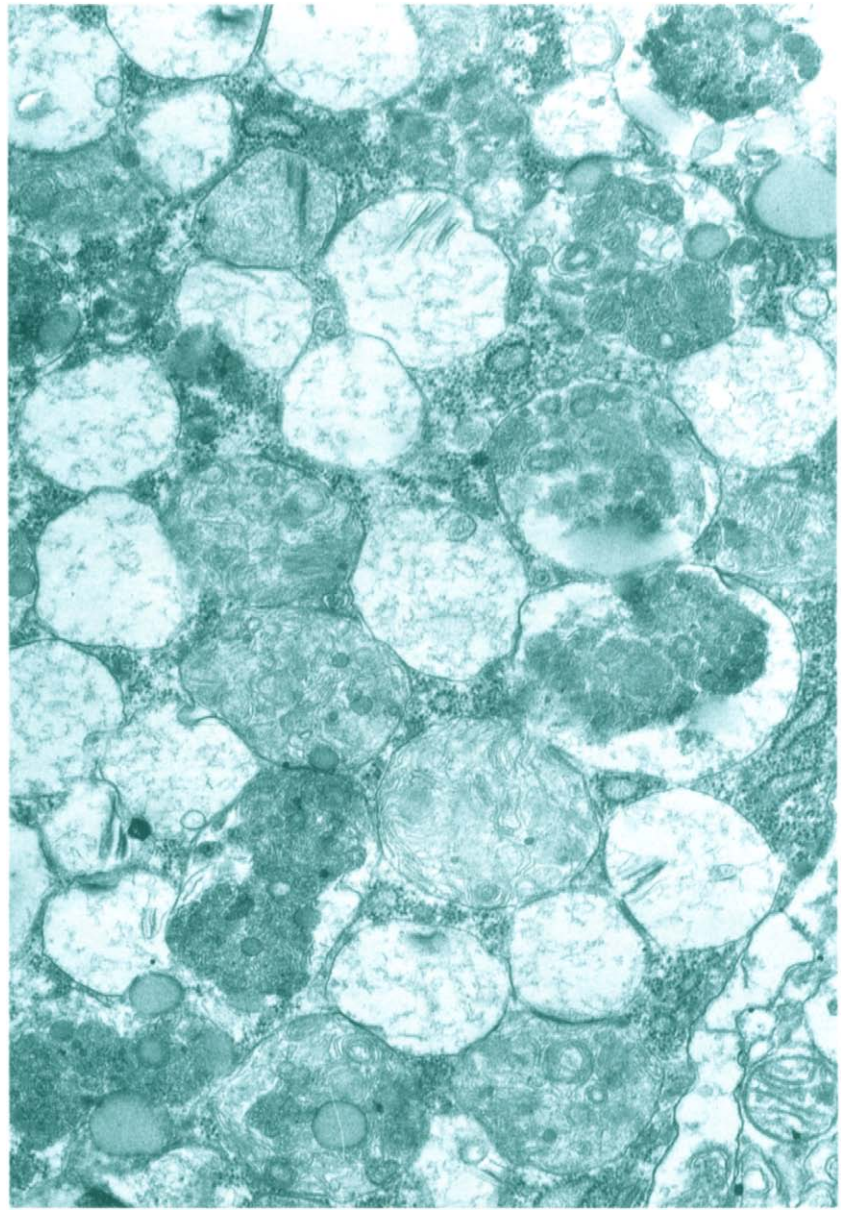


Fig. 31 A neuron of sector CA2 of the hippocampus. Mixed accumulation of cytoplasmic vacuoles (CV) with fine granules and loose lamellar material, and membrane-bound fingerprint-like lamellar pleomorphic inclusions (PI) with tiny lipid droplets. Uranyl lead stain, ×24,000. (Reproduced from Oyanagi *et al.*, 1991a.)

maturation (Verheijen *et al.*, 1985). Protective protein is considered a multifunctional protein with esterase/deamidase/carboxypeptidase activities. It is required for aggregation of β-galactosidase monomers and is essential for activation of neuraminidase (Galjaard *et al.*, 1987). Its mutation in galactosialidosis results in deficiency of these three enzyme activities (Kase *et al.*, 1990). Shimamoto *et al.* (1993) identified four different protective protein cDNA mutations in galactosialidosis patients with various phenotypic manifestations.

Carbohydrate-Deficient Glycoprotein Syndrome

Jaeken *et al.* (1980) described the first patients with carbohydrate-deficient glycoprotein (CDG) syndrome. Since then some 120 cases have come to light and the protean manifestations of this metabolic defect have been reviewed by Jaeken *et al.* (1991); Jaeken and Carchon, 1993). The organs involved include the nervous system, eyes, skeleton, subcutaneous fat, liver, kidneys, gonads, and the immune system. After the age of 15, the disease was mainly characterized by neurological symptoms consisting of nonprogressive ataxia associated with cerebellar hypoplasia, stable mental retardation, variable peripheral neuropathy, and strabismus. One third of the patients had generalized seizures, usually sporadic (Stibler *et al.*, 1994). In the CNS the hindbrain is almost invariably involved, in the form of infantile olivopontocerebellar atrophy (see p. 600).

The biochemical abnormality consists of a partial deficiency of the carbohydrate moiety of secretory and probably also membranous glycoproteins. Terminal trisaccharides, sialic acid, galactose, and *N*-acetylglucosamine are particularly affected. This results in abnormalities in serum glycoproteins, including transport proteins, enzymes, hormones, coagulation factors, and immunoglobulins. The most sensitive test is isoelectric focusing of serum transferrin, which normally consists predominantly of tetrasialotransferrin with small amounts of other sialotransferrins. In CDG syndrome a partial deficiency of sialic acid leads to an increase in asialo- and disialotransferrin with a pronounced decrease in tetra- and pentasialotransferrin, causing a cathodal shift of the isoelectric point.

Other biochemical abnormalities not directly related to glycoprotein deficiency include hypoalbuminemia as well as variable hyperinsulinism and increased levels of serum growth hormone.

In recently reported cases of a classical neonatal CDG syndrome (Clayton *et al.*, 1992), the biochemical abnormalities in the structure of glycoproteins appeared only in the second and third weeks postnatally, suggesting that the glycosylation disturbances may be secondary to an unidentified basic defect.

The CDG syndromes are familial, with the pattern of inheritance suggestive of an autosomal-recessive trait. Partial biochemical expression has been found in some clinically normal parents (Petersen *et al.*, 1993).

Some families have recently been reported with a distribution of lesions deviating from the classical (type I) pattern of CDG syndrome. One without cerebellar atrophy and peripheral neuropathy has been designated type II (Ramackers *et al.*, 1991), and another type, III, is characterized by profound but stationary psychomotor retardation, tetraparesis, infantile spasms, cerebral and optic atrophy, dysmyelination, and pigmentary skin

changes, in the absence of cerebellar hypoplasia, polyneuropathy, and retinal degeneration (Stibler *et al.*, 1993). Apart from the primary genetic forms of CDG syndrome, similar metabolic abnormalities may occur as secondary manifestations in chronic alcoholism (Stibler and Borg, 1991) and in classical galactosemia (Ornstein *et al.*, 1992). In the latter condition these abnormalities disappear completely when the patient is placed on a galactose-free diet (Jaeken *et al.*, 1992).

Sialuria (UDP-*N*-acetylglucosamine 2-Epimerase Deficiency)

Fontaine *et al.* (1968) described a patient with hepatomegaly, psychomotor retardation, and massive excretion of *N*-acetylneuraminic acid (sialic acid) in the urine. Apart from hepatomegaly and psychomotor retardation, the affected children suffer from a general impairment of development, which becomes apparent a few months after birth. Epileptic seizures may be an early symptom. *N*-Acetylmannosamine, *N*-acetylglucosamine, and 2-D-oxy-2,3-D-hydroacetylneuraminic acid are found in the urine. Kammerling *et al.* (1979) found, in addition, 2-acetamidoglucal. Only biopsy material has been examined so far. Giant mitochondria with paracrystalline inclusions and collagen fibers were found in hepatocytes. No abnormalities were found in the kidneys. The disorder is caused by defective feedback inhibition of the cytosolic enzyme UDP-*N*-acetylglucosamine 2-epimerase, leading to a massive overproduction of sialic acid (Mancini *et al.*, 1991). Further disorders with a marked increase in the excretion of free sialic acid are an infantile form of the disease and Salla disease.

Infantile Sialic Acid Storage Disease

A severe form of sialuria, apparently different from that described by Fontaine *et al.* (1968), was identified by Tondeur *et al.* (1982). Further cases have been reported by Stevenson *et al.* (1983), Gillan *et al.* (1984), Pueschel *et al.* (1988), and Cameron *et al.* (1990).

Clinical Picture The disease may present at birth with congenital ascites (Gillan *et al.*, 1984). The common symptoms are hypotonia, dysmorphic features, hypopigmentation, hepatosplenomegaly, and cardiomyopathy (Cameron *et al.*, 1990). Most patients die during the first year of life. Prenatal diagnosis can be made based on biopsy of the chorionic villi (Lake *et al.*, 1989).

Pathology *Light microscopy.* Vacuolation of the cytoplasm is found in most tissues, including hepatocytes, Kupffer's cells, sinusoids of the spleen, renal tubules and glomeruli, myocardium, bone marrow, lymphocytes, and epidermis.

Electron microscopy. Fibrillogranular material was seen in membrane-bound vacuoles in lymphocytes and in liver and conjunctival biopsies (Tondeur *et al.*, 1982).

Neuropathology *Gross Appearances.* The brain is atrophic, largely at the expense of the considerably reduced white matter, while the cortical ribbon appears normal (Lake, 1992).

Light microscopy. Neuronal storage is ubiquitous throughout the CNS and the peripheral nervous system and is most pronounced in the brain stem and the spinal cord. There is some loss of Purkinje cells with Bergmann's gliosis and formation of axonal balls (torpedos). Numerous axonal swellings are also present in the cerebral white matter and the brain stem (Lake, 1992). The atrophic white matter shows diffuse gliosis. Neuronal storage of a PAS-positive granular substance can be shown in cryostat sections of the gut stained by the protected PAS method.

Pathogenesis Sialic acid (*N*-acetylneuraminic acid) is stored in all affected organs and excreted in the urine in quantities up to 200 times normal values. The disorder is caused by progressive accumulation of free sialic acid within lysosomes due to defective efflux, probably caused by defective transport across the lysosomal membrane (Mancini *et al.*, 1986; Cooper *et al.*, 1988). The enzymatic defect has not been identified to date. The disease is inherited as an autosomal-recessive trait.

Salla Disease (Storage of *N*-Acetylneuraminic Acid

Aula *et al.* (1979) described four patients in a family with psychomotor retardation. Enzyme investigations precluded their inclusion under any known syndrome. Subsequently, more patients came to light, mostly inhabitants of the Salla district of Lapland, but also from other regions (Dodelson De Kremer *et al.*, 1990). Until a definitive classification becomes available, we have retained the eponym *Salla disease.*

Clinical Picture Salla disease becomes apparent between the ages of 1 and 2 years and manifests itself by a delay in the development of speech and walking. Occasionally, neonatal ascites has been reported (Gillan *et al.*, 1984). A generalized motor weakness may be present in the first year of life. The subsequent course is slowly progressive or stationary, and patients may survive into the fourth decade. Precocity and severity of the neurological damage in Argentine patients, contrary to the progressive neurological regression described for the classical syndrome, suggests a clinical form of Salla disease. Some patients showed mild to prominent coarsening of the facial features. Neurological symptoms include ataxia, dysdiadochokinesis, athetosis, and occasional spastic quadriplegia. The speech is dysarthric. All patients are severely mentally retarded.

Pathology The lymphocytes in peripheral blood show marked vacuolation. In skin biopsies cytoplasmic inclusions 0.5–1 μm in diameter are present in fibroblasts and histiocytes (Fig. 32B). The vacuoles contain amorphous granular material, fragments of membranes, and small osmiophilic spherical bodies. The latter are particularly abundant in the cells of sweat glands and in hepatocytes. Similar inclusions, albeit less abundant, are found in endothelial and smooth muscle cells. They have also been demonstrated in 80% of the cultured fibroblasts.

Neuropathology *Gross appearances.* The striking feature is severe atrophy of the white matter (Autio-Harmainen *et al.*, 1988).

Light microscopy. A severe loss of axons and myelin sheaths is apparent in the white matter. The neurons contain a lipofuscin-like pigment in their expanded cytoplasm. Gliosis is prominent. In the subiculum and the locus coeruleus, neurofibrillary tangles and axonal swellings have been observed (Autio-Harmainen *et al.*, 1988). Axonal swellings are also present in the ascending and descending tracts of the spinal cord.

Electron microscopy. Vacuolar inclusions are seen in Schwann cells (Fig. 32A). Axonal swellings are surrounded by a thin myelin sheath, and the Alzheimer neurofibrillary tangles consist of paired helical filaments (Autio-Harmainen *et al.*, 1988).

Pathogenesis No enzyme defect has hitherto been discovered. Renlund *et al.* (1979) found a 10-fold increase in the urinary *N*-acetylneuraminic acid in several patients. This appears to be due to a defect in the transport of sialic acid through the lysosomal membrane (Renlund *et al.*, 1986).

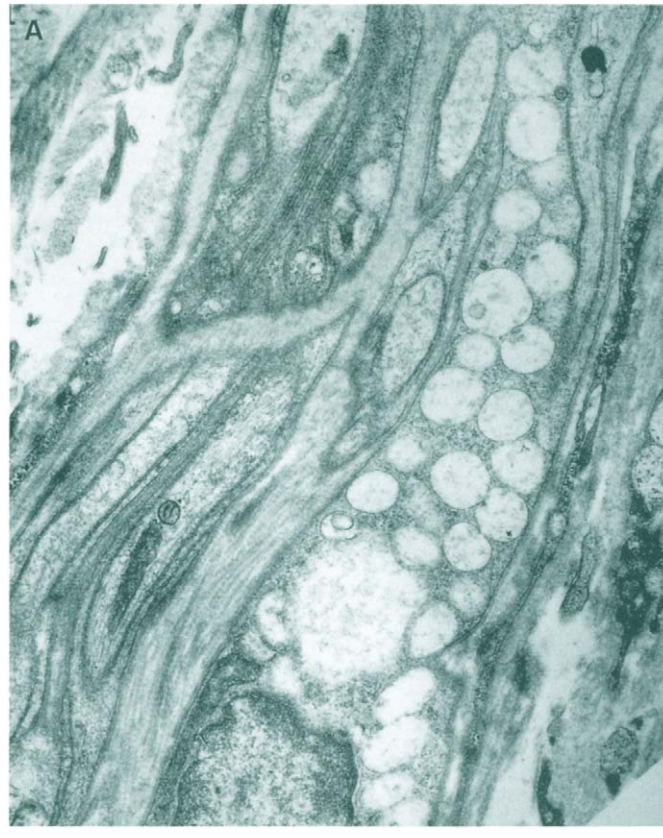


Fig. 32 Salla disease. (A) Multiple membrane-bound vacuoles in a Schwann cell, ×18,200. (B) An epidermal cell with multiple vacuoles containing osmiophilic spheroids, ×6,000.

Hancock-Type Sialidosis

Hancock *et al.* (1982) reported lysosomal storage of *N*-acetylneuraminic acid in a male patient.

Clinical Picture The patient presented with hepatosplenomegaly and signs of psychomotor retardation. He died at the age of 5 months after a rapidly progressive course of the disease.

Pathology *Light microscopy.* Liver biopsy revealed vacuolation of hepatocytes and Kupffer's cells. The vacuoles contained PAS-positive material at the margins, but most of the contents appear to have been lost. Similar PAS-positive inclusions were found in the neurons of the CNS and in cultured fibroblasts.

Electron microscopy. Granular and floccular material was seen in lysosomes.

Biochemical investigation. Biochemical investigation revealed large quantities of sialic acid in the brain, liver, and kidneys. This was identified as free *N*-acetylneuraminic acid.

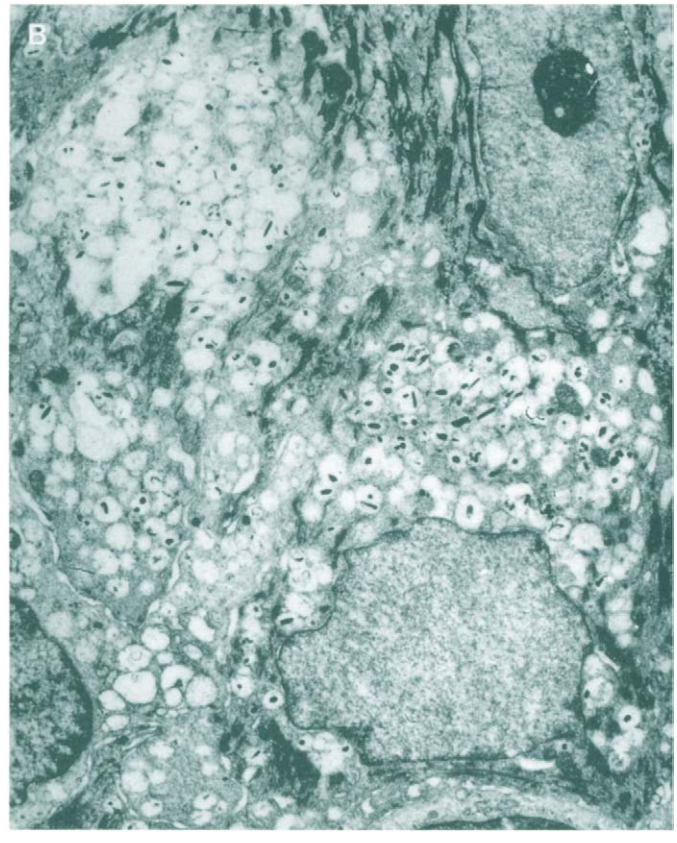


Fig. 32 Continued.

The concentrations of neutral glycolipids, galactosylceramide, and sulfogalactosylceramide were considerably reduced. The distribution of gangliosides reflected a nonspecific degeneration of the CNS. The activity of lysosomal enzymes concerned with the breakdown of cellular glycoproteins was normal. The condition appears to be due to a generalized defect in the metabolism of glycoconjugates.

Schindler's Disease (α-*N*-Acetylgalactosaminidase Deficiency)

Schindler *et al.* (1988) reported the cases of two siblings, the offspring of distantly related German parents, with progressive psychomotor deterioration, the morphological substrate of which closely resembled that of Seitelberger's infantile neuroaxonal dystrophy. Biochemical investigation revealed a deficiency of lysosomal α-*N*-acetylgalactosaminidase (Van Diggelen *et al.*, 1987; Schindler *et al.*, 1989).

Clinical Picture The early development of the two brothers was normal. The elder brother started deteriorating at the age of 12 months; the younger, at 9 months. The loss of acquired skills was followed by profound psychomotor retardation, visual impairment, nystagmus, muscular hypotonia, and myoclonic jerks. By the age of 4 years, they reached a stage of decerebrate rigidity. CT and MRI revealed atrophy of the cerebellum, brain stem, and cervical cord. EEG showed multifocal spikes and spike-and-wave complexes. Auditory, somatosensory, and visual evoked potentials had low amplitudes. Urinary oligosaccharide excretion was abnormal and showed a characteristic pattern on chromatography (Van Diggelen *et al.*, 1988). Peripheral nerve conduction velocities were normal. Thin-layer chromatography of the urine showed excretion of an abnormal oligosaccharide.

Neuropathology Morphological studies were confined to a frontal cortical biopsy and a rectal biopsy (Schindler *et al.*, 1989).

Light microscopy. There was no obvious neuronal loss in the cerebral cortex. There were numerous large dense axonal swellings or spheroids throughout the cortex with no apparent laminar distribution. Very few similar formations were seen in the axons in the subcortical white matter. The swellings were sharply demarcated and contained prominent angular or curved clefts with a darker amorphous background.

Electron microscopy. These structures appeared exclusively within preterminal or terminal axons. They were morphologically heterogeneous and comprised dense, labyrinthine, membranous tubulovesicular formations, looser membranous whorls, regular or paracrystalline vesicular arrays, and angular electron-lucent clefts, all intermingled with a few mitochondria, lysosomes, and microtubules. Tubulovesicular aggregates were also seen lying free in the cytoplasm of the preterminal and terminal axons in the myenteric plexus.

Pathogenesis Both brothers showed a severe deficiency of α-*N*-acetylgalactosaminidase in fibroblasts, lymphocytes, and tissue homogenates. Low values of the enzyme, compared with levels in normal controls, were found in both parents. Investiga-

tions of eight cases of infantile neuroaxonal dystrophy showed normal values of the enzyme, thus proving that Schindler's disease was a separate nosological entity.

The cause of the abnormality is a single transition from guanine to adenine at nucleotide 973 of the coding region of the gene located on chromosome 22q13→ter. This point mutation resulted in an E-to-K substitution at residue 325 of the enzyme polypeptide (Wang *et al.*, 1990). How this disturbance in carbohydrate metabolism expresses itself in the form of neuroaxonal dystrophy is not known.

Polysaccharidoses

Polysaccharides are carbohydrates, the molecules of which consist of more than 10 monosaccharides. Homopolysaccharides (homoglycans) are built from a single type of monosaccharide; heteropolysaccharides (heteroglycans), from multiple types. The homopolysaccharide glycogen forms the reserve carbohydrate in the energy metabolism of vertebrates. It is of paramount importance in the regulation of blood sugar levels. It is built up from glucose molecules in all tissues, particularly the liver and skeletal muscles. In certain enzymopathies unusual polysaccharides appear, normally present only in plants (amylopectin in glycogenosis type IV) or in bacteria (dextrin of the cell wall in glycogenosis type III).

Biochemistry of Glycogen

Glycogen is a large polysaccharide with a molecular weight between 2500 and 4500 kDa. Its basic component is α-D-glucose. A single molecule of glycogen may contain up to 10,000 of these units. The main linkage between glycosyl units is between carbon atoms 1 and 4, but a small part binds at α-1,6. These links are established by the action of the amylo-1,4–1,6-transglycosidase (branching enzyme) which leads to the characteristic branching structure of glycogen. The α-1,6 bindings and their glycosyl content account for 6–8% of the mass of glycogen. The chains beyond the last branching points of the tree are substantially longer than the inner chains. Each outer chain in human glycogen consists of seven to 10 units, and these account for about 40% of the mass of the glycogen molecule. The average length of the inner chain is four glycosyl units.

In the synthesis of glycogen in the liver, glucose is phosphorylated by the action of hexokinase or glucokinase to glucose 6-phosphate. This is transformed into glucose 1-phosphate by the action of phosphoglucomutase. This phosphorylated sugar is then transformed into UDPglucose by the action of glucose 1-phosphate uridylyltransferase. Under the influence of glycogensynthetase, the glucose unit is then added to a preexisting glycogen molecule.

The breakdown of glycogen in mammals proceeds through a combined action of phosphorylase and amylopectin-1,6-glucosidase (debranching enzyme) and yields a mixture of glucose 1-phosphate (93%) and glucose (7%). The glucose 1-phosphate arises through phosphorylation of the numerous 1,4-bound glycosyl components, while the free glucose

is produced by hydrolysis of the 1,6 bindings. Over and above this there is a glycogen-hydrolyzing enzyme system to which the lysosomal α-1,4-glucosidase belongs. Lack of this enzyme underlies glycogenosis type II. Biochemical estimations have revealed only a small glycogen reserve in the mammalian brain, and this is rapidly exhausted during hypoglycemia.

Morphology of Glycogen

The first morphological (i.e., histochemical) demonstration of glycogen was achieved by Best in 1906. Husemann and Ruska (1940) were the first to demonstrate glycogen particles on electron microscopy. Drochmaus (1962) observed, in centrifuge-isolated glycogen granules, three ultrastructurally different appearances of these particles. The γ-elements have a diameter of 13–15 nm and form the basic macromolecular structure of glycogen. They can combine to form larger units of variable size and configuration. β-Particles have a diameter of 20–40 nm; α-particles, 60–200 nm.

The easily soluble glycogen remains in tissues fixed with glutaraldehyde only if it is bound to protein. Aldehydes do not fix pure glycogen. The morphology of glycogen varies in different tissues. In the CNS one can recognize isolated β-particles (Fig. 33A), under certain pathological conditions one can also find α-particles (Fig. 33B), which are common in other organs, such as the liver.

Topographical Distribution of Glycogen in the Central Nervous System

Perfusion fixation and the use of appropriate fixatives and staining methods have made possible a detailed study of the distribution of glycogen in the brains of various species. Astrocytes contain glycogen in the cytoplasm in normal brains. Neurons of various species show glycogen granules only in specific nuclei. Oligodendroglial cells contain glycogen granules only in pathological situations, and rarely even then. The areas rich in glycogen are the hypothalamus and the area postrema. Furthermore, glycogen is found around blood vessels throughout the brain, as well as in subependymal tissue, in the membrana gliae limitans, and in the subcommissural and subfornical organs. The choroid plexuses contain little glycogen.

Glycogenoses

The glycogenoses are a group of metabolic disorders characterized by abnormal storage of glycogen in various organs or by formation of abnormal glycogens. They form a group of genetically determined metabolic disorders, and their classification is based on the underlying enzyme defect. Approximately 20% of the cases are of type I (glucose-6-phosphatase deficiency), 20% are type II (α-1,4-glucosidase deficiency), less than 1% are type IV (amylo-1,4–1,6-transglycosidase deficiency), 5% are type V (muscle phosphorylase deficiency), and 25% are types VI and VII (liver phosphorylase deficiency and phosphofructokinase deficiency, respectively) (Steinitz, 1967). To these may be added types

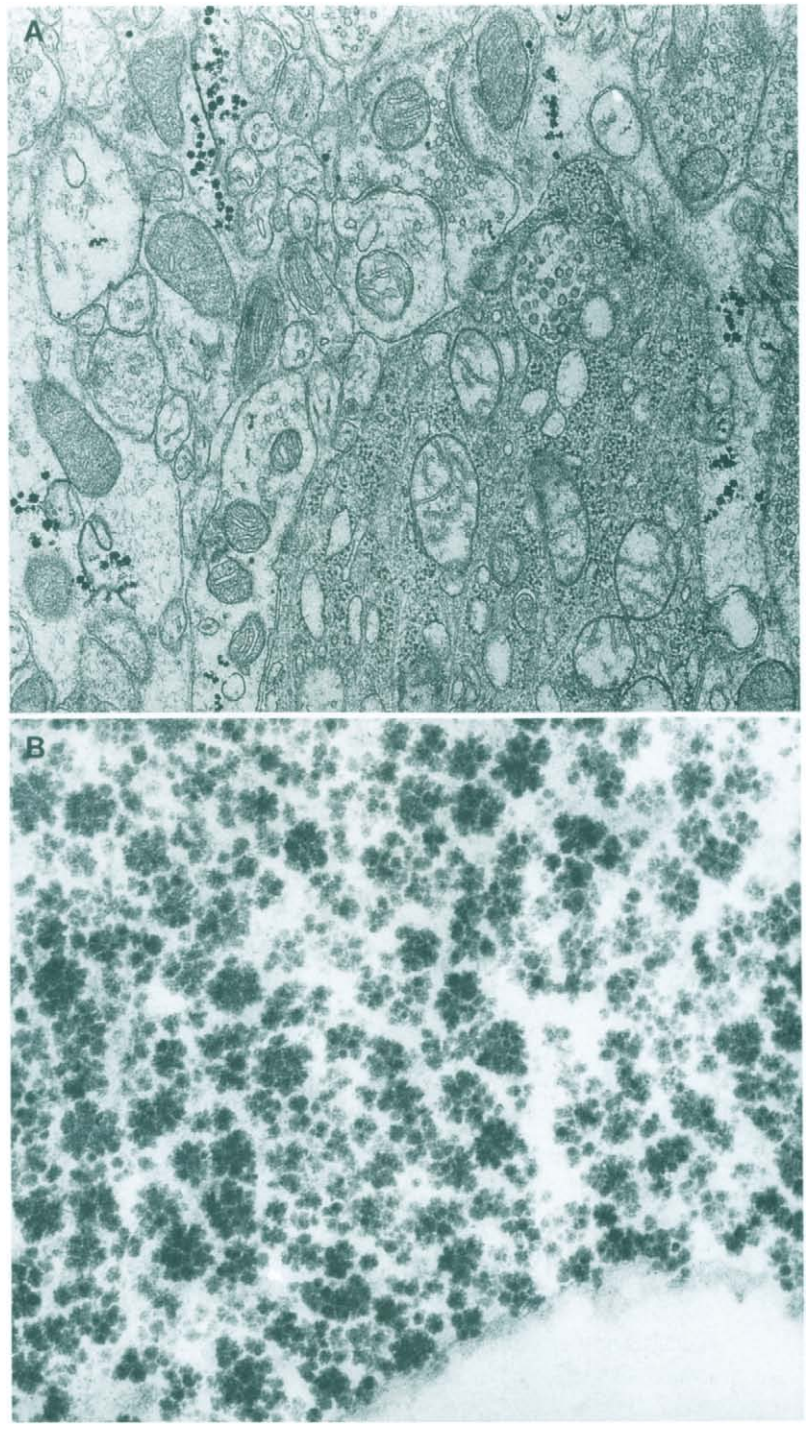


Fig. 33 (A) Scattered β-glycogen granules in an astrocyte of cat brain tissue, ×36,000. (B) An aggregation of α-glycogen particles in an axonal polyglucosan body, ×36,000.

VIII and IX, thought to be due to a delayed activation of phosphorylase and absence of liver phosphorylase kinase, respectively. The enzyme defects in types X and XI are unknown. Inheritance is autosomal recessive in all glycogenoses.

About 25–30% of the hitherto observed glycogen storage diseases cannot be allocated to any of the above types, in spite of extensive biochemical investigations. It is therefore to be assumed that the future will witness the identification of new types, which may even lead to a revision of the present classification.

Types II, IV, and VIII are of importance for the nervous system, although some secondary hypoglycemic damage (see p. 26) may occur in the different glycogenoses (Arico *et al.*, 1987). In rare instances direct cerebral involvement can be found in other glycogenoses. Among the complications due to the tendency to infection related to neutropenia and phagocytic dysfunction in glycogenosis type I, brain abscess has been reported (Park *et al.*, 1991; Garty *et al.*, 1992). Epileptic seizures and peripheral neuropathies have been recorded in types I and III (Ugawa *et al.*, 1986). The CNS is affected only in some cases of type IV (see p. 92). In 10% of the cases of type V, disturbances of consciousness or epileptic seizures may occur after severe strain (Spatz *et al.*, 1983). In a patient with severe psychomotor retardation due to phosphofructokinase deficiency (type VII), cerebral atrophy (Danon *et al.*, 1981) and neuroaxonal dystrophy (Servidei, 1987) were recorded.

Glycogenosis Type II (Pompe's Disease; α-1,4-Glucosidase Deficiency; Acid Maltase Deficiency; Generalized Glycogenosis)

Classical Pompe's disease represents the most severe type of glycogenosis (Pompe, 1933) caused by deficiency of acid maltase (acid α-1,4-glucosidase) (Hers, 1963). It affects all organs and tissues and is therefore known as generalized or diffuse glycogenosis.

Clinical Picture According to the degree of insufficiency of the enzyme, severe or relatively mild forms may occur. In the severe form the disease is generalized and affects skeletal muscle, heart, liver, kidneys, and other organs, including the CNS and the peripheral nervous system. Infants with this affliction show little mobility of the limbs from birth. One may therefore conclude that the disease originates *in utero*. A few months after birth, there is severe generalized muscle weakness with hypotonia, cardiomegaly, and hepatomegaly. Dyspnea, cyanosis, difficulty in sucking, and a weak cry are prominent symptoms. Macroglossia is present in most cases. The electromyogram may show a predominantly myopathic or predominantly neuropathic pattern; paramyotonic discharges may also be present. Glycosuria and acetonuria are rare. The disease progresses rapidly, with increasing weakness, frequently including bulbar symptoms, and leads to death from myocardial and respiratory failure during the first year. Fusiform aneurysms of the basilar artery and ischemic lesions in the brain were demonstrated by MRI (Braunsdorf, 1987).

In the milder form the glycogenosis is less pronounced. In particular, the heart and the liver are not enlarged and the life expectancy is decidedly more favorable. The principal symptoms are severe hypotonia with reduced or absent tendon reflexes and retardation in motor development. Bulbar symptoms may supervene. The disease may also present in adolescence or adulthood in the form of a slowly progressive myopathy (Di Mauro *et al.*,

1978; Pongratz *et al.*, 1984). The acid maltase deficiency can be demonstrated biochemically in heterozygotes (Schröder, 1982). In the severe form a prenatal diagnosis can be made as early as the 14th to16th weeks of pregnancy by the culture of amniotic cells obtained by amniocentesis.

Pathology All organs and tissues can be involved in glycogen storage in generalized glycogenosis.

Light microscopy. The heart muscle appears severely vacuolated and contains abundant coarsely granular glycogen deposits. In the lung glycogen storage affects the smooth muscle of the bronchi and blood vessels, the cartilage cells, and, to a lesser extent, the reticulum cells of intrapulmonary lymph nodes. Abundant glycogen is present in the liver, particularly in the periphery of the lobules. Glycogen granules fill the smooth muscle of the urinary bladder and of the entire gastrointestinal tract, as well as the histiocytic elements of the intestinal mucosa. Glycogen infiltration of skeletal muscle is extreme in the infantile form of the disease. There is an extensive vacuolar myopathy with dissolution of the myofibrillary pattern. The vacuoles are filled with PAS-positive diastase-digestible material. In the adult form a vacuolar myopathy is also present, but this affects only a few muscle fibers.

Electron microscopy. In the liver the glycogen granules accumulate in the lysosomes of hepatocytes. In the infantile form glycogen can be demonstrated in skeletal muscle both in lysosomal vacuoles and lying loose in the cytoplasm (Schröder, 1982). The muscles can also contain excessive lipid (Sarnat *et al.*, 1982). In the adult form glycogen is present both in autophagic vacuoles and free between the myofibrils. Pokorny *et al.* (1982) demonstrated massive accumulation of glycogen in all tissues of the eye (with the exception of the iris and the retina) of a 16-week fetus.

Pralle and Löffler (1976) found electron-dense inclusions, consisting of proteins and polysaccharides, in the plasma cells of two brothers with α-1,4-glucosidase deficiency.

Neuropathology From the available reports one may conclude that involvement of the CNS appears in two forms. Storage in neurons and glial cells may be absent (Van Der Walt *et al.*, 1987) or minimal, in some cases with severe involvement of the heart and the liver, and contribute little to the clinical picture of the disease. In the mild form, on the other hand, involvement of the CNS in the storage of glycogen may be of decisive clinicopathological importance (the neuromuscular form of the disease).

Light microscopy. The cells involved in storage show, in both H&E and Nissl stains, numerous small and large vacuoles in which the glycogen is deposited. The contents of the vacuoles stain positively with Best's carmine (red), Bauer-Feulgen (sky blue), and PAS (deep red). The cerebral cortex is the part of the brain least involved in glycogen storage. The case reported by Mancall *et al.* (1965) is an exception. In the brain stem the nuclei of cranial nerves are, as a rule, the most severely affected. Selberg (1953) found the most severe neuronal damage with neuronophagia in the hypoglossal nucleus and the nucleus ambiguus. The cells with abundant storage show ballooning of the cytoplasm and regressive changes in the nuclei in the form of pyknosis, spindle-shaped deformity, and karyolysis. The glycogen content of the red nucleus is sparse, as a rule. The cells of the substantia nigra are only moderately affected. On the other hand, glycogen accumulation

in the globus pallidus and the subthalamic nucleus is often prominent. Storage in the striatum, thalamus, and hypothalamus is generally slight. The large striatal cells tend to be more affected than the small ones.

Diffuse gliosis, particularly striking in the subependymal zone, has been seen in all cases in which the CNS has been examined (Mancall *et al.*, 1965). The ependyma, choroid plexuses, astrocytes, oligodendrocytes, and walls of the blood vessels may all contain glycogen (Crome *et al.*, 1963). Quantitative estimations have revealed a higher concentration of glycogen in the white matter than in the cortex (Crome *et al.*, 1963). Schnabel (1965) found a deposition of mucopolysaccharide-like substances as well as glycogen in the astrocytes of the subcortical white matter.

In the cerebellar cortex the Purkinje and granule cells are generally spared. The Golgi cells of the granular layer stand out through their abundant glycogen content. Both in the cortex and in the white matter the astrocytes are the main carriers of glycogen. This is particularly striking in the granular layer, while Bergmann's astrocytes appear less conspicuous. Glycogen storage has been demonstrated in the pituitary gland (Hui *et al.*, 1985).

In the spinal cord glycogen storage is abundant in the anterior horn cells, in which the nucleus is displaced peripherally. The cell processes are free of glycogen. These changes are present at all levels without appreciable regional differences. A loss of neurons in the anterior horn with accompanying gliosis has been reported occasionally. In some cases the lesions are limited to the anterior horn cells of the spinal cord and the motor nuclei of the brain stem. Glycogen storage may also be found in the intermediolateral nucleus, the other cells of the pars intermedia, the cells of Clarke's column, and those of the nucleus proprius of the posterior columns. In all of these cells, the storage is less prominent than in the anterior horn cells. The ependyma of the central canal contains abundant glycogen. A fine diffuse gliosis is present throughout the spinal cord. The cells of the posterior root ganglia show abundant storage, ballooning of the cytoplasm, and peripheral displacement of the nuclei. In peripheral nerves storage is seen in Schwann cells, but only occasionally in the mesenchymal cells of the endoneurium. In the autonomic nervous system sparse glycogen deposits have been demonstrated in the neurons of the Auerbach's and Meissner's plexuses and their satellite cells. The neurons of the celiac and pancreatic plexuses also contain glycogen.

Pathogenesis Glycogenosis type II differs from all other glycogenoses in that the enzyme defect is not in the enzyme systems involved in the normal glycogen metabolism, but in the lysosomal α-1,4-glucosidase, concerned with the intralysosomal breakdown of glycogen (see p. 86). It was during observations of this disease that Hers (1963) developed the concept of "lysosomal storage diseases" (see p. 4). The pathogenetic mechanism consists of the inability of the primary lysosome to break down the glycogen contained in autophagic vacuoles. This, however, does not explain the accumulation of free glycogen in the cytoplasm of muscle cells, as this should be metabolized by the enzymes of the intact phosphorylation pathway.

Various authors (Hudgson and Fulthorpe, 1975) have therefore postulated a more complex disturbance of carbohydrate metabolism that could not be laid at the door of a defective single enzyme. Possible causes of the difference between the mild (neuromuscular)

and severe (generalized) forms of the disease have been listed by Hudgson *et al.* (1968) as follows: differences in (1) the severity of the enzyme defect, (2) the distribution of the enzyme, and (3) the carbohydrate balance. Di Mauro *et al.* (1978) found lesions confined to the skeletal muscles in a 28-year-old patient with acid maltase deficiency. The relative impairment of the enzyme was present in all tissues, but the residual activity was lowest in muscle. The authors attributed the selective involvement of muscle in the late form of the disease to these regional differences.

Glycogenosis Type IV (Deficiency of Branching Enzyme; Amylopectinosis; Andersen's Disease)

Anderson (1952) discovered the storage of an abnormal glycogen in one patient. The abnormality consisted of excessively long inner and outer chains with very few branches. Because of the similarity with the plant polysaccharide amylopectin (Illingworth and Cori, 1952), glycogenosis type IV is also known as amylopectinosis. Involvement of the CNS was recorded by Craig and Uzman (1958).

Clinical Picture Children with this very rare type of glycogenosis are normal at birth. Hepatomegaly develops during the first few months; the spleen may also be enlarged. The infants do not thrive and suffer from muscle hypotonia and atrophy (Schochet *et al.*, 1970). A progressive cirrhosis of the liver develops early. The prognosis is unfavorable, with most children dying before the age of 3 years. Seizures have not been observed in any of the patients. Noort *et al.*, (1993) reported a congenital variant in the three related patients and Tang *et al.* (1994) did so in a sporadic case. A juvenile hereditary form has been described by Schröder *et al.* (1993).

Pathology The liver shows a nodular cirrhosis. There is no increase in glycogen content.

Light microscopy. Irregularly polygonal PAS-positive inclusions are found in the liver, spleen, and lymph nodes as well as in smooth cardiac and skeletal muscle. Immunohistochemically, the cardiac inclusions appear to be identical to Lafora's bodies and polyglucosan bodies (Yokota *et al.*, 1987).

Electron Microscopy. The deposits consist of fibrillary material (McAdams *et al.*, 1974).

Neuropathology Macroscopically, the brain weight (1660 g) in the juvenile case was unusually high (Schröder *et al.*, 1993).

Light microscopy. Polyglucosan bodies are found in the white matter, mainly in the perivascular and subcortical distribution, and in the gray matter (Noort *et al.*, 1993; Schröder *et al.*, 1993). They are lightly basophilic in H&E and strongly positive with PAS, Best, and iodine stains. Sidbury *et al.* (1962), Servidei *et al.* (1987), and Tang *et al.* (1994) found similar deposits in the spinal cord; Gallen *et al.* (1986) discovered them in neurons in the dentate nucleus of the cerebellum. Herrick *et al.* (1994) reported the involvement of the neuronal perikarya, with large neurons being more affected. The changes were most marked in motor nuclei of cranial nerves II, VI, VII, and XII and in the nucleus ambiguus, large motor neurons of the spinal cord, and neurons of the dorsal

root ganglia. The storage resulted in distention of the perikarya by pale blue finely granular material that sometimes coalesced into irregularly shaped coarse granules or developed into better-structured round polyglucosan bodies measuring up to 16 μm in diameter. The accumulated substance was intensely PAS positive and diastase resistant. These inclusions were found in large numbers in the epithelium of the choroid plexus (Servidei *et al.*, 1987) as well as in the smooth muscle cells of blood vessels, especially in the leptomeninges (Schröder *et al.*, 1993).

Electron Microscopy. Several authors (Schochet *et al.*, 1970; Ishihara *et al.*, 1987) pointed out the ultrastructural similarity of these deposits to the Lafora's bodies of myoclonus epilepsy (see p. 99). They consist of intertwined irregularly arrayed fibrils (Fig. 34A and B) and were found to be exclusively intraastrocytic. However, Herrick *et al.*

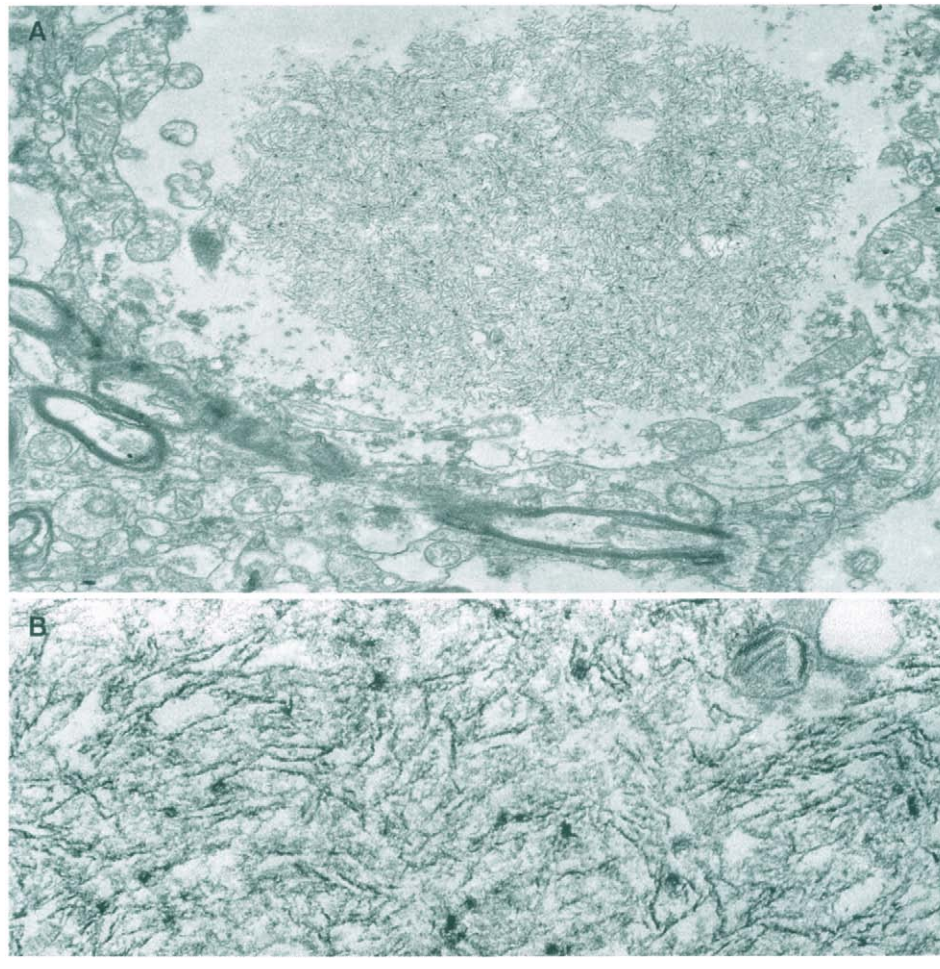


Fig. 34 Glycogenosis type IV. Subcortical white matter of the parietal lobe, showing deposits of amylopectin fibers in an astrocyte, (A) ×6000 and (B) ×50,000.

(1994) demonstrated storage material also in oligodendroglia and neuronal cells in the brain and the spinal cord.

Pathogenesis Brown and Brown (1966) demonstrated that a deficiency of the branching enzyme amylo-1,4–1,6-transglycosidase was the basic defect in glycogenesis type IV. Three hypotheses have been advanced to explain the fact that, despite the absence of the branching enzyme, no long chains of a totally unbranched polysaccharide can be demonstrated: (1) the presence of an alternative branching system, (2) a prenatally active branching enzyme that loses its activity after birth, and (3) the synthesis of some branching points by the debranching enzyme (Huijing, 1975).

Adult Amylopectinosis (Suzuki's Disease)

Robitaille *et al.* (1980) reported on a series of patients who developed muscular weakness, sensory disturbances, and dementia between the ages of 45 and 50 years. Clinically and neuropathologically, these cases resembled those of Suzuki *et al.* (1971) and Peress *et al.* (1980), as well as those of Torvik (1974), with symptoms of myopathy, tremor, and dementia (see p. 687), in which basophilic deposits were found in the skeletal muscles and the myocardium.

Pathology Deposits of a strongly basophilic substance are found in cardiac, skeletal, and smooth muscles. On electron microscopy these display a finely granular and filamentous structure. The deposits are not separated by a membrane from the surrounding cytoplasm (Torvik *et al.*, 1974; Peress *et al.*, 1980).

Neuropathology *Gross appearances.* The cerebral cortex, basal ganglia, and spinal cord may be diffusely or focally atrophic and of a firm consistency (Peress *et al.*, 1980).

Light microscopy. Numerous inclusions are found in astrocytes and, even more strikingly, in axons and dendrites. They vary considerably in size; the smaller ones are barely visible, while the largest reach a diameter of 60 μm. The small ones predominate in the cerebral cortex; the large ones, in the gray matter of the spinal cord (Suzuki *et al.*, 1971). The inclusions are strongly positive with PAS and Best's carmine and stain deep brown with iodine. Rarefaction of the neuronal population is occasionally observed in the cerebral cortex, as well as in the Purkinje cell layer of the cerebellum. Changes in the white matter range from demyelination to microcystic degeneration. The affected areas are the site of dense gliosis. Inclusions have also been seen in axons of the peripheral nerves.

Electron microscopy. The inclusions show the typical structure of polyglucosan bodies. In contrast with Lafora's bodies (see p. 100), they are not present in the neuronal perikarya.

Pathogenesis Peress *et al.* (1980) demonstrated that the polysaccharide is resistant to glycogen catalytic enzymes, but can be broken down by a combination of amylase and α-1,6-glycosidase, which also digests amylopectin. It must be taken into account that ba-

sophilic substances must possess anionic radicals such as SO_4^{2-}, PO_4^{3-}, and sialic acid. The lesions appear closest to those seen in glycogenosis type IV.

Glycogenosis Type VIII

Résibois-Gregoire and Dourov (1966) described a new type of glycogenosis affecting exclusively the CNS. Hug *et al.*, (1967) reported on a patient who presented predominantly with neurological symptoms, but also with moderate hepatomegaly. He called this variant of glycogenosis type VIII. Both cases showed similar lesions in the CNS.

Clinical Picture The first symptoms appear soon after birth and consist of difficulty in drinking and swallowing, as well as dyspnea and cyanosis during sucking. These are followed by hypotonia, ataxia, nystagmus, psychomotor retardation, and blindness. Late stages of the disease are marked by a spastic quadriplegia. Patients may die during the first year of life (Résibois-Gregoire and Dourov, 1966) or survive longer, with increasing signs of decerebration. Increased amounts of adrenaline and norepinephrine are excreted in the urine.

Pathology Apart from a slight increase in the glycogen content of the liver (8% of dry weight) without structural abnormalities, all other organs were normal in the case of Résibois-Gregoire and Dourov (1966). Repeated liver biopsies in the case of Hug *et al.*, (1967) showed a gradual increase in liver glycogen over the course of several years. The glycogen granules were predominantly loose in the cytoplasm and only occasionally in autophagic vacuoles. Skeletal muscles contained a normal amount of glycogen.

Neuropathology *Gross appearances.* Some cases showed severe cerebral atrophy, most pronounced in the cerebellum.

Light microscopy. The striking feature was the presence of numerous PAS-positive and argyrophilic spheroids in the neuropil of the cerebral cortex, thalamus, and cranial nerve nuclei, as well as in the subcortical white matter (Fig. 35). They reach a diameter of 30 μm. With PAS they either stain homogenously or show a central pallor with peripheral condensation of the stain. The PAS positivity disappears after diastase treatment. The neurons of the medulla oblongata, particularly of the inferior olives, contained similar inclusions in their cytoplasm.

Electron microscopy. Glycogen granules of three morphological types were present. β-Particles were found most commonly in processes of the astrocytes and the oligodendrocytes and were most abundant in the perivascular astrocytic foot plates. α-Particles with a diameter of 60–120 nm with a typical rosettelike morphology were seen beside giant α-particles (150–350 nm in diameter) in axons and dendrites (Fig. 36), and occasionally also in presynaptic terminals in close association with synaptic vesicles. In contrast with glycogenosis type II, glycogen was never seen in lysosomes.

Pathogenesis The activity of hepatic phosphorylase is reduced, although the total amount of the enzyme (active and inactive) is normal. The activity increases in the course

of the test without addition of phosphorylase kinase. A delay in the activation of phosphorylase is therefore suspected. Enzymatic differences in various organs and tissues do not provide an adequate explanation for the preferential storage of glycogen in the CNS. There are differences between the glycogen phosphorylases of the liver and the brain. The latter appears to be identical to that of smooth muscle, which is not involved in glycogen storage in glycogenosis type VIII.

Glycogenosis in Animals Generalized glycogenosis of type II was found in cattle of different breeds in Australia (Cook *et al.*, 1982). Liver, heart, and skeletal muscle is affected. The neurons of the CNS and the autonomic nervous system show swelling, vacuolation, and glycogen storage. Similar changes are present in the retinal neurons. Glial and Schwann cells are also involved. Cook *et al.* (1982) found glycogen both in membrane-bound vesicles and loose in the cytoplasm. The glycogen content in brain, spinal cord, liver, and skeletal muscle was increased. The activity of α-glucosidase was reduced in the liver to 2% of normal values; in brain, heart, and skeletal muscle, to 5% (Cook *et al.*,

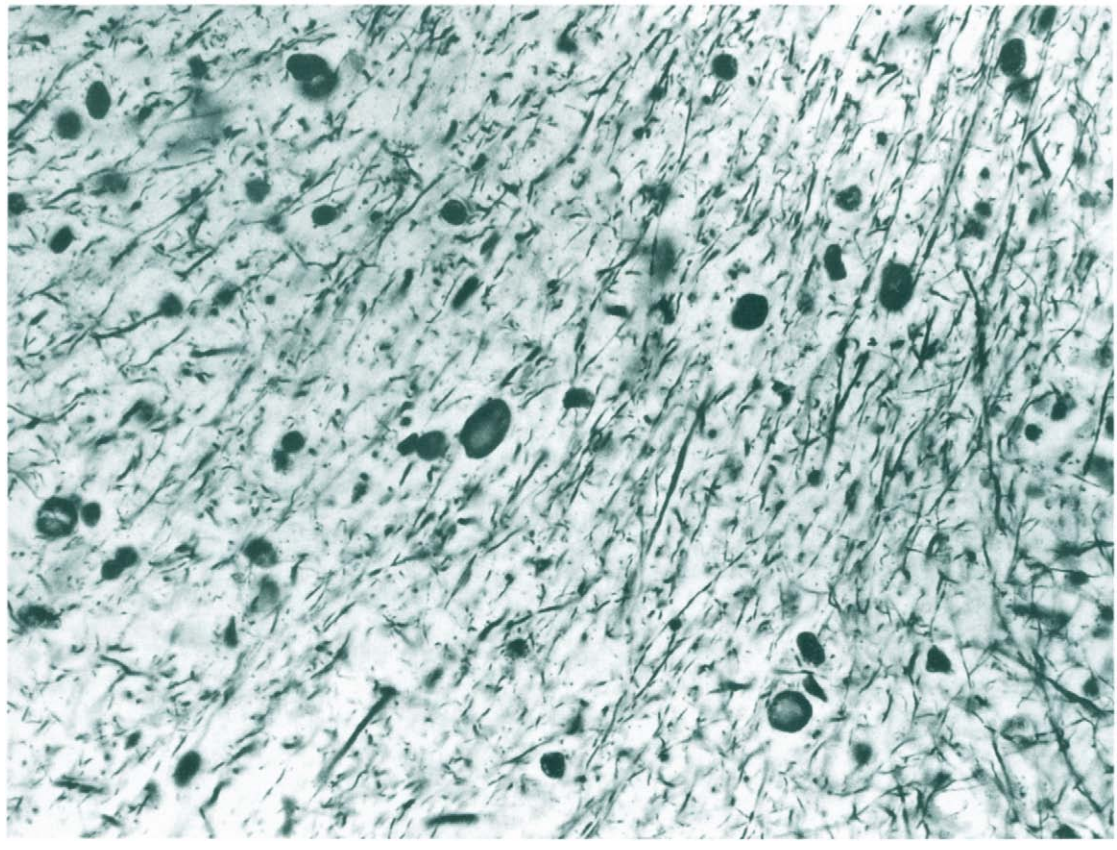


Fig. 35 Glycogenosis type VIII. Multiple spheroids in the subcortical white matter of the frontal lobe. Bodian stain, ×450. (Reproduced from Kornfeld and Le Baron, 1984.)

1982). Examples of generalized glycogenosis with CNS involvement in dogs were reported by Walvoort *et al.*, (1985) in Lapland dogs and by Rafiquzzaman *et al.* (1976) in German shepherds. Glycogen granules in the form of β-particles were seen lying free in the cytoplasm. In the CNS of cats, Sandström *et al.* (1969) found both membrane-bound and free glycogen deposits in the cytoplasm of neurons. Most were in the form of β-granules (20–25 nm), with some α-granules (60–100 nm).

Polyglucosan Inclusions in Nervous Tissues

In light microscopic examination many types of inclusions and deposits were described, some characteristic of various diseases, others occurring in normal or aging

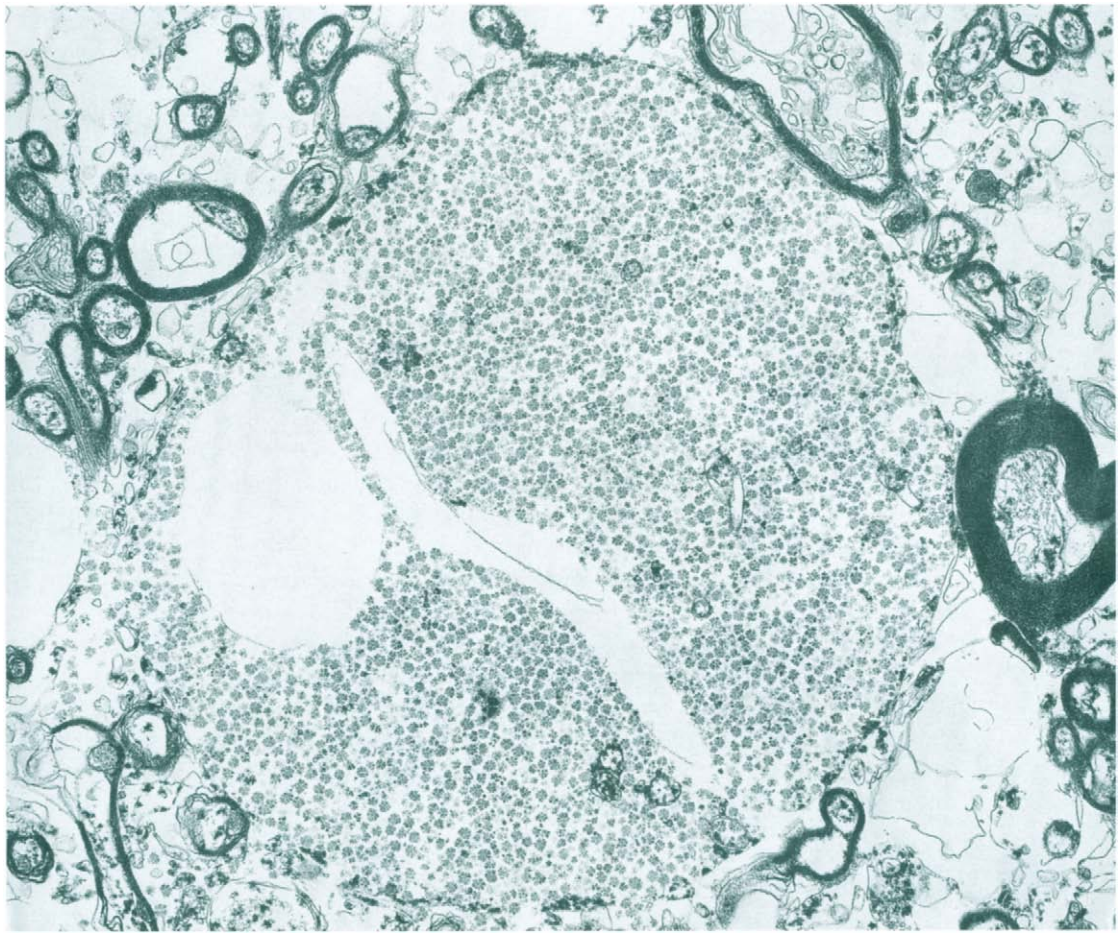


Fig. 36 Same case shown in Fig. 35. Axonal swelling with α-glycogen granules, a membrane-bound slit, and a vacuole, ×10,530.

brains. Here belong the corpora amylacea, Lafora's bodies, Bielschowsky bodies, Lewy bodies, Pick bodies, eosinophilic hyaline bodies, axonal spheroids, etc. Their localization, size, structure, and tinctorial properties were decisive for their classification. The introduction of electron microscopy made it possible to study the ultrastructure of these inclusions. In many cases this confirmed their nature, surmised from light microscopic and histochemical observations. In the remaining instances this led to a more precise ultrastructural definition.

Inclusions in which the ultrastructure suggested a similarity of chemical composition include the corpora amylacea, Lafora's bodies, and Bielschowsky bodies. Biochemically, all of these inclusions consist of polyglucosans, built up from amylopectin-like glucose polymers. A slight biochemical heterogeneity was established for the different types of polyglucosan inclusions.

The differentiation of the three types of polyglucosan inclusions necessitates a comprehensive overview of the available data. This is rendered difficult by the fact that in some publications the inclusions have received a designation unsupported by any differential criteria. In addition, numerous reports have appeared in recent years of similar inclusions in various species of animals. The frequently used designation "Lafora-like bodies" has only added to the terminological confusion. Robitaille *et al.* (1980) therefore proposed the use of the comprehensive term *polyglucosan bodies* to cover all these inclusions.

The Lafora's bodies of Lafora's disease are dealt with here first, followed by an account of the other polyglucosan inclusions.

Lafora's Disease (Progressive Myoclonic Epilepsy; Unverricht–Lundborg's Disease; Myoclonus Body Disease)

From the various conditions associated with myoclonus (irregularly occurring lightning muscular twitches), Unverricht (1891) isolated a clinical syndrome presenting with myoclonus and generalized epileptic seizures. In a detailed family study Lundborg (1912) established the recessive inheritance of the disease.

The macroscopic appearances of the brain are inconspicuous and the search for an anatomical substrate of the disease remained unsuccessful for many years. Various hypotheses were advanced until Lafora and Glück (1911) discovered peculiar inclusions in the neuronal cytoplasm in a patient's brain. Following Lafora's comprehensive studies these inclusions became generally known as Lafora's bodies. The coexistence of myoclonus and epileptic seizures does not constitute a specific disease entity, but represents a symptom complex that may occur in etiologically and histologically different diseases. Three main groups of anatomopathological lesions may be distinguished.

1. Atrophic changes in certain extrapyramidal motor centers and in the cerebellum in degenerative disorders (e.g., dyssynergia cerebellaris myoclonica; see p. 613).
2. Lysosomal storage diseases affecting preferentially the same extrapyramidal motor centers (e.g. ceroid lipofuscinosis; see p. 364).
3. Cases characterized by the presence of Lafora's bodies in neurons. Only this group constitutes Lafora's disease in a strict clinical and anatomical sense.

Clinical Picture The disease is familial, sometimes hereditary, and rarely sporadic, and affects men and women with equal frequency. The cardinal symptoms are epileptic seizures, myoclonus, and dementia. The lack of a uniform pathogenesis of myoclonic epilepsy and the publication of cases without anatomical confirmation led to various, often contradictory, classifications.

Vogel *et al.* (1965) proposed a classification, based on clinical features, that recognized three groups of cases. This classification was subsequently accepted by several authors.

1. A recessive form as defined by Unverricht begins between the ages of 5 and 15 years with generalized epileptic seizures. Myoclonic jerks appear later and are not accompanied by disturbances of consciousness. These consist of irregular, nonrhythmical, lightning contractions of a single muscle or group of muscles, usually with little interference with voluntary movements. Complex myoclonic twitches may appear affecting the trunk and the limbs or, less commonly, the head, pharynx and diaphragm. This motor unrest may become so severe as to render the patient completely helpless. Extrapyramidal disturbances may develop, usually of a parkinsonian type, with rigidity, tremor, and propulsion. Dementia develops simultaneously with the motor disturbances. In the final stage seizure and myoclonus become less common, and spasticity, immobility, and a high-grade dementia supervene. These patients die usually 10–15 years after the onset of symptoms due to intercurrent infections.
2. The recessive form of Lundborg is less common, begins between the ages of 10–25 years, and runs a benign course. Patients may retain a somewhat reduced earning capacity up to the age of 40 or 50 years. Perhaps some cases included in the adult variant (see p. 102) belong to this group.
3. The dominant form of Hartung resembles the recessive form of Lundborg and differs from it only by the mode of inheritance. It is the rarest of the three forms and has been reported largely by Japanese authors.

May and White (1968) pointed out some clinical differences between the cases of Unverricht and Lundborg and those of Lafora. They concluded that these were probably different diseases. Some other authors reached a similar conclusion based on a large series of cases examined clinically and, in part, anatomopathologically. Eldridge *et al.* (1981) included cases different from Lafora's disease in the group of "Baltic myoclonus epilepsy."

Pathology *Gross appearances.* Examination reveals no evidence of a storage disease.

Light microscopy. Many liver cells, particularly at the periphery of the lobules, appear swollen and rounded. They contain some weakly basophilic material in their cytoplasm, which may surround or displace the nucleus (Harriman *et al.*, 1955). The material stains strongly with PAS and with periodic acid–methenamine silver. Occasionally, similar deposits are also found in Kupffer's cells. Many hepatocytes show a finely granular appearance of their cytoplasm. A few cells show foamy vacuolation. Intracellular deposits are also found in cardiac muscle (Harriman *et al.*, 1955). The substance is dense, homogeneous, basophilic, and anisotropic. It frequently occupies the whole transverse section of a muscle fiber. More commonly, it forms a perinuclear sharply circumscribed structure free of myofibrils. The tinctorial properties of the inclusions resemble those of the "basophilic mucoid

degeneration" of the hypertrophic aging heart. In contrast with Lafora's bodies, the deposits in the liver, heart, and skeletal muscle are not birefringent. Typical Lafora's bodies are present in eccrine duct cells and in the peripheral nerve on skin biopsies (White and Gomez, 1988). Drury *et al.* (1993) stated that, in cases in which a reasonably certain clinical diagnosis can be established, supported by biopsy proof in some family members, repeated biopsy specimens even at advanced stages of the disease may be negative.

Electron microscopy. The liver cells contain homogeneous electron-dense material in vacuoles. Granular and lipid-containing lysosomal inclusions are also present. Vazquez and Padro-Mindan (1979) found deposits similar to Lafora's bodies in the hepatocytes of alcoholics treated with Antabuse. The myocardial deposits in myoclonic epilepsy correspond ultrastructurally to those of the mucoid, or basophilic, degeneration in old age. The inclusions in myoclonic epilepsy are, however, more massive; furthermore, they occur in young patients.

The granules in skeletal muscle are of two sizes: small ones, 2–13 nm in diameter, and larger ones, identical to the β-granules of glycogen. Both can be removed by digestion with α-amylase for 1 hour. Lafora's bodies, in the peripheral portion of the eccrine sweat gland duct, appear as fine pale-staining filament, fine dark-staining granules, and dark-rimmed vacuoles within non–membrane-bound inclusions (White and Gomez, 1988).

Neuropathology *Light microscopy.* The characteristic feature is the presence of Lafora's bodies in the CNS. They are ubiquitous in the gray matter, while the white matter is spared. The nuclei of the ascending reticular system are the site of predilection in the brain. The inclusions are most numerous in the dentate nucleus and the substantia nigra, where few unaffected cells can be found. The thalamus, red nucleus, inferior olive, and cerebral cortex follow, in descending order.

The myoclonus bodies are situated mainly in the neuronal perikarya and less commonly in the processes. They are round, 1–30 μm in diameter, and often exceed the size of the nucleus, which is displaced to the periphery and compressed into a crescentic shape. Single or multiple inclusions may be found in a single cell. The neuron itself appears impaired in its function. Neurofibrils and Nissl bodies can still be seen even in advanced stages. Van Hoof and Hageman-Bal (1967) classified Lafora's bodies into two types, according to size and internal structure. Type I bodies are homogeneous and, as a rule, less than 20 μm in diameter. Type II bodies are concentrically laminated around a central core and exceed 20 μm in diameter. The latter stain with hematoxylin, some more intensely in the center, others in the periphery, or in concentric layers. Intensely staining basophilic granules, representing sequestrated material, may surround the inclusion. With methyl violet only a part of the inclusion stains reddish metachromatically, while most of the body remains unstained or contains a deep blue core. The same pattern appears with other basic aniline stains. In bi- or trichromatic stains the bodies display a pattern of contrasting colors. With iodine–potassium iodide the inclusions stain a deep brown, and are not affected by the addition of sulfuric acid. Histochemical investigations have confirmed the carbohydrate nature of the material, in that it stains, at least in parts, with Best's carmine and PAS. The staining is not abolished by predigestion with saliva. The separation of the central core from the outer shell in type II bodies may be due to the inclusion of an intervening layer of organelles. The protein content in the central core, which may

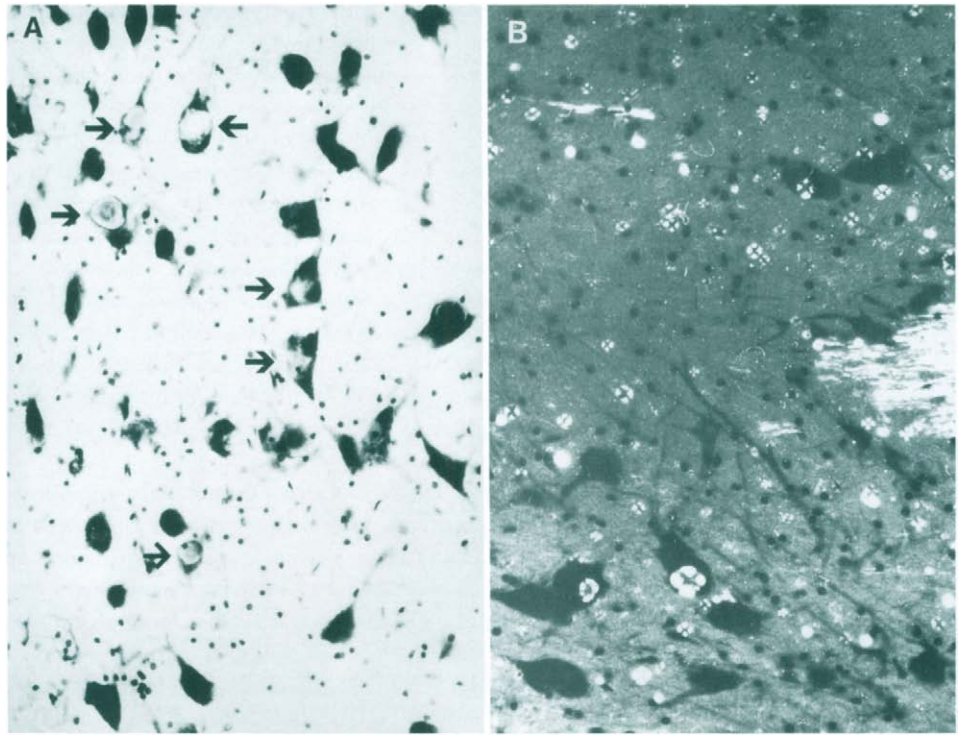


Fig. 37 Lafora's disease in the parietal cortex. (A) Numerous myoclonus bodies (arrows) in the neuronal perikarya. (B) Birefringence of myoclonus bodies under polarized light. Nissl stain, ×200. (Courtesy of W. Schlote, Frankfurt, Germany.)

be demonstrated with appropriate stains, suggests its formation on a preexisting structure. In polarized light the core displays intense birefringence with negative Maltese crosses (Fig. 37B). This is enhanced by the use of the coupled tetrazolium reaction. In the periphery of type II bodies, only small radially arranged rods are birefringent. In isolated Lafora's bodies 5% is protein; the remainder, carbohydrate.

Positive staining of Lafora's bodies was found with antibodies to 160- and 200-kD neurofilaments and to desmin. Positive staining with concanavalin A showed different patterns of inhibition with glucose and mannose, suggesting that the latter hexose contributes to the 10% nonglucose carbohydrate content of these bodies (Lewis *et al.*, 1990). Ubiquitin epitopes have been detected in both type I and II Lafora's bodies (Hessler *et al.*, 1990).

With adequate enzyme concentrations and incubation times Lafora's bodies can be digested by α-amylase and, to a lesser extent, by β-amylase.

Electron microscopy. Lafora's bodies consist of fibrillary material interspersed in a granular matrix. Bodies 5–20 μm in diameter show an incipient condensation in the center, while smaller ones are entirely homogeneous. The latter were called "dust particles" by Van Hoof and Hageman-Bal (1967); these form about 90% of all inclusions. Homogeneous and

laminated bodies are present. Numerous subcellular organelles are included in the deposits, their number increasing toward the periphery. While they are clearly recognizable at the margins of the inclusion, they become smaller and simplified in deeper layers and disappear completely in the central core. In those bodies that show a clear laminar differentiation, the central core is clearly demarcated from the outer shell and is strictly homogeneous and monomorphic in structure. Smaller bodies contain star-shaped central structures, consisting of short filaments arranged radially. Treatment with $Pb(OH)_2$ enhances the contrast. The filaments can be followed only over short distances. They appear more concentrated toward the center of the structure. Ultrastructural studies have revealed that those bodies which, under light microscopy, appear to lie loose in the neuropil, are, in fact, situated within axons and dendrites, particularly in synaptic terminals. Extracellular deposition is never seen. Contrast enhancement with $Pb(OH)_2$ facilitates the recognition of the inclusions in the processes. The inclusions are not membrane bound. Ante mortem diagnosis of Lafora's disease is possible by brain or liver biopsy (Nishimura *et al.*, 1980).

Pathogenesis Myoclonus is caused by localized destruction or functional disturbance in subcortical centers, leading to activation of the motor cortex by way of the ascending reticular system. This hypothesis is supported by various experimental models (Halliday, 1975). This localization can occur in a variety of structurally and etiologically different disorders. Lack of involvement of the relevant structures may explain the occurrence of cases of epilepsy with typical Lafora's bodies, but without myoclonus. The nosological position of these cases, however, is debatable. Schochet *et al.* (1971) drew attention to the histochemical and ultrastructural similarities between Lafora's bodies and the deposits in glycogenosis type IV. Spectrophotometric analysis of brain and liver tissue in two cases of myoclonic epilepsy revealed long chains of glycogen similar to the amylopectin of glycogenosis type IV. No deficiency of amylo-1,4–1,6-transglycosidase activity could be demonstrated, however, in Lafora's disease. The absence of a hypothetical branching enzyme can only be assumed.

The question as to whether myoclonic epilepsy is a lysosomal storage disease is linked with the contradictory observations on whether Lafora's bodies are membrane bound in the initial stage of their formation. Most authors failed to find such membranes.

The gene locus for Lafora's disease has not yet been mapped. Exclusion of linkage to the chromosome 21q22.3 region where the *EPM1* locus lies has been reported in three Italian families (Lehesjoki *et al.*, 1992).

The gene for the Unverricht–Lundborg type was assigned to chromosome 21q22.3 by linkage analysis in 12 Finnish families. The maximum multipoint lod score was 10.08 (Lehesjoki *et al.*, 1991, 1992). Multipoint linkage analysis determined a location of the disease gene at 6.0 cM distal to locus *BCE1* and 0.8 cM proximal to locus *D21S154*. Malafosse *et al.* (1992a) showed that the Mediterranean type of progressive myoclonus epilepsy is probably due to the same mutation as that of Baltic progressive myoclonic epilepsy (Malafosse *et al.*, 1992b).

Adult Type of Lafora's Disease

Dastur *et al.* (1966) described a case of myoclonic epilepsy in a 41-year-old patient whose symptoms began at the age of 33. The inclusions differed both morphologically

and histochemically from typical Lafora's bodies, and the authors concluded that the case represented a separate, adult, type of the disease. Similar cases were reported subsequently.

Neuropathology *Gross appearances.* Cerebral atrophy is conspicuous (Dolman, 1975). *Light microscopy.* Numerous PAS-positive inclusions are present in neurons. They are strongly eosinophilic and vary considerably in size. Some differentiation of the core and the outer shell may be seen in the larger bodies. They react with amide black and the coupled tetrazolium reaction, indicating the presence of proteins. Dastur *et al.* (1966) found a dusting with sudanophilic material in the cytoplasm of neurons free of inclusions. The glial reaction is sparse and the white matter is unremarkable. The degenerative neuronal changes lead to blurring of the laminar pattern of the cortex. The pyramidal cells are preferentially affected with consequent accentuation of the lesion in the third and fifth layers. In comparison with typical cases of Lafora's disease, the number of inclusions in individual neurons is far greater. Apart from the cerebral cortex, the extrapyramidal centers are severely affected. The dentate nucleus is heavily involved, while the cerebellar cortex appears virtually intact. The histochemical reactions differ considerably from those with typical Lafora's bodies, as they did in the case of Dastur *et al.* (1966).

An unclassified case was reported by Palmucci *et al.* (1982) in a 17-year-old patient suffering from myoclonic epilepsy. Polyglucosan bodies were present in astrocytes, and the activity of hexosaminidases A and B was reduced.

Pathogenesis Biochemical analysis revealed an accumulation of glycoprotein, which led to the formation of inclusion bodies. They were not birefringent under polarized light. It has been assumed that the basic metabolic defect was similar to that in classical Lafora's disease. The differences in the morphology of the inclusions have been ascribed to a reduced intensity of the metabolic disturbance, which still permitted the cell to react to the accumulated product by its inactivation.

Myoclonic Epilepsy in Animals Lafora's bodies are found in dogs suffering from a hereditary progressive epilepsy (Kaiser *et al.*, 1984). The first seizures appear between the ages of 5 and 12 years. They are of the grand mal type, are associated with myoclonus, and increase gradually in frequency and severity until they terminate in fatal status epilepticus at a relatively advanced age. The PAS-positive inclusions average 9.4 (± 2.8) μm in diameter and exhibit all the characteristic features of Lafora's bodies. Under electron microscopy they consist of filaments of variable density and thickness (3.5–8.5 nm) on a granular background. These inclusions are found predominantly in the thalamus, but are also seen in the neocortex (layers II, V, and VI), the basal ganglia (except the caudate nucleus), the midbrain (substantia nigra, medial, and lateral geniculate bodies), and the cerebellum.

Corpora Amylacea

Corpora amylacea are the most common polyglucosan inclusions, ubiquitous in astrocytic processes. They were originally described by Purkinje (1839). Their name is de-

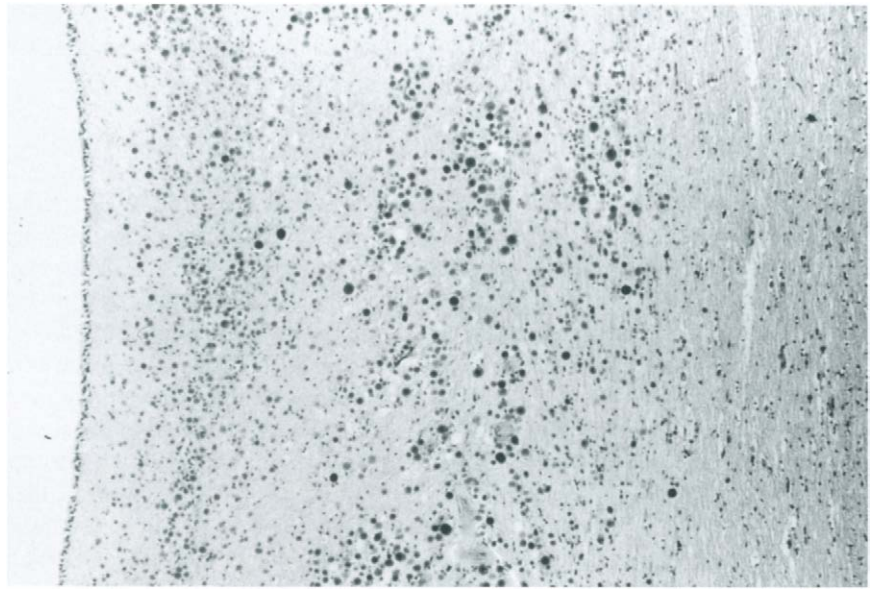


Fig. 38 Senile brain tissue, showing a subependymal accumulation of corpora amylacea.

rived from their similarity to starch granules (Kölliker, 1852). In spite of their lack of pathological significance, they gave rise to an extensive literature. Ramsay (1965) demonstrated by electron microscopy that they were intracytoplasmic inclusions in expanded astrocytic processes.

Morphology *Light microscopy.* The corpora amylacea appear as round or oval, partly homogeneous, partly concentrically laminated, basophilic bodies, which may reach a diameter of 17 μm in the largest examples. They congregate near the subpial and subependymal surfaces (Fig. 38), and around blood vessels. Tinctorially, they are characterized by an affinity to iodine, are stainable with Nile blue sulfate and neutral red, are intensely positive with PAS and Best's carmine, and show a weak metachromasia with aniline dyes. They represent nonspecific degenerative phenomena and consist of glycogen-like substances bound to sulfate and phosphate radicals. By chemical analysis Stam and Roukema (1973) found 80% glycogen-like substance, 1.1% phosphate, and 0.72% sulfate.

Electron microscopy. The structure of the bodies is complex. They consist predominantly of short, irregular, tapelike structures devoid of any specific orientation (Fig. 39A). Their width is approximately 17 nm and their thickness is approximately 5 nm. They have a strong affinity for lead. The central parts of the corpora amylacea contain a dense homogeneous matrix. The bodies are sharply delimited from the remaining thin seam of astrocytic cytoplasm, but are not membrane bound. There is a spatial relationship between glycogen granules and the tapelike structures (Fig. 39B). The predominant localization of the corpora amylacea is in fibrillary astrocytes in the neighborhood of blood vessels and under the leptomeninges.

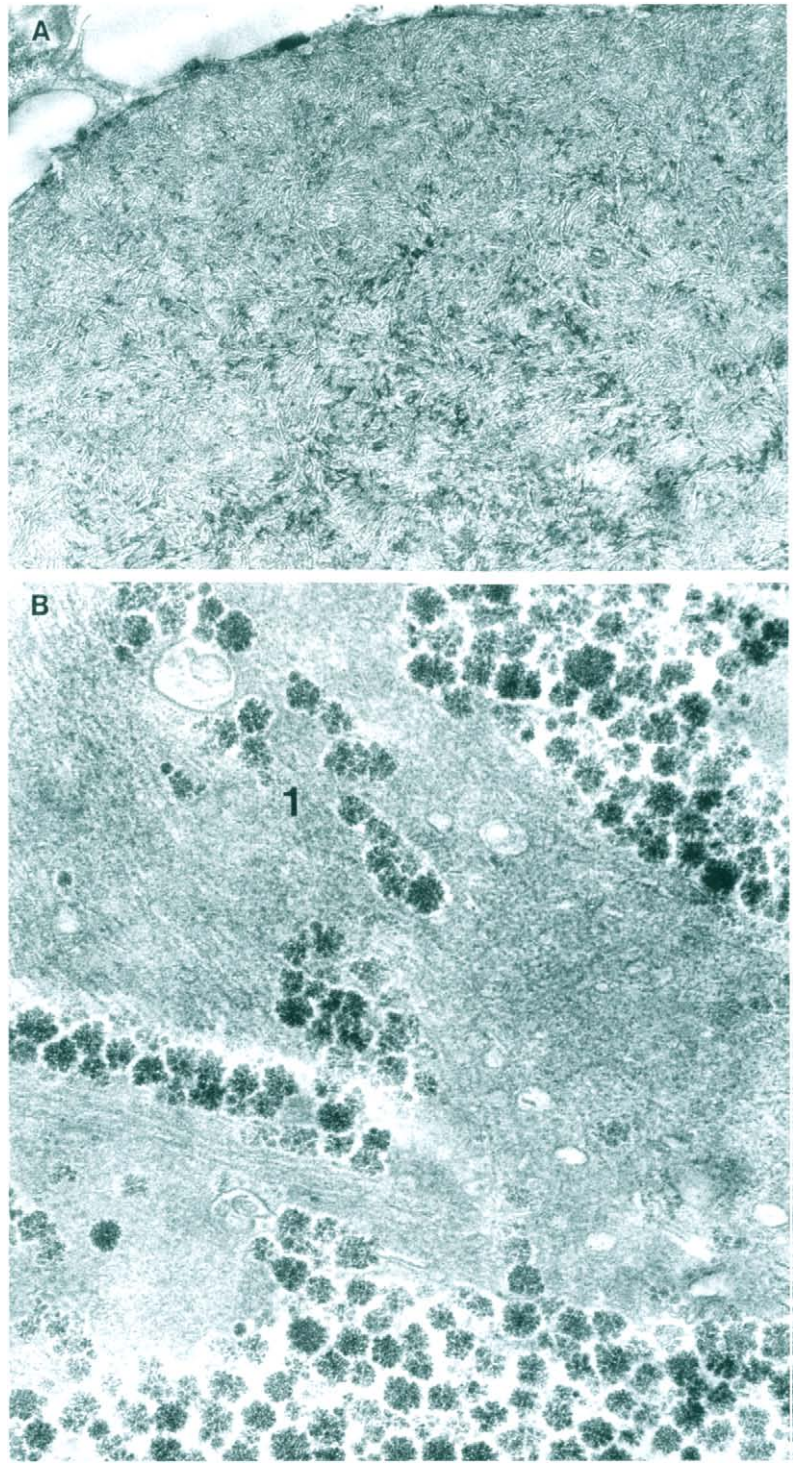


Fig. 39 Senile brain. (A) Corpus amylaceum in the process of an astrocyte, containing exclusively tapelike structures, ×8000. (B) Tapelike structures interspersed with an accumulation of α-glycogen particles, ×40,000.

Occurrence Corpora amylacea are abundant in aging brains and in degenerative diseases. They can already be seen in the third or fourth decade and multiply with age. Difficulties arise in the differentiation of corpora amylacea from other polyglucosan deposits, particularly those found other than in astrocytes. Such inclusions are found in neurons of the cerebral cortex in a variety of neurological diseases without myoclonus. They also occur in old patients free of neurological disorders in Pick's disease, in the striatum in Huntington disease, in Alzheimer's disease, and in anterior horn cells in amyotrophic lateral sclerosis (ALS). They have also been described in the peripheral nervous system (Gertz *et al.*, 1985).

Intraaxonal polyglucosan bodies are found most frequently in the nucleus gracilis, followed closely by the anterior horns of the spinal cord. Other sites, in descending order, were the lateral geniculate bodies, reticular substance, the sensory and motor nuclei of the cranial nerves, and the cerebellum and cerebral cortices. In the basal ganglia and the thalamus they were exceedingly rare. In spite of their predilection for the nucleus gracilis, these must be distinguished from axonal spheroids (see p. 511). The spheroids show weak PAS staining, if any, while the corpora amylacea always stain strongly positive.

Origin Transition from glycogen granules to the tapelike structures has been convincingly demonstrated (Suzuki *et al.*, 1979).

Polyglucosan Bodies in Animals The inclusions found in dogs of many breeds unaffected by myoclonic epilepsy, situated in the neuronal perikarya, particularly in Purkinje cells, and resembling Lafora's bodies in both their staining properties and ultrastructure, may be included in the group of polyglucosan bodies. The inclusions observed by Suzuki *et al.* (1978) in dogs of various breeds without neurological symptoms should be similarly classified. They occur in aged animals of various species (Kamiya *et al.*, 1991; Yanai *et al.*, 1994).

More problematic is the classification of inclusions seen in aging mice and cats (Suzuki *et al.*, 1979) and called "Lafora-like bodies," despite the fact that they are found only in neuronal processes and never in the perikarya. Similar Lafora-like bodies were found in various species of animals suffering from infections and intoxications.

Adult Polyglucosan Body Disease

This disease was identified by Robitaille *et al.* (1980) based on its characteristic clinical picture and the presence of polyglucosan bodies in the CNS and the peripheral nervous system.

Clinical Picture The symptoms appear in late adulthood and consist of involvement of the upper and lower motor neurons, pronounced sensory loss, predominantly in the lower extremities, disturbances of bladder function, and dementia. Clinically and biochemically, polyglucosan body disease is heterogeneous and may include patients presenting with ALS (Cafferty *et al.*, 1991; McDonald *et al.*, 1993). A juvenile familial case of polyglucosan body disease with total branching enzyme deficiency and extensive polyglucosan body storage has been reported by Schröder *et al.* (1993).

Most cases are sporadic, but familial occurrence was noted in some patients (Cafferty *et al.*, 1986). Cortical atrophy with slight involvement of the white matter was seen in CT (Vos *et al.*, 1983). The course of the disease is progressive over 3–21 years. A shorter course of several months in older patients with intercurrent cerebral infarct and heart failure was reported (Chretien *et al.*, 1993). Polyglucosan body diseases in adults, contrary to infantile cases (Andersen's disease, glucogenosis type IV, or amylopectinosis), are usually not associated with a significant deficiency of the branching enzyme. Bruno *et al.* (1993) have found a branching enzyme deficiency in a subgroup of Jewish patients and suggest that adult polyglucosan body disease has more than one biochemical basis.

Neuropathology Moderate cerebral and spinal atrophy has been reported in some cases. Numerous polyglucosan bodies, staining with PAS, silver proteinate, and iodine, are seen under light microscopy. They vary in size and shape and are distributed widely throughout the cerebral hemispheres, cerebellum, brain stem, and spinal cord (Gray *et al.*, 1988). The polyglucosan bodies are situated in the neuronal processes, astrocytes, and microglia (Wierzba-Bobrowicz and Stroinskakus, 1994), but not in the neuronal perikarya, in contrast with Lafora's bodies. They are particularly large in myelinated axons of the CNS and the peripheral nervous system. An abundance of polyglucosan bodies can be detected in the myoepithelial cells of the axillary apocrine glands (Busard *et al.*, 1991). In the white matter ill-defined areas of myelin loss and small necrotic foci were present in some cases (Chretien *et al.*, 1993). In the demyelinated areas Rosenthal fibers were present.

On electron microscopy they show the characteristic structure of polyglucosan bodies, consisting of filamentous and granular elements.

Bielschowsky Bodies

In the context of various diseases of the basal ganglia, inclusions may be found in pallidal neurons, particularly in their dendrites. They were first described by Bielschowsky (1912) in a case of double athetosis and subsequently were called Bielschowsky bodies.

Light microscopy. These bodies appear as round, ovoid, or elongated structures (Fig. 40A and B). They may contain a dense central core and a concentrically laminated shell, or a lighter center. They can reach a size of 20–50 μm, or form smaller units, 1–2 μm in diameter, occurring singly or arranged in chains. Positive staining may be obtained with iodine, Best's carmine, PAS, alcian blue, and methenamine silver; all fat stains yield negative results.

Electron microscopy. The bodies are not membrane bound. They consist frequently of a core and a shell and contain a feltwork of filamentous and tapelike structures with strong affinity to lead, particularly in the core. The tapelike structures were thought to be the result of stacking processes occurring in intracellular metabolic disorders.

Occurrence Bielschowsky (1912) found these inclusions in a case of status marmoratus of the putamen. Ule and Volk (1975) saw them in cases of isolated degeneration of the external nucleus of the globus pallidus (see p. 543). Bielschowsky bodies have

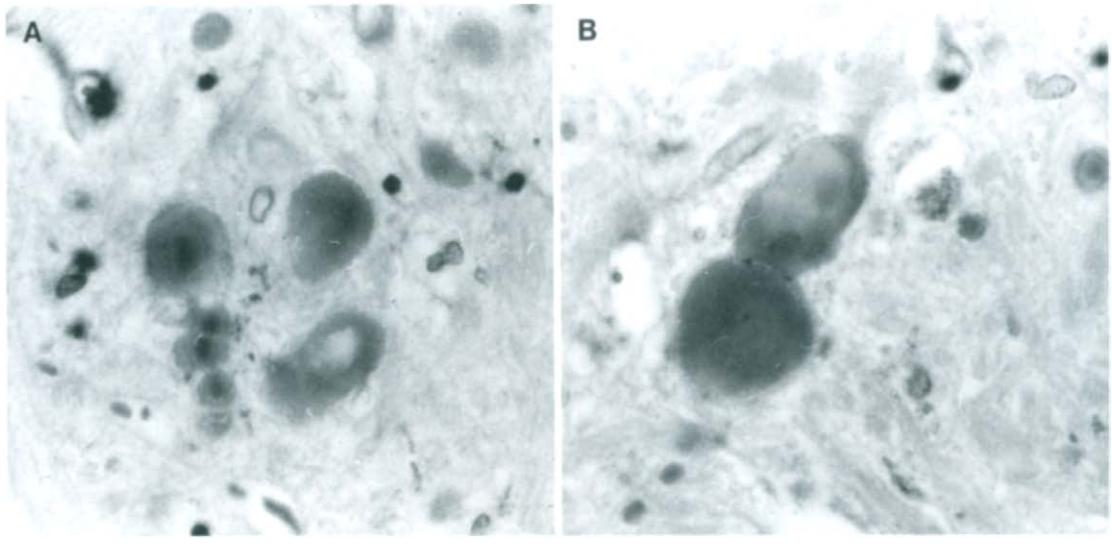


Fig. 40 Pallidal degeneration. Bielschowsky bodies in the external nucleus of the globus pallidus. Periodic acid–Schiff stain, (A) ×250 and (B) ×750. (Courtesy of B. Volk, Freiburg, Germany.)

been found in the hypothalamus, the tegmentum of the midbrain, and the medulla, as well as in the external pallidum, the substantia nigra, and the pallidothalamic, pallidonigral, and nigrostriatal tracts (Sugiyama *et al.*, 1993).

Origin Bielschowsky bodies are evidently an epiphenomenon, localized at a specific site, but occurring in a variety of conditions of different etiology and even without association with any clinical symptoms (Sugiyama *et al.*, 1993). They are an expression of a disturbance of carbohydrate metabolism that plays no part in the pathogenesis of the underlying disease. Such a role would be highly unlikely in cases of status marmoratus. It could be an indirect result of a loss of striatal influence on the pallidum, leading to stacking of polyglucosan molecules in pallidal neurons. It is not clear why this occurs only in the external nucleus.

Terminology and Definition of Polyglucosan Inclusions

Histochemical and ultrastructural investigations have confirmed that Lafora's bodies, Bielschowsky bodies and corpora amylacea consist of polyglucosans. In all of these structures, the accumulated material is the same branched polysaccharide, probably synthetized by a reversal of the branching process similar to that responsible for glycogenosis type IV (see p. 92). The significance of these structures depends on their regional distribution. The resemblance does not imply a common etiology for all conditions in which such bodies occur; it is probably a common sharing of the final path in their causative pathway (Loiseau *et al.*, 1993). Chemically and ultrastructurally, they are not easily distinguished. Nevertheless, the terms must not be used indiscriminately. The term *Lafora's*

bodies or *myoclonus bodies* can be used only in the context of myoclonic epilepsy. Only in this disease do they reach a size that is unusual in Bielschowsky bodies or corpora amylacea. There are further differences between Lafora's bodies and corpora amylacea. In polarized light both quantitative and qualitative differences appear, making histological differentiation possible. Independent of size and anisotropy, corpora amylacea are always birefringent. The cores of type II Lafora's bodies never display positive Brewster crosses. Polyglucosan inclusions can be called Bielschowsky bodies only if they are found in various diseases but exclusively in the external nucleus of the globus pallidus. Aside from their characteristic localization, their pleomorphism helps in their differentiation from other polyglucosan bodies, which are generally round.

Polyglucosan inclusions that do not conform to the definition of either Lafora's or Bielschowsky bodies and are of no pathological significance should be called simply polyglucosan bodies, in recognition of their chemical structure, or, conventionally, corpora amylacea. The contention of Ramsay (1965), that they are found exclusively in astrocytic processes, is no longer tenable. While this is undoubtedly their preferential site, they can also occur in other structures of the neuropil as well as in peripheral axons. A strict differentiation of corpora amylacea from the inclusions of the adult polyglucosan body disease is therefore impossible at present. The term *Lafora-like bodies* should, if possible, be avoided.

In the normal brain the number of polyglucosan bodies is related to increasing age. In patients under the age of 40, polyglucosan bodies can be found sporadically in cases without a neurological disorder, but in the cases of Lafora's disease their number is incomparably higher (Busard *et al.*, 1994).

Disorders of Glycosaminoglycan Metabolism (Mucopolysaccharidoses)

The mucopolysaccharidoses (MPSs) are inborn genetically determined disturbances of glycosaminoglycan metabolism. They were first described by Hunter (1917) as a rare condition in two brothers. The terminology of the early writers was based on the phenotypic appearance of the patients. Ellis (1936) coined the term *gargoylism.*

In 1952 Brante demonstrated an accumulation of mucopolysaccharides in the liver of a patient with Hurler syndrome and introduced the term *mucopolysaccharidosis.* Dorfman and Lorincz (1957) drew attention to the excessive excretion of mucopolysaccharides in the urine. The absence of mucopolysaccharidurie distinguishes the closely related mucolipidoses (see p. 137) from the MPSs.

Biochemistry and Occurrence of Glycosaminoglycans

Proteoglycans are hybrid molecules consisting of a carbohydrate moiety, the glycosaminoglycans, and a protein component. The polysaccharides form 95% or more of the molecular weight. This distinguishes them from the glycoproteins, in which the mono- or oligosaccharides form between 1% and 40% of the total weight. Because of their regular structure, composed of disaccharide units, the polysaccharide part of proteoglycans has received the name *glycosaminoglycan.* The widely accepted older term *mucopolysaccharide* is based on the fact that these substances were first isolated from mucus.

The acid mucopolysaccharides are anionic polymers that contain alternating units of an acetylated or sulfated amino sugar and a uronic acid or galactose. The periodically

repeated disaccharide units build long unbranched chains, consisting of up to 1000 units. The mucopolysaccharides were originally considered to be exclusively a component of the extracellular matrix. They are, however, present in the plasma membrane of nearly all cells and form a component of various cell organelles. In the CNS mucopolysaccharides are present in all cell types. Margolis and Margolis (1974) found the highest concentration of mucopolysaccharides in the neuronal perikarya, followed by that of the astrocytes, in the brains of cattle. The lowest concentrations appeared in the oligodendrocytes: about one fifth of the values obtained in neurons.

Of the eight known types of acid mucopolysaccharides, which differ from each other in their mucosaccharide component, their sulfate content, and the type of linkage of the mucosaccharide units, four are involved in the storage process in the MPSs. Chondroitin 4-sulfate is a polyglycosaminoglycan composed of repeated disaccharide units consisting of glucuronic acid and the amino sugar *N*-acetyl-β-D-galactosamine 4-sulfate. Dermatan sulfate is an isomer of chondroitin sulfate, the disaccharide units of which consist of α-L-iduronic or β-D-glucuronic acid and *N*-acetyl-β-D-galactosamine 4- (or 6-) sulfate. In heparan sulfate the disaccharide consists of α-L-iduronic or β-D-glucuronic acid combined with the amino sugar acetyl-α-D-glucosamine or *N*-sulfo glucosamine. In contrast with other mucopolysaccharides, the linkage of glucuronic acid with the amino sugar is effected by an α-(4)-glycosidic binding. Furthermore, it contains sulfonamide groups instead of acetamide ones. It differs from heparin in that it carries a sulfate radical only on every other amino sugar, alternating with acetyl radicals. In keratan sulfate the disaccharide units consist of α-acetyl-β-6-glucosamine 6-sulfate.

The disaccharide units of the glycosaminoglycans are broken down by a large number of enzymes into monosaccharides and inorganic sulfates. The degradation of heparan sulfate, for instance, requires three sulfatases, three exoglycosidases, and several endoglycosidases.

Pathobiochemistry and Classification of Mucopolysaccharidoses

The extracellular and membrane mucopolysaccharides are ingested into the cell through receptor-mediated endocytosis and digested by lysosomal enzymes. The disturbances of mucopolysaccharide metabolism are caused by a failure of the degradation of the repeated disaccharide units to monomers. The defects involve only one of the chain of enzymes of the catabolic pathway. The lack of genetic coding leads to the production of inactive lysosomal enzymes and the storage of mucopolysaccharides in mesenchymal tissues, viscera, and the nervous system. In all known MPSs the storage has been lysosomal. Different forms of MPSs arise according to the nature of the enzyme defect, in each of which a specific mucopolysaccharide is excreted in the urine. MPS I-S was formerly classified as type V. Type I-S and Hurler syndrome (I-H) share the same enzyme deficiency, which led to a revision of the terminology. To avoid confusion, position V has been left vacant.

All MPSs are inherited as autosomal-recessive traits, with the exception of type II (Hunter's syndrome), which is X linked. All MPSs may affect the nervous system. Types I-S, IV, and VI are not associated with mental retardation, but may present with other neurological symptoms.

Lysosomal storage is found in practically all organs. However, there are quantitative and qualitative differences responsible for variations in clinical symptomatology. A broad heterogeneity has been revealed: identical enzyme defects may lead to severe mental and physical deterioration and death during childhood or to mild forms with normal adult height. Conversely, identical phenotypes may result from mutations or different genes (Warzok *et al.*, 1990, 1992). Incubation of fibroblasts of Hurler syndrome patients with those of patients with Hunter's syndrome normalizes their metabolism. The coculture of fibroblasts from different patients with the same type of MPS does not correct the metabolic error. Normal fibroblasts, however, correct the metabolism of all types of MPSs. This correction of abnormalities suggests that the enzymes missing in diseased fibroblasts are secreted by normal cells, taken up by the abnormal fibroblasts, and incorporated into their lysosomes, where they display their hydrolytic activity.

These observations are also of diagnostic importance. If fibroblasts of patients with an unclassified MPS are incubated with those of a known type, mutual correction of their metabolism implies that they belong to different entities, while persistence of the abnormality indicates that they are the same.

Mucopolysaccharidosis I-H (α-L-Iduronidase Deficiency)

Clinically, MPS I-H can be divided into three subtypes: Hurler syndrome (MPS I-H), Scheie's syndrome (MPS I-S), and the Hurler-Scheie phenotype (MPS I-H/S). The identification of different mutations documents the expected genetic heterogeneity in MPS type I and provides molecular explanations for the broad range of clinical phenotypes observed.

Hurler Syndrome (Pfaundler–Hurler Syndrome; Gargoylism)

The first patient with Hurler syndrome was described clinically by Pfaundler (1919) and anatomopathologically by Hurler (1919).

Clinical Picture Some patients present with striking symptoms already at birth or during the neonatal period. These symptoms, apart from clouding of the cornea, are of limited diagnostic value. In most cases unequivocal symptoms appear in the second half of the first year. These include hernias, kyphosis, psychomotor retardation, a protuberant abdomen, and a large head with a strikingly dysmorphic facies, caused partially by deformities of both the cranial and facial parts of the skull. A probably fortuitous association with diastematomyelia was observed by Keohane *et al.* (1991). Due to the similarity of the facial features to the gargoyles of Gothic cathedrals, the disease received the name *gargoylism*. In this stage of the disease, one can also recognize corneal opacities, he-

patomegaly, and some contractures at major joints. The condition is progressive and the severity of the disease increases with the patient's age.

Apart from mental retardation, neurological symptoms are inconspicuous, in spite of the severity of the morphological changes in the CNS. Acute attacks of raised intracranial pressure may present as a frequently fatal encephalopathy. Chronic intracranial hypertension is a constant feature. Some patients may exhibit reduced or increased tendon reflexes associated with other pyramidal signs. A case with a clinical phenotype mimicking Friedreich's disease was reported by Jellinger *et al.* (1990). The skeletal musculature is, with few exceptions, atrophic and hypotonic. Radiological features include abnormalities of the sella and widened canals of the emissary veins, particularly in the occipital bone. Some cases show marked hydrocephalus, which can be secondary to cerebral atrophy. The possibility of an intracranial tumor should be considered. Changes in the mucopolysaccharide metabolism may be associated with an increased risk of developing neoplasms (Stockler *et al.*, 1993). The features most commonly observed on CT and MRI are diffuse changes in the white matter, hydrocephalus, cerebral or perivascular cysts, and spinal cord compression (Gabrielli *et al.*, 1992). Recurrent pneumonias and increasing cardiovascular insufficiency lead to death before the age of 14 years.

Pathology *Light microscopy.* Clear cells or gargoyle cells are present in all affected tissues: the myocardium, cartilage, tendons, periosteum, blood vessels, and cornea. In the skeletal system the epiphyseal cartilages are more severely affected than the articular ones. Strands of connective tissue traverse and destroy the cartilage and may even break through the metaphyseal plate. Instead of a regular proliferative zone, one finds isolated (or grouped in small nests) cartilage cells that show only moderate storage. On the other hand, storage is pronounced in the periosteum and the perichondrium, particularly in the marrow spaces. In the liver both Kupffer's cells and the hepatocytes have a foamy cytoplasm or contain coarse vacuoles with a concurrent decrease in the number of lysosomes. Changes in the splenic sinusoids are less pronounced. The heart valves are thickened at the edges due to a nodular proliferation of dense fibrous tissue, interspersed with large clear cells. Similar changes are found in the peri-, endo-, and myocardium. All blood vessels, particularly coronary ones, show thickening of their walls through proliferation of connective tissue with included clear cells. In the eyes the main feature is the presence of granular or clear cells infiltrating or replacing Bowman's membrane.

Electron microscopy. Lagunoff *et al.* (1962) were the first to describe cytoplasmic inclusions with clear, sometimes floccular, granular or vesicular contents in the mitral valve. Similar changes have been observed in the liver and other tissues, lymphocytes, and skin fibroblasts (Fig. 41).

Neuropathology *Gross appearances.* The leptomeninges are thickened and opaque (Fig. 42), particularly at the base (Russell, 1948). The ventricles are always dilated and may be twice their normal size. Slight cerebral and cerebellar atrophy may be present, particularly in the vermis. Russell (1948) ascribed the hydrocephalus to impaired flow of CSF through the leptomeninges, thickened by an accumulation of mucopolysaccharides. Neuhauser *et al.* (1968) observed the presence of arachnoid cysts. A striking feature of MPS I-H is the dilatation of perivascular spaces in the centrum ovale, often visible macroscopically.

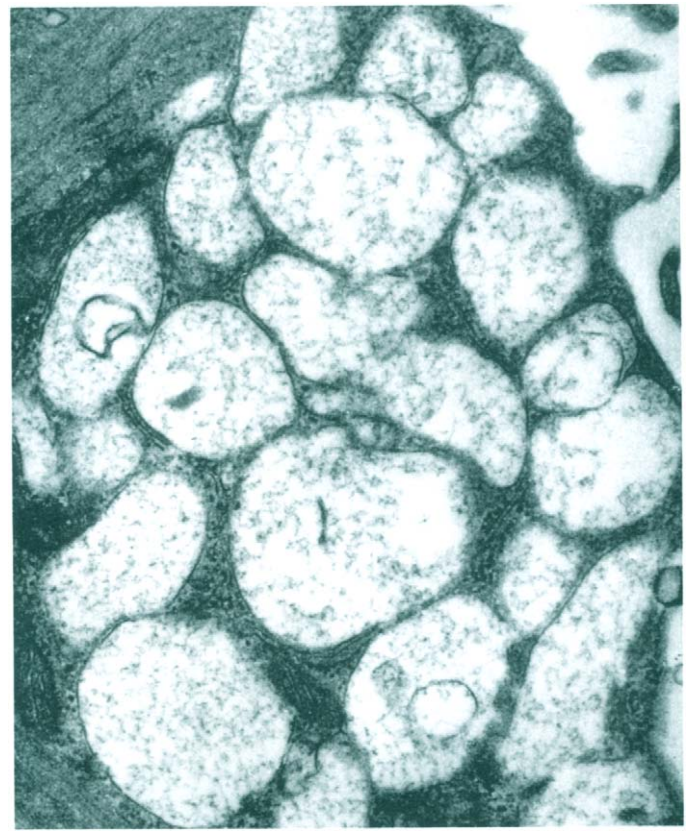


Fig. 41 Mucopolysaccharidosis I-H. Lysosomal vacuolation in a skin fibroblast, ×49,700. (Reproduced from Cervós-Navarro and Goebel, 1989.)

Light microscopy. There is an increase in collagen in the leptomeninges, with interspersed vacuolated fibroblasts and foam cells (Watts *et al.*, 1986). Considerable thickening of the intima and the adventitia is seen in the blood vessels (Fig. 43A). Most neurons in the cerebral cortex, midbrain, pons, and medulla show expansion of the perikaryon by storage of granular substances (Fig. 43B). Ballooning of the neurons is a common finding in the dentate nucleus, Purkinje cells, pyramidal cells of the cerebral cortex, and anterior horn cells of the spinal cord. Storage has been recorded in neurons of the autonomic nervous system. The nucleus is, as a rule, displaced to the periphery. There is a striking expansion of the Purkinje cell dendrites by ovoid structures, which may exceed the perikaryon in size. With the exception of these ovoids, no storage of acid mucopolysaccharides can be demonstrated in the swollen neurons.

Electron microscopy. In the neuronal cytoplasm some inclusions contain zebra bodies, approximately 1 μm in diameter. Occasionally, the lamellae are arranged concentrically. Various areas of the zebra body show a homogeneous finely granular structure. Other inclusions

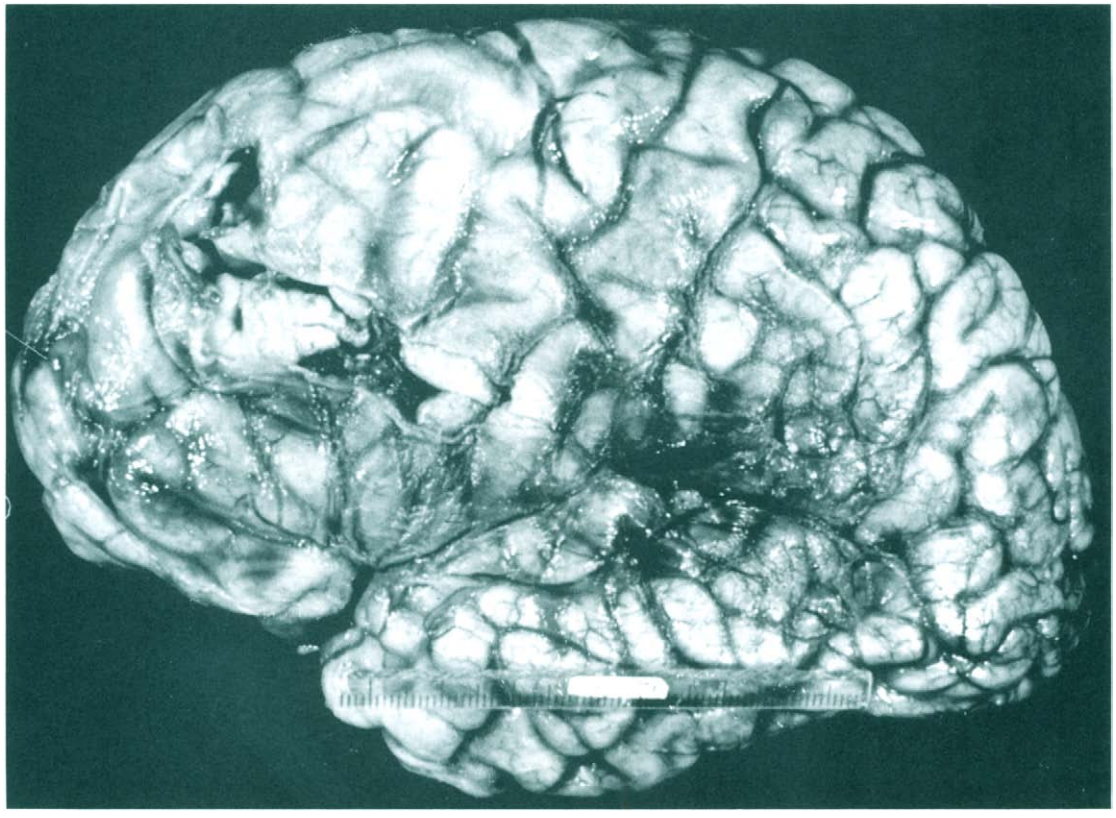


Fig. 42 Same case shown in Fig. 41. Marked fibrous thickening of the frontoparietal leptomeninges.

consist almost entirely of homogeneous granular material with some included internal membranes (Fig. 44). The zebra and granulomembranous bodies may be confluent and form large conglomerates (Watts *et al.*, 1986; Jellinger *et al.*, 1990).

A type of inclusion, less common in neurons, is the clear vacuoles, approximately 0.5 μm in diameter, surrounded by their own membranes. The meningeal and intracerebral blood vessels show swollen endothelia with an aggregation of vacuolar inclusions that rarely display lamellar profiles. The pericytes around cerebral capillaries are increased in number and filled with intracytoplasmic vacuoles, up to 2 μm in diameter. They are generally electron lucent, and occasionally contain remnants of lamellar bodies. In the adventitia of arterioles and venules, the enlarged perivascular spaces contain nests of collagen and fibroblasts.

Mucopolysaccharidosis I-S (α-L-Iduronidase Deficiency; Scheie's Syndrome)

Scheie *et al.* (1962) described a relatively benign form of MPS in adults, originally classified as type V, and later allocated to type I-S (see p. 111).

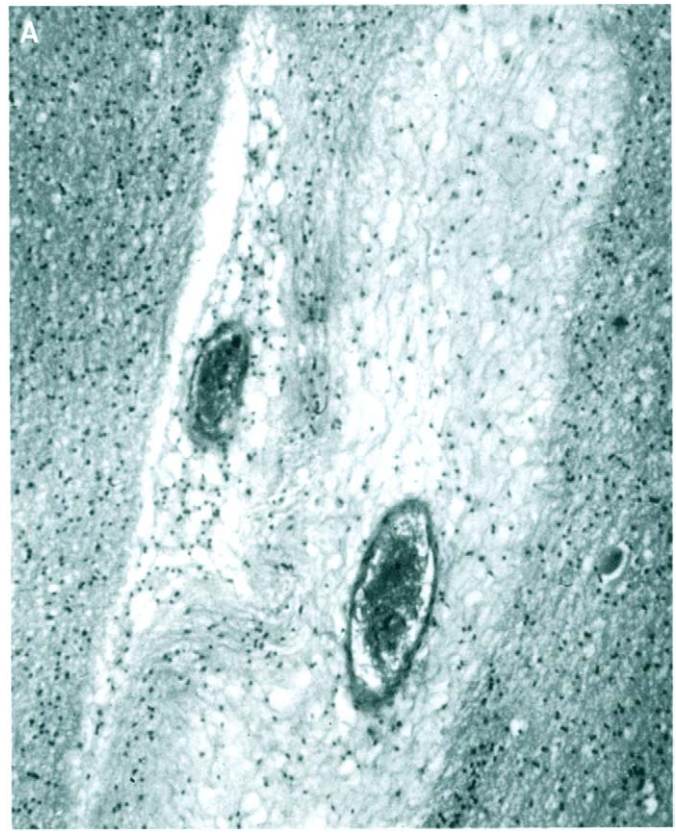


Fig. 43 Same case shown in Fig. 41. (A) Coarse reticular fibrosis in the perivascular space. Hematoxylin–eosin stain; original magnification ×120. (B) Neurons with ballooned perikarya and impregnated processes. De Myer's silver impregnation, ×1700.

Clinical Picture This condition is usually diagnosed at puberty or later. The first symptoms include restricted mobility in the joints, claw fingers, hernias, and corneal clouding. Coarse facial features are less prominent than in MPS I-H. In most patients an aortic valve insufficiency develops, but remains compensated until advanced age. In CT and MRI thickening of the dura mater at the craniocervical junction can be observed (Taccone *et al.*, 1993). Compression of the spinal cord may lead to paraparesis and other neurological deficits. Atrophy of the thenar muscles can similarly be ascribed to carpal tunnel syndrome. Patients retain normal intelligence.

Pathology *Gross appeareances.* Jellinger *et al.* (1984) found a marked whitish thickening of the heart valves.

Light microscopy. The valves contained numerous clear cells. In skin, corneal, and conjunctival biopsies (Scheie *et al.*, 1962) lesions were found to be identical to those seen in MPS I-H. There is an overgrowth of collagen in the carpal ligament.

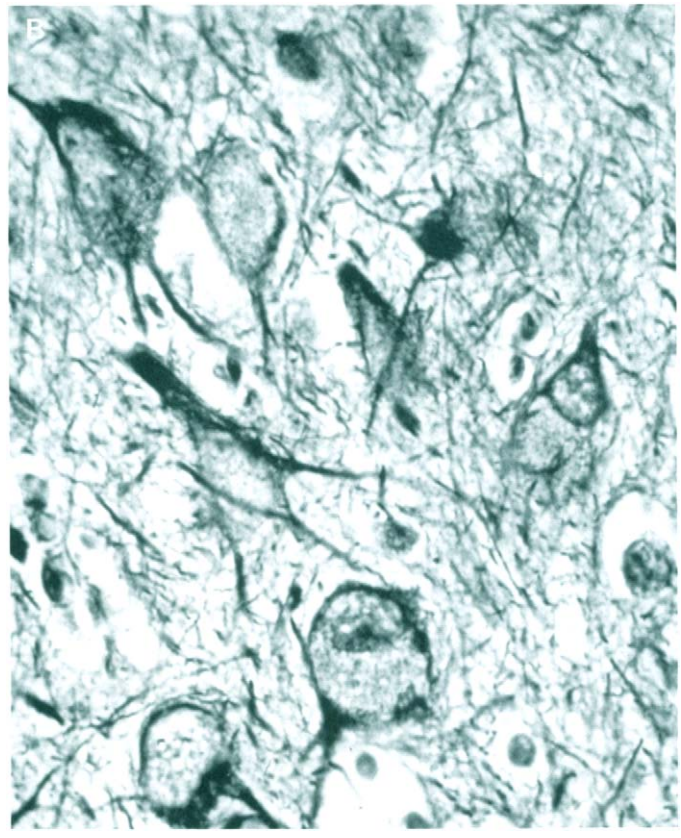


Fig. 43 Continued.

Electron microscopy. Jellinger *et al.* (1984) found not only vacuolated cells in the heart valves, but also some containing laminated zebra bodies. In skin and conjunctival biopsies the fibroblasts and the conjunctival epithelia showed membrane-bound granulofibrillary inclusions, mainly in the neighborhood of the Golgi apparatus.

Neuropathology Both the dura mater and the leptomeninges may be thickened (Paulson *et al.*, 1974). In a case described by Dekaban *et al.* (1976), the vascular adventitia in the white matter showed changes identical to those seen in MPS I-H, but the neurons were unaffected. Jellinger *et al.* (1984), however, found, apart from lipid-laden macrophages in dilated perivascular spaces, storage in neurons of the thalamus, hypothalamus, and hippocampus, in brain stem nuclei, and in spinal motor neurons, as well as in Purkinje dendrites.

Electron microscopy. Electron microscopy of these neurons revealed a complex intracytoplasmic storage of large pleomorphic lipofuscin granules, which contained lipid droplets, fingerprint-like structures, and curvilinear and zebra bodies (Fig. 45). Similar deposits were

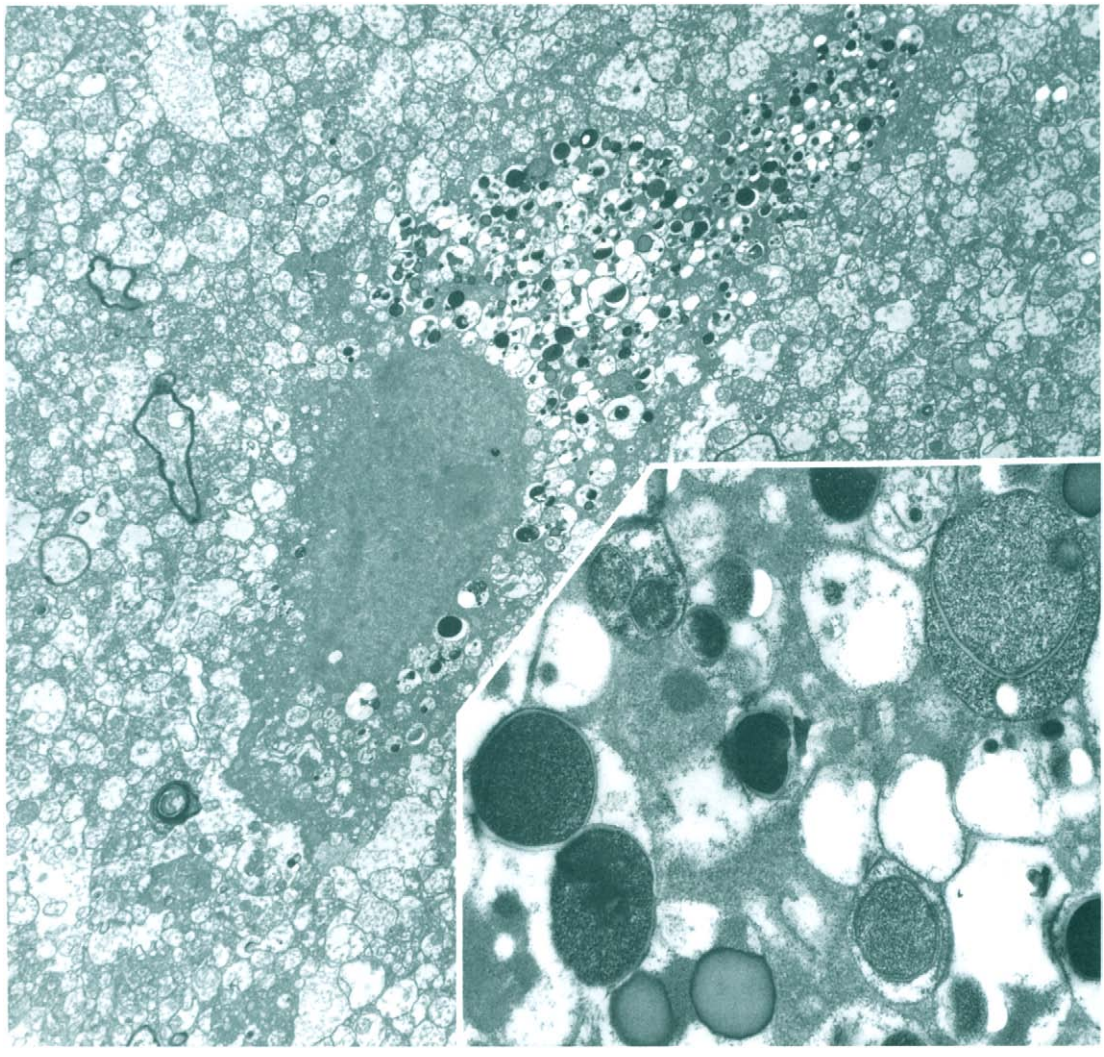


Fig. 44 Mucopolysaccharidosis I-H. A neuron from the frontal cortex with numerous pleomorphic inclusions, ×2800 (inset ×24,000).

seen in the oligodendrocytes. Vascular pericytes, dural fibroblasts (Fig.46), and Schwann cells of otherwise unremarkable peripheral nerves showed multiple vacuoles.

Intermediate Type of Mucopolysaccharidosis I (Mucopolysaccharidosis I-H/S)

A number of patients show phenotypic characteristics intermediate between the Hurler and Scheie syndromes. In this intermediate type neurological symptoms due to spinal cord compression by the thickened dura are particularly prominent (Wassman *et al.*, 1982). Neu-

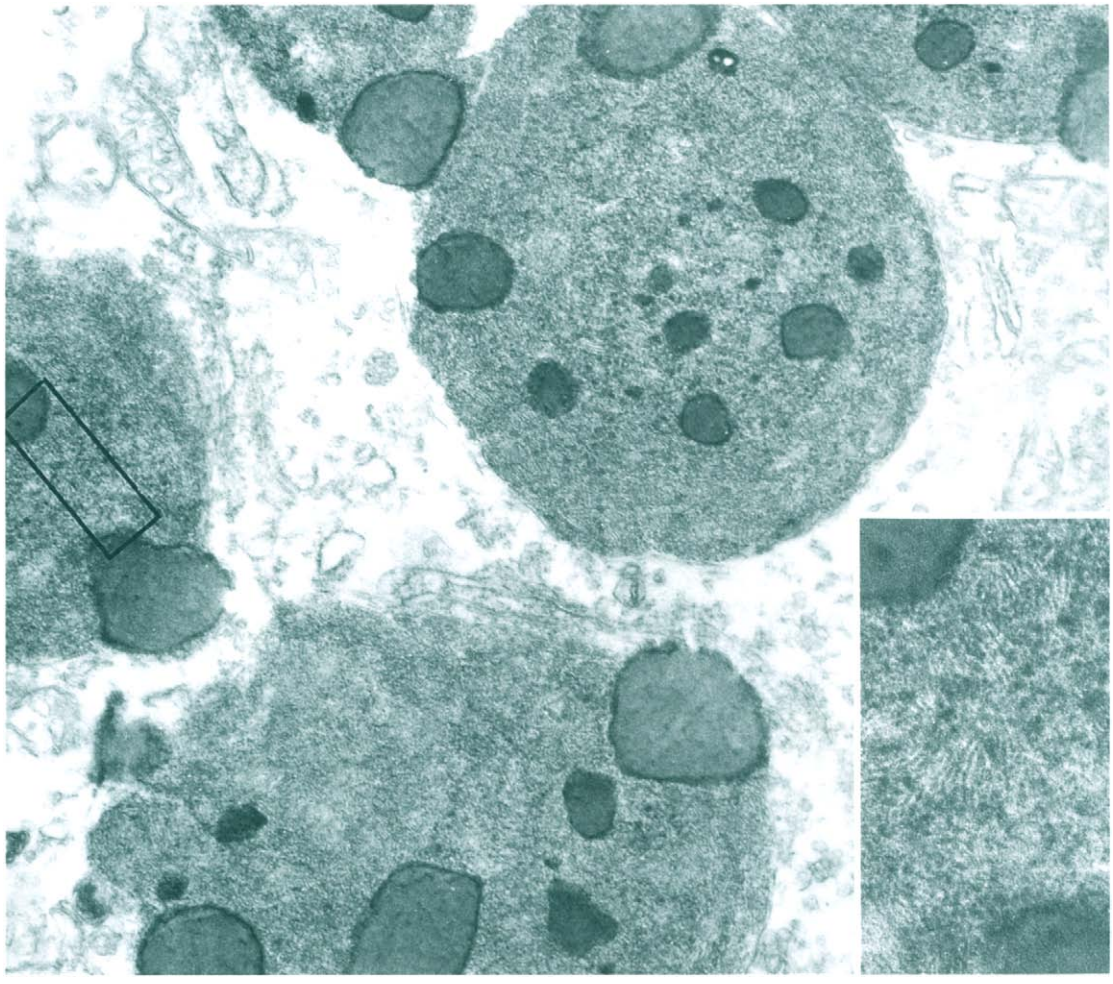


Fig. 45 Mucopolysaccharidosis I-S. A thalamic neuron with pleomorphic inclusions, ×17,000 (inset ×39,100). (Courtesy of K. Jellinger, Vienna, Austria.)

ropathologically, lesions may be found resembling those in type I-H or, more likely, those in type I-S (Wassman *et al.*, 1982).

Pathogenesis Lack of α-L-iduronidase is the cause of MPS I-H (Bach *et al.*, 1972). The same defect is found in type I-S (Bach *et al.*, 1972). As both heparan sulfate and dermatan sulfate contain iduronic acid, the storage of both substances can be explained by blockage of the catabolism at the level of the splitting off of iduronic acid (Ikeno *et al.*, 1982).

The difference in severity between the two types may be explained by the higher residual activity of α-L-iduronidase in type I-S. The deficiency of the β-galactosidase isoen-

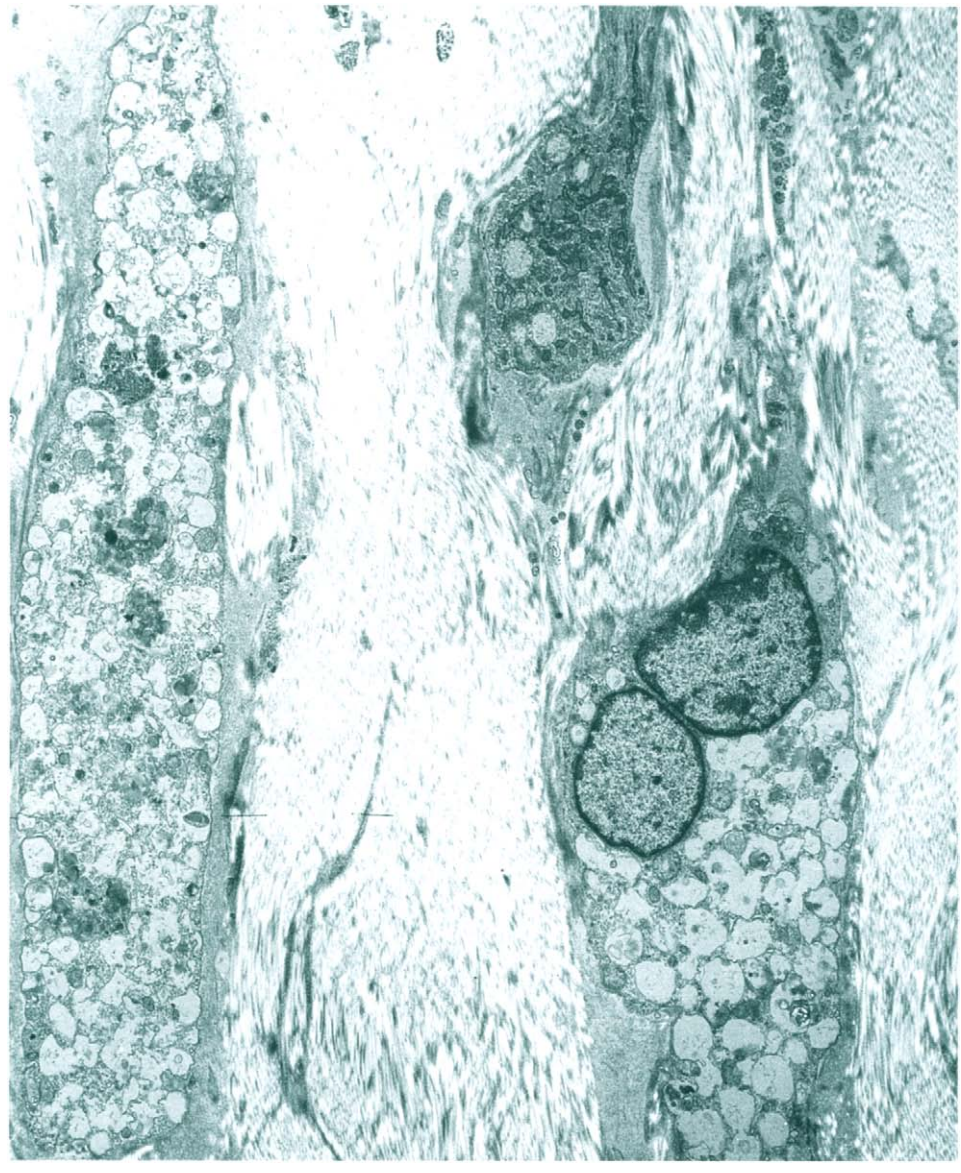


Fig. 46 Same case shown in Fig. 45. The cytoplasm of the dural fibroblasts, studded with clear vesicles, ×12,000.

zyme, originally believed to be responsible for type I-H, is a secondary phenomenon caused by the massive accumulation of mucopolysaccharides. A similar mechanism was

advocated to explain the reduction of sialidase activity in homogenates of fibroblasts from patients with MPS. The acute and chronic raised intracranial pressure is caused by the thickening of the leptomeninges, which interferes with the free flow of CSF. Disturbances of absorption at the level of pacchionian granulations have also been discussed. Even when the storage of mucopolysaccharides is highest in the meninges and the blood vessels and relatively low in the neurons, the neurological symptoms and mental retardation can be ascribed to the high concentration of heparan and dermatan sulfates. This may act through a direct or indirect influence on the composition of gangliosides (Constantopoulos *et al.*, 1980). It is remarkable that the total amount of gangliosides in the brain is only slightly raised. The increase in GM_3 and GD_3 is due to the large amounts of newly synthesized lysosomal membranes and not through the inhibition of the GM_3 sialidase caused by the accumulation of mucopolysaccharides. The zebra bodies are formed from lipid-enriched membranes of lysosomal origin. The lack of correlation between the normal concentration of gangliosides and the number of zebra bodies was attributed to large amounts of protein in the latter.

Scott *et al.* (1992) reported three mutations in the gene locus *22q11*, one that introduces a stop codon at position 70 (*Q70X*) and another that alters the P at position 533 to R (*P533R*) in the 653-amino acid α-L-iduronidase protein. Both mutations are associated with an extremely severe clinical phenotype in homozygotes. MPS I patients heterozygous for either mutation may have a wide range of clinical phenotypes. The third mutation is a single-base substitution that introduces a stop codon at position 402 (*W402X*) of the α-L-iduronidase protein. *R89Q* and *678-7g fwdarw a* were found to be present in 40% of Scheie's syndrome alleles. *678-7g fwdarw a* was found to be a mild mutation, since it was present in Scheie's syndrome in combination with a severe allele (*W402X*). This mutation appears to allow a very small amount of normal mRNA to be produced from the allele, which is likely to be responsible for the mild clinical phenotype observed (Scott *et al.*, 1993c). Besides these most common mutations, novel mutations have been described (Bunge *et al.*, 1994).

Mucopolysaccharidosis II (Iduronate 2-sulfatase Deficiency; Hunter's Syndrome)

This disease was first described by Hunter (1917) in two brothers, aged 8 and 10 years. The clinical features resemble those seen in MPS I-H, but are generally less severe and present at a later age. Heparan and dermatan sulfates are excreted in the urine. Corneal clouding is not apparent on slit lamp examination. This feature, together with the later appearance of symptoms, allows a differential diagnosis from MPS I-H. Furthermore, Hunter's syndrome is the only MPS inherited as an X-linked recessive trait.

Clinical Picture Since the report by Lichtenstein *et al.* (1972) describing a patient with a milder form of MPS II, one may distinguish between a juvenile and a late form, designated types A and B, respectively. In the juvenile form a rapid physical and mental

decline sets in between the ages of 3 and 5 years. Disturbances of hearing and skin nodules—both features found exclusively in this type of MPS and present in about one quarter of the cases—are the most common early symptoms. Phenotypically, the patients present with features similar to those in patients suffering from MPS I-H, although the deformities tend to be less prominent. In contrast with MPS I-H, the neurological abnormalities resemble a degenerative process, with hypertrophy of the musculature, hyperreflexia, and appearance of pathological reflexes. In a few years the patients develop into bedridden, spastic, quadriplegic idiots. Both generalized and petit mal seizures have been observed. These patients die of intercurrent infections, usually before the age of puberty. Children with the late form are generally normal mentally. Deafness is one of the earliest symptoms. Mild deformities appear about the age of 7 years. Only later, a Hurler-like phenotype develops. Adults may reach a maximum height of 150 cm. The head circumference is increased. The voice is hoarse; the speech, husky and guttural. The intellectual capacity is slightly impaired or normal. Papilledema indicates a raised intracranial pressure. Urinary retention as a result of cervical myelopathy was encountered by Koyama *et al.* (1994). Thickened leptomeninges may cause compression of the spinal cord (Ballenger *et al.*, 1980). An atypical RP was observed in a few cases. These patients die usually at an early adult age of increasing heart failure caused by progressive valvular disease. Occasionally, survival to the age of 60 has been recorded.

Pathology *Gross appearances.* In the juvenile form the heart, liver, and spleen are grossly enlarged, as a rule (Kurihara *et al.*, 1992). The skull bones are thickened in most cases.

Light microscopy. The cells of the heart valves and the fibroblasts of various organs show marked vacuolation. In formalin-fixed frozen sections stained with Sudan III, some vacuoles remain empty, while others retain some sudanophilic material. In the parenchyma of the liver and of most other organs, Sudan III-negative vacuoles are abundant. In the clinically transparent cornea the storage of mucopolysaccharides is prominent in endothelial cells.

Electron microscopy. Vacuoles containing floccular material and ring-shaped structures (Fig. 47) are seen in skin fibroblasts and in cells of the heart valves. The hepatocytes and the endothelia of the splenic sinusoids contain clear vacuoles with included electron-dense spheroids and ring-shaped structures, considered to be typical of mucolipidosis I (see p. 137). The presence of gargoyle cells in the clinically transparent cornea and in the conjunctiva has been confirmed ultrastructurally (McDonnell *et al.*, 1985).

Alder–Reilly bodies, consisting of membrane-bound vacuoles containing dense granular and membranous material, have been described in the blood lymphocytes. Occasional fingerprint bodies have also been recorded (Markesbery *et al.*, 1980).

Neuropathology *Gross appearances.* Clouding of the leptomeninges is seen both over the convexity and at the base of the brain (McDonnell *et al.*, 1985). Cerebral atrophy is apparent in the widening of the sulci, reduction of white matter, and ventricular dilatation (Kurihara *et al.*, 1992). Dilatation of the perivascular spaces, in both the gray and white matter, resembles that seen in Hurler syndrome. Occasionally, this perivascular cavitation may reach a considerable size, particularly in the basal ganglia (Norman *et al.*, 1959).

Light microscopy. In the juvenile form one finds ballooned cells, resembling fibro-blasts, in the leptomeninges and the perivascular spaces of intracerebral vessels, particularly in the

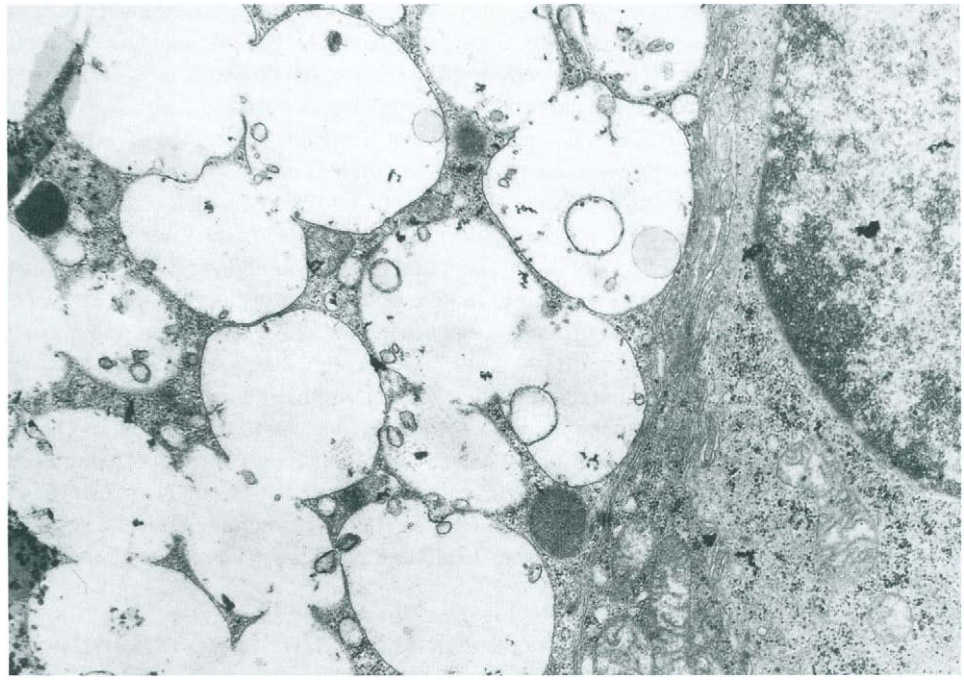


Fig. 47 Mucopolysaccharidosis II. A skin fibroblast with vacuoles containing ring-shaped structures, ×9000. (Courtesy of J. Vazquez, Pamplona, Spain.)

white matter. In the cerebral cortex the number of neurons is reduced, particularly in layers II to IV. Surviving neurons show ballooning and storage of PAS-positive material (McDonnell *et al.*, 1985). The neurons of the basal ganglia, brain stem, cerebellum, and spinal cord are similarly affected. In frozen sections stained with Sudan III, the stored material appears deep orange. Occasional metachromasia may be seen in sections stained with toluidine blue. Neuronal storage of glycolipids has been confirmed. A diffuse loss of myelin and gliosis are apparent in the white matter.

In the late form clear vacuoles containing dark granules are found in the cytoplasm of leptomeningeal cells. Some storage is present in neurons of the late form, although it is far less conspicuous than in the juvenile form. The perivascular spaces are dilated, particularly in the white matter.

Electron microscopy. Inclusions of membranous and densely granular material are found in the cytoplasm of neurons in the CNS and the peripheral ganglia. The leptomeningeal cells contain electron-lucent vesicles with membranous inclusions (Murphy *et al.*, 1983). Storage in the endothelial cells precedes the appearance of lipid storage in the cerebral neurons (Warzok *et al.*, 1992).

Pathogenesis The enzyme defect consists of a deficiency of iduronate 2-sulfatase. Heparan sulfate is stored in the liver; both dermatan and heparan sulfates, in the kidneys. The

total amount of stored mucopolysaccharide is much larger in the liver than in the kidneys. In the CNS increased amounts of the gangliosides GM_3, GM_2, and GD_3 are found.

Although the residual activity of the respective enzymes in MPS I-H and in MPS II lies well below 50%, mental retardation is less pronounced in MPS II, in both the juvenile and late forms. The possible cause of this difference was ascribed to a different composition of the stored mucopolysaccharides or to a different distribution of two types of heparan sulfate.

The iduronate 2-sulfatase gene is split into nine exons spanning approximately 24 kb. Bunge *et al.* (1992) found missense or nonsense point mutations, deletions of 1, 2, or 60 bp, and a 22-bp insertion. The broad clinical variability among the patients with Hunter's syndrome may be due to the extensive genetic heterogeneity. About 20% of the patients have deletions of the whole gene or other major structural alterations, and about 57% carry point mutations (Bunge *et al.*, 1994).

A number of mutations in the X-chromosomal human iduronate 2-sulfatase gene have been identified as the primary genetic defect leading to this condition. The mutations include different deletions and splice site and point mutations. All patients with full deletions or gross rearrangements have severe clinical presentations (Hopwood *et al.*, 1993).

Heterogeneity of DNA and RNA in Hunter's syndrome patients, suggesting deletions or rearrangement in the iduronate 2-sulfatase gene, has been reported (Annella *et al.*, 1993).

Mucopolysaccharidosis III (Sanfilippo's Syndrome; Mucopolysaccharidosis I-H/S)

Harris (1961) mentioned a case with mild mental retardation, hepatosplenomegaly, and excessive urinary excretion of heparan sulfate. Sanfilippo *et al.* (1963) described the clinical course of this case in detail and separated it from other forms of MPS.

Clinical Picture MPS III may be caused by a deficiency of four different enzymes (Kresse *et al.*, 1980). The clinical picture of the four different subtypes does not differ, however, in any essential details. Development during the first few years is usually normal. Exceptionally, symptoms already appear in infancy. The first symptoms are usually disturbances of sleep and recurrent respiratory infections. At the age of 3–4 years, changes in behavior appear. The gait becomes unsteady; speech, indistinct. By the age of 6–8 years, the children are completely out of touch with their environment and display considerable motor unrest. RP also appears occasionally.

This state may last for several years; in other cases a stage is rapidly reached with spastic quadriplegia and a vegetative state. The patients die between the ages of 10 and 20 years. In a study comprising 73 cases, Van Der Kamp *et al.* (1981) established that patients of subtype A run a more severe course than those of subtype B, with those of subtype C occupying an intermediate position. The small number of patients of subtype D, commonly of Italian extraction, is still insufficient for valid conclusions.

Pathology Despite the differences in the nature of the deficient enzymes, the phenotype is identical in all subtypes.

Gross appearances. Some cases show splenomegaly, as well as some enlargement of the lymph nodes and the mesentery.

Light microscopy. Marked vacuolation is seen in fibroblasts, hepatocytes, Kupffer's cells, renal tubules, lymph nodes, and chondrocytes. The sclera—and, less so, the cornea—contain aggregates of granular material.

Electron microscopy. Various organs contain membrane-bound vacuoles which, in the liver, may reach a diameter of 10 μm. They are mostly electron lucent or contain finely floccular material. Haust *et al.* (1971) pointed out the presence of paracrystalline mitochondrial inclusions and mitochondrial budding. They believed the mitochondria to be responsible for the formation of some of the vacuoles (Haust *et al.*, 1971). About 50% of the blood monocytes contain fingerprint bodies and tubular inclusions (Markesbery *et al.*, 1980).

Neuropathology *Gross appearances.* The brain is slightly or moderately atrophic. Severe atrophy is rare (Fig. 48A). Both the cortex and the white matter are affected (Fig. 48B) and the ventricles are dilated. The cerebellum usually shows no atrophy. The leptomeninges are considerably thickened and slimy. On light microscopy a conspicuous loss of neurons is apparent in the cerebral cortex with corresponding gliosis. All surviving neurons, particularly the pyramidal cells of layers III and V (Dekaban and Patteau, 1971), as well as the cells of the thalamus, striatum, pallidum, brain stem, perikarya, and dendrites of Purkinje cells (Fig. 49A, and B), and the Golgi cells of the granular layer (Tamagawa *et al.*, 1985), in addition to all cells of the spinal cord, dorsal root ganglia, and myenteric plexus, show distinct storage. The stored material stains with oil red O, Sudan black, and PAS and shows strong autofluorescence in ultraviolet light (Oldfors and Sourander, 1981). The dendrites of Purkinje cells are expanded by large ovoids, which can reach a diameter of 70 μm. The astrocytes also show numerous granular inclusions (Dekaban and Patteau, 1971).

Electron microscopy. Zebra bodies and concentric membranous bodies are found particularly in dendrites (Fig. 50) (Oldfors and Sourander, 1981). There appear to be differences in the ultrastructure of stored material in the different subtypes. Inclusions of fine slightly curved membranes are found in subtype A; zebra bodies, in subtype B; and membranogranular inclusions, in subtype C. This does not apply to all cases, however (Fig. 51). Inclusions also appear in glial cells, endothelia, and pericytes and in the cellular processes forming the neuropil. Conspicuously vacuolated cells are found in the adventitia of the intracerebral blood vessels (Teller *et al.*, 1964). In some cases of both subtype A (Wisniewski *et al.*, 1982) and subtype (Cervós-Navarro, unpublished observation), the neuronal inclusions may resemble those of ceroid lipofuscinosis. In peripheral nerves electron-lucent inclusions are seen in endoneurial cells.

Pathogenesis MPS III is genetically heterogeneous. Subtype A is caused by a deficiency of heparan *N*-sulfatase; subtype B by a deficiency of *N*-acetyl-α-D-glucosaminidase (O'Brien, 1982); subtype C, by an inactivity of a synthesizing lysosomal enzyme, acetyl-CoA: α-glucosaminide-*N*-acetyltransferase (Klein *et al.*, 1978); and subtype D, through a lack of *N*-acetyl-α-D-glucosaminide-β-sulfatase (Gatti *et al.*, 1982).

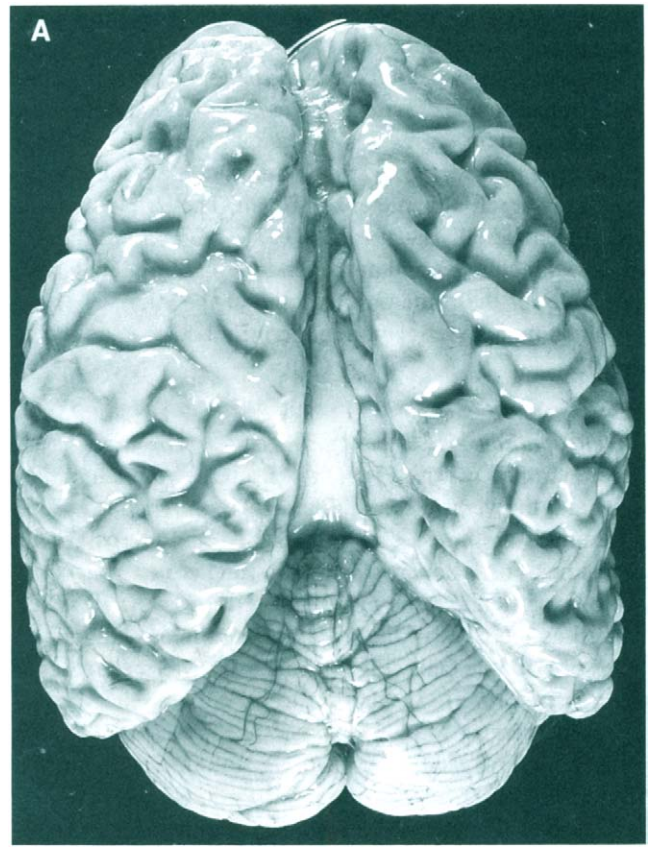


Fig. 48 Mucopolysaccharidosis III type A. (A) Cerebral atrophy and leptomeningeal fibrosis. The cerebellum appears normal. (B) The atrophy affects the cortex and the white matter. (Courtesy of R. Warzok, Greifswald, Germany.)

The enzyme defects were demonstrated in fibroblasts, and in subtype B also in the liver, kidneys, and serum. All four enzymes are involved in the catabolism of heparan sulfate, leading to an accumulation of this substance, and therefore a clinically indistinguishable phenotype. Kida *et al.* (1993) found in MPS III distinct immunostaining of a certain proportion of neurons, mainly those located in the third cortical layer.

The relatively mild skeletal abnormalities and visceromegaly compared with the severe mental retardation in MPS III may be attributed to the absent or minimal storage of dermatan sulfate.

Mucopolysaccharidosis IV (Morquio's Syndrome)

In 1929 Morquio published a case of skeletal malformation. Wiedemann (1954) coined the term Morquio–Ullrich syndrome. Maroteaux and Lamy (1965) demonstrated the ex-

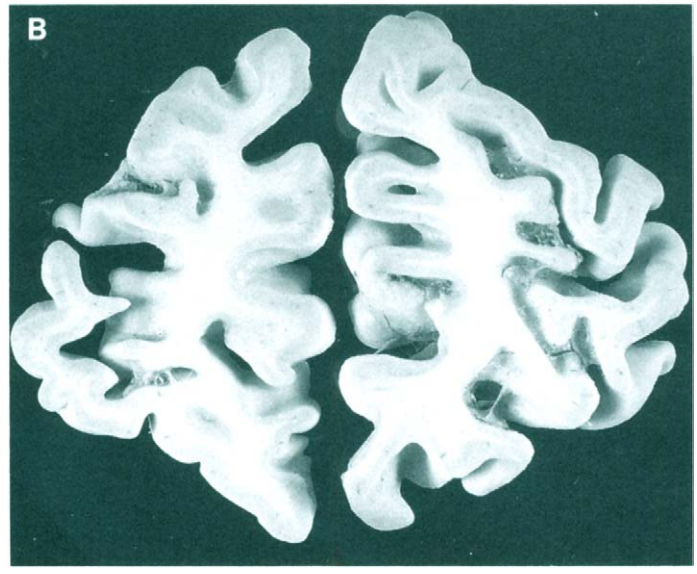


Fig. 48 Continued.

cretion of polysaccharides in the urine and included Morquio's syndrome in the group of MPSs as MPS IV A. The milder form of the condition was called MPS IV B.

Clinical Picture The first suspicious symptoms appear between the ages of 18 months and 2 years. Scoliosis, kyphosis, and genu valgum can sometimes be traced to an earlier age. At the age of 4–6 years, the clinical picture appears fully developed. The patients are dwarfs with short trunks, slight corneal opacities, and dysplastic skeletons and they excrete keratan sulfate in the urine. Repeated and careful neurological examinations should be carried out in every patient with Morquio's syndrome, to detect early signs of spinal cord compression, such as exaggerated reflexes, clonus, pathological reflexes, or sensory disturbances. With advancing age the patients develop paraparesis and quadriparesis. A picture of complete transverse section of the cord may develop. Spinal cord compression due to atlantoaxial subluxation at the craniovertebral junction is a major cause of disability and death in these patients (Ashraf *et al.*, 1991). Atrophy of the skeletal muscles is almost always present. As a rule, the patients are not mentally retarded. Patients in whom an impairment of intelligence was reported cannot with certainty be included in the framework of Morquio's syndrome. However, in two siblings with a proven diagnosis of MPS IV, mental retardation was evident (Giugliani *et al.*, 1987).

Pathology The pathological lesions are often confined to cartilage and consist of an amorphous or fibrillary change in the matrix with aggregations of foamy cells. Storage vacuoles are also present in Kupffer's cells and in the epidermis.

Electron microscopy. Vacuolar inclusions are present in Kupffer's cells and less pronounced ones are seen in hepatocytes.

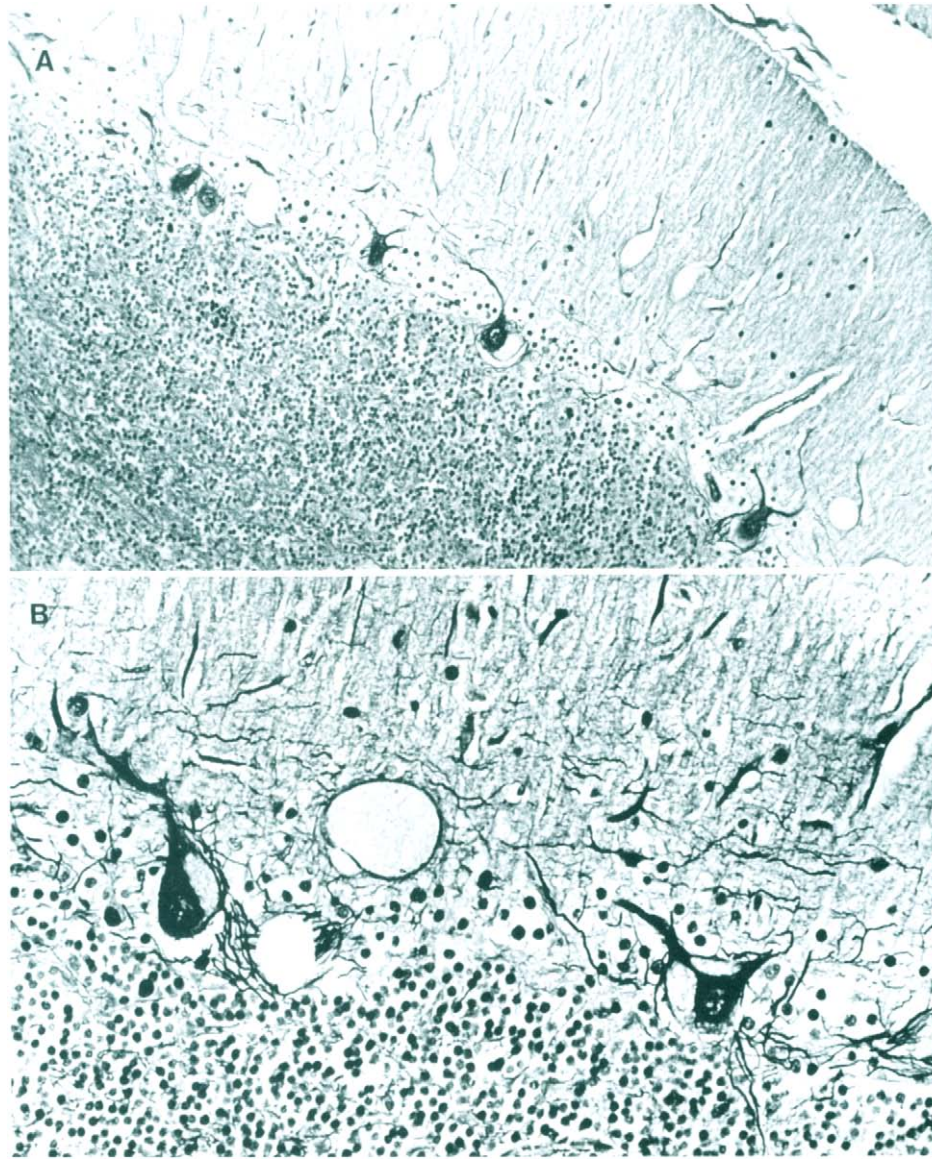


Fig. 49 Same case shown in Fig. 48. (A) Ovoid expansions of Purkinje dendrites, ×70. (B) Intracytoplasmic storage in Purkinje cells with compression of the neurofilaments. Palmgren's silver impregnation, ×140.

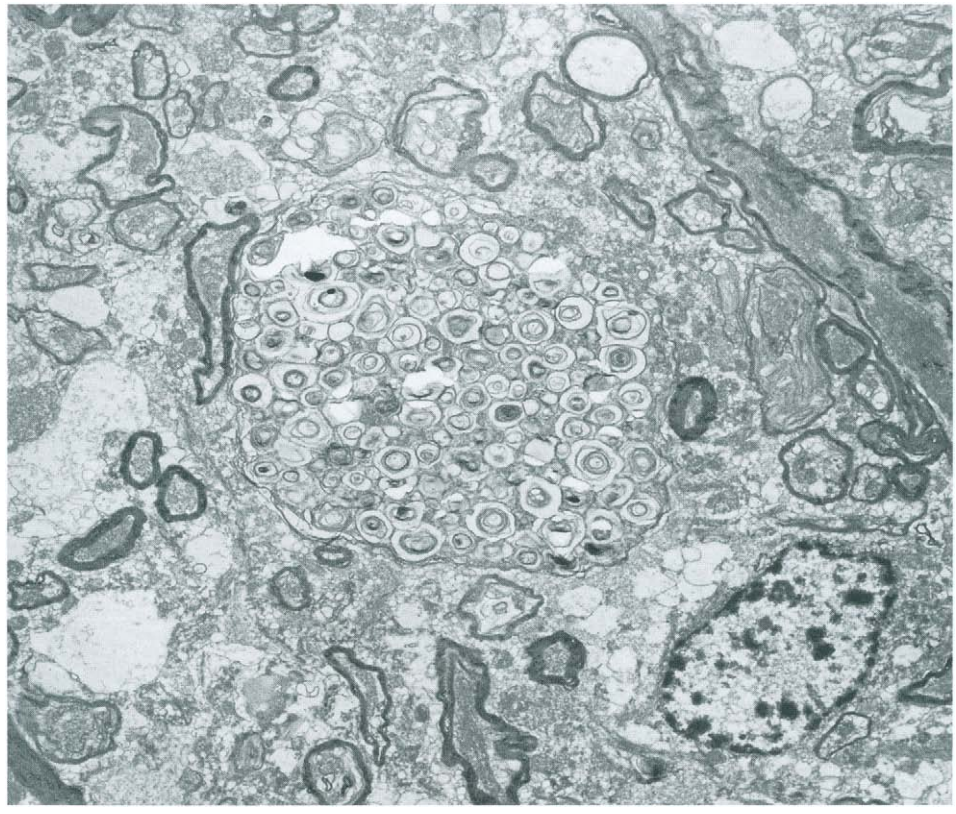


Fig. 50 Mucopolysaccharidosis III type C. A dendritic process studded with membranous inclusions, ×6000.

Neuropathology *Gross appearances.* There is no cortical atrophy, but ventricular dilatation is present. This affects predominantly the third ventricle. The medulla oblongata and the spinal cord are often deformed and flattened.

Light microscopy. No intraneuronal storage is present, as a rule. In circumscribed areas some swelling of the neuronal cytoplasm may be found with multiple small eosinophilic inclusions (Gilles and Deuel, 1971). They are strongly sudanophilic, measure 2–7 μm in diameter, and up to 10 may be found in a single neuron. Free inclusions may be found in the neighborhood of neuronophagia. Perivascular macrophages may also contain similar occlusions. Some loss of nerve cells with corresponding gliosis may be found in the thalamus, and to a lesser extent in Ammon's horn in sectors CA_2 and CA_3 (Gilles and Deuel, 1971). Spinal cord compression may lead to degeneration of the descending tracts.

Electron microscopy. Gilles and Deuel (1971) found zebra bodies and lipofuscin-like structures in swollen thalamic nuclei.

Pathogenesis Matalon *et al.* (1974) demonstrated a deficiency of the enzyme *N*-acetylgalactosamine-6-sulfatase. This, however, does not explain the disturbance of

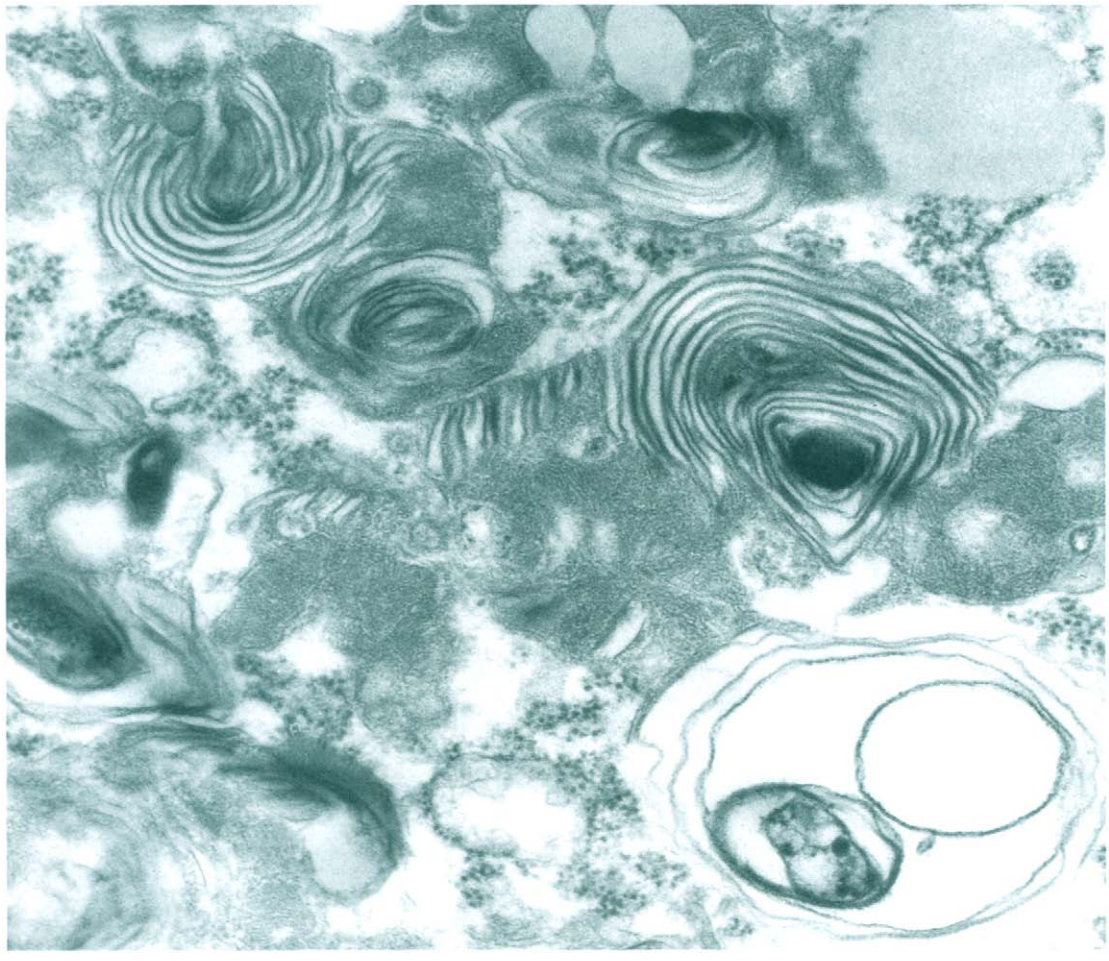


Fig. 51 Same case shown in Fig. 48. Numerous zebra bodies in the perikaryon of a parietal neuron, ×40,000.

keratan sulfate catabolism, as this mucopolysaccharide does not contain *N*-acetylgalactosamine-6-sulphatase. More relevant may be the lack of β-galactosidase, which was demonstrated in two cases of MPS IV B in which the level of *N*-acetylgalactosamine-6-sulfatase was normal (Groebe *et al.*, 1980). The absence of storage or excretion of heparan sulfate may account for the generally normal intelligence of these patients.

The anatomical cause of the spinal cord compression is the narrowing of the spinal canal at the level of a thoracic or thoracolumbar gibbus or—more commonly—an atlantoaxial dislocation. This occurs through the combination of a hyperplasia of the odontoid process with an unusual laxity of the longitudinal ligaments at the dysplastic upper end of the spinal canal.

In Morquio's syndrome type B between different β-galactosidase gene mutations, a change from W to L at position 273 (mutation *F*) in many families was the unique factor associated with clinical manifestations (Oshima *et al.*, 1991).

A clinical syndrome closely resembling Morquio's syndrome, but with a different enzyme defect, was described by Ginsberg *et al.* (1978). The defective enzyme was *N*-acetylglucosamine-6-sulfatase. This entity was given the designation *MPS VIII.*

Mucopolysaccharidosis VI (Arylsulfatase B Deficiency; Maroteaux–Lamy Syndrome)

The first description of MPS VI was probably that by Nonne (1925). Maroteaux and Lamy (1965) separated it from other MPSs on clinical and biochemical criteria. The main feature is the exclusive excretion of dermatan sulfate in the urine. Severe (VI A) and mild (VI B) forms can be distinguished. The boundary between the two forms is fluid, and thus not all cases can be accurately allocated.

Clinical Picture The severe form of MPS VI may be obvious at birth, when it manifests itself with enlargement of the skull and deformities of the thorax. Recurrent infections, hernias, and restricted joint mobility appear in infancy. Stunted growth, hepatosplenomegaly, cardiac anomalies, corneal opacities, and a coarse facies are other features.

Neurological complications can arise from hydrocephalus (Sheridan *et al.*, 1992) or from arachnoid cysts and occasionally may present as pseudotumor cerebri (Sheridan and Johnston, 1994). Spastic paraplegia caused by atlantoaxial subluxation or compression of the cord by a thickened dura mater has also been described (Pouliquen *et al.*, 1982). Normal mental development is a remarkable feature of the disease. Exceptions, however, do occur (Vestermark *et al.*, 1987). The prognosis is unfavorable due to cardiovascular complications.

The mild form manifests itself in moderately stunted growth, corneal opacities, limited joint motility, and dysplasia of the femoral head. It is often recognized only in adolescence or early adult life, although Pilz *et al.* (1979) examined two brothers aged 38 and 40 years, respectively. An intermediate form can be recognized based on the criteria of body height, radiological findings, and life span.

Pathology *Light microscopy.* In the mild form of this condition, Pilz *et al.* (1979) found vacuoles, acid phosphatase granules, and metachromatic inclusions in the peripheral lymphocytes. Granulocytes and monocytes contained excessive azurophil granules.

Electron microscopy. Clear membrane-bound vacuoles were seen in lymphocytes, fibroblasts, Schwann cells, cells of the blood vessels, and the epidermis.

Neuropathology *Light microscopy.* A biopsy of the thickened spinal dura revealed cells resembling chondrocytes, with swollen cytoplasm, which stained metachromatically with toluidine blue (Banna and Hollenberg, 1987).

Electron microscopy. The cytoplasm contained vacuoles filled with a finely reticular substance, occasional zebra bodies, and irregular concentric lamellar inclusions.

Pathogenesis This disease is based on lysosomal storage of partially degraded dermatan sulfate, and possibly also chondroitin sulfate. A deficiency of arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase) with a severe reduction of activity in the liver, kidneys, spleen, and brain has been reported (Beratis *et al.*, 1975). The various forms of the disease were attributed to different mutations of the arylsulfatase gene, as early as 1974 by Glaser *et al.*

The isolation and characterization of the arylsulfatase B gene facilitated the analysis of molecular defects underlying the different phenotypes. Besides two polymorphisms that cause V-to-M substitutions in the arylsulfatase B gene, four point mutations resulting in amino acid substitutions, a 1-bp deletion, and a 1-bp insertion have been detected (Isbrandt *et al.*, 1994). The different mutations suggest a broad molecular heterogeneity of Maroteaux–Lamy syndrome and contribute to the establishment of a genotype–phenotype correlation in this disease (Voskoboeva *et al.*, 1994). In a patient with the intermediate form of the disorder, a mutation due to a deletion of exon 5 causing a mutation of the translational stop codon to a glutamine codon (*534Q*) was detected. *534Q* mutant polypeptide with escape degradation is sorted to dense lysosomes with 9-fold higher catalytic efficiency than in the wild type.

MPS VI also has also been described in Siamese cats. A gross deletion or rearrangement of the arylsulfatase B gene, present in one affected animal, was reported by De Luca *et al.* (1993).

Mucopolysaccharidosis VII (β-Glucuronidase Deficiency)

Beaudet *et al.* (1972) and Sly *et al.* (1973) defined a new form of MPS due to β-glucuronidase deficiency.

Clinical Picture Stunted growth, hepatosplenomegaly, and deformities resembling those of Hurler syndrome appear in various degrees of expression and are associated with a variable life span. The radiological appearances are those of dysostosis multiplex. Mental retardation may be present in the first few months (Beaudet *et al.*, 1972) or may develop in later infancy (Sly *et al.*, 1973). Peripheral leukocytes contain inclusions resembling those of MPS VI (Markesbery *et al.*, 1980). Acid mucopolysaccharides are excreted in the urine, but their characterization remains controversial (Beaudet *et al.*, 1972; Bell *et al.*, 1977). Heparan and dermatan sulfates are certainly present. The enzyme defect can be demonstrated in leukocytes, fibroblasts, and serum.

Pathology Apart from the bony changes and hepatosplenomegaly, already apparent clinically, a hypoplasia or agenesis of the gonads has been described (Wilson *et al.*, 1982). Microscopic evidence of lysosomal storage was found in the bone, cartilage, lymph nodes, eyes, and adrenal and pituitary glands (Vogler *et al.*, 1994).

PAS-positive vacuoles are present in the cells of the liver and the spleen. Nodules of clear cells may be seen in the heart, blood vessels, and pulmonary septa. Vacuoles are particularly numerous in the cells of the eccrine glands of the skin (Fig. 52).

Neuropathology A hypoplastic brain (300 g at the age of 18 days) was recorded by Wilson *et al.* (1982). Light microscopy revealed vacuolation of neurons. Ultrastructurally, the vacuoles were either clear or contained granular, and in parts membranous, material.

Pathogenesis The variability of the phenotype and the immunological differences suggest different allelic mutations in individual patients. Tomatsu *et al.* (1990) found in a 6-year-old girl with MPS VII a C-to-T transition, causing a single A-to-V change at amino acid 619.

Mucopolysaccharidoses in Animals Haskins *et al.* (1983) described the defective activity of α-L-iduronidase in cats. The neurons throughout the CNS showed ballooning of the cytoplasm and contained zebra bodies. Similar findings were reported in α-L-iduronidase deficiency in dogs (Constantopoulos *et al.*, 1985). A deficiency of β-glucuronidase was reported in mice (Morrow *et al.*, 1950). These animals were symptom free. The same enzymopathy in dogs produced symptoms similar to those in human MPS VII (Haskins *et al.*, 1984).

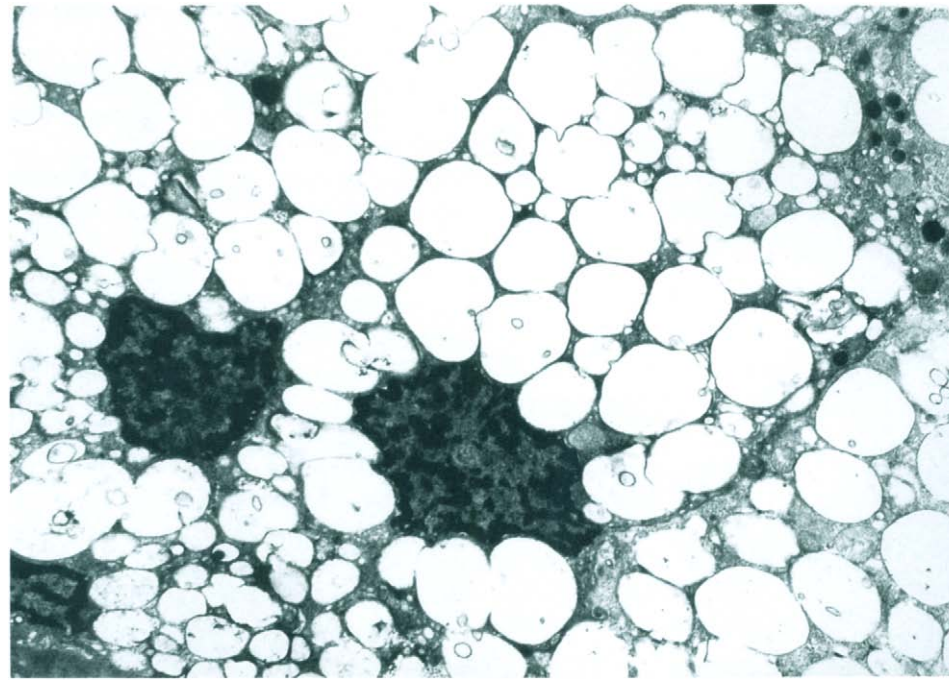


Fig. 52 Mucopolysaccharidosis VII. A skin biopsy, showing the cytoplasm of the sweat gland cells studded with clear vacuoles, ×2800. (Courtesy of J. Vazquez, Pamplona, Spain.)

Oculocerebrorenal Syndrome (Lowe Syndrome)

Oculocerebrorenal syndrome, a X-linked developmental disorder, was first described by Lowe *et al.* in 1952. Subsequent reports under the same name covered a wide range of clinical and metabolic abnormalities. The anatomopathological changes are also difficult to classify.

Clinical Picture The pleiotrophic phenotype affects the lens, brain, and kidneys. The ocular lesions, consisting of cataracts, megalocornea, and occasional keloids, are already present at birth. Psychomotor retardation follows, with hypotonia, areflexia, proteinuria, aminoaciduria, and acidosis. Arthropathies may occur, as well as irregular fevers and a cri cerebral. The reports of glycosaminoglycan excretion in the urine are contradictory, but most authors found increased concentrations of these substances (Kieras *et al.*, 1984). Elevated maternal serum α-fetoprotein appear to occur at a higher than expected frequency in pregnant women carrying a fetus with oculocerebrorenal syndrome. The mechanism of elevation of α-fetoprotein may be related to fetal renal tubular dysfunction (Miller *et al.*, 1994). Periventricular and patchy white matter lucencies were detected by MRI (Pueschel *et al.*, 1992; Carroll *et al.*, 1993).

This syndrome was initially reported only in boys, but later it was found to occur also in girls. The course of the disease is protracted and patients may reach adult age with careful treatment. The main causes of death are renal failure and intercurrent infections.

Pathology Aside from cataracts, the ocular lesions include changes in the cornea and the ciliary bodies. In advanced cases diffuse tubular, with minimal glomerular, lesions can be seen in the kidneys. Severe atrophy of the lower leg muscles and circumscribed lipomatosis of the soleus muscle were also observed.

Electron microscopy. Fibroblasts contain clear vacuoles or electron-dense inclusions (Wisniewski *et al.*, 1984). Lopez-Garrido *et al.* (1985) described abnormal mitochondria in the proximal renal tubules.

Neuropathology *Gross appearances.* While some patients show no abnormalities in the CNS, a variety of lesions have been reported in others. These include hydrocephalus, cerebral and cerebellar atrophy (Giannakopoulos *et al.*, 1990), thinning of the corpus callosum, and meningeal fibrosis, macrogyria, and microgyria.

Light microscopy. Diffuse fibrosis of the leptomeninges is seen. The cerebral cortex shows rarefaction of the molecular layer, shrunken nerve cells, and moderate hyperplasia of Alzheimer's type II astrocytes. Central chromatolysis was observed by Giannakopoulos *et al.* (1990). Foci of acute demyelination may be found in the white matter, interpreted as secondary. In the basal ganglia changes in the blood vessels consist of proliferation, granulomas invading the vessel wall, and calcification (Fig. 53A and B).

A fine diffuse gliosis is present in the subcortical white matter with subependymal accentuation. Loss of Purkinje cells may be seen in the cerebellum, as well as glial nodules and microgranulomas in the cerebellar white matter and the pontine tegmentum, with sparse perivascular lymphocytic infiltration.

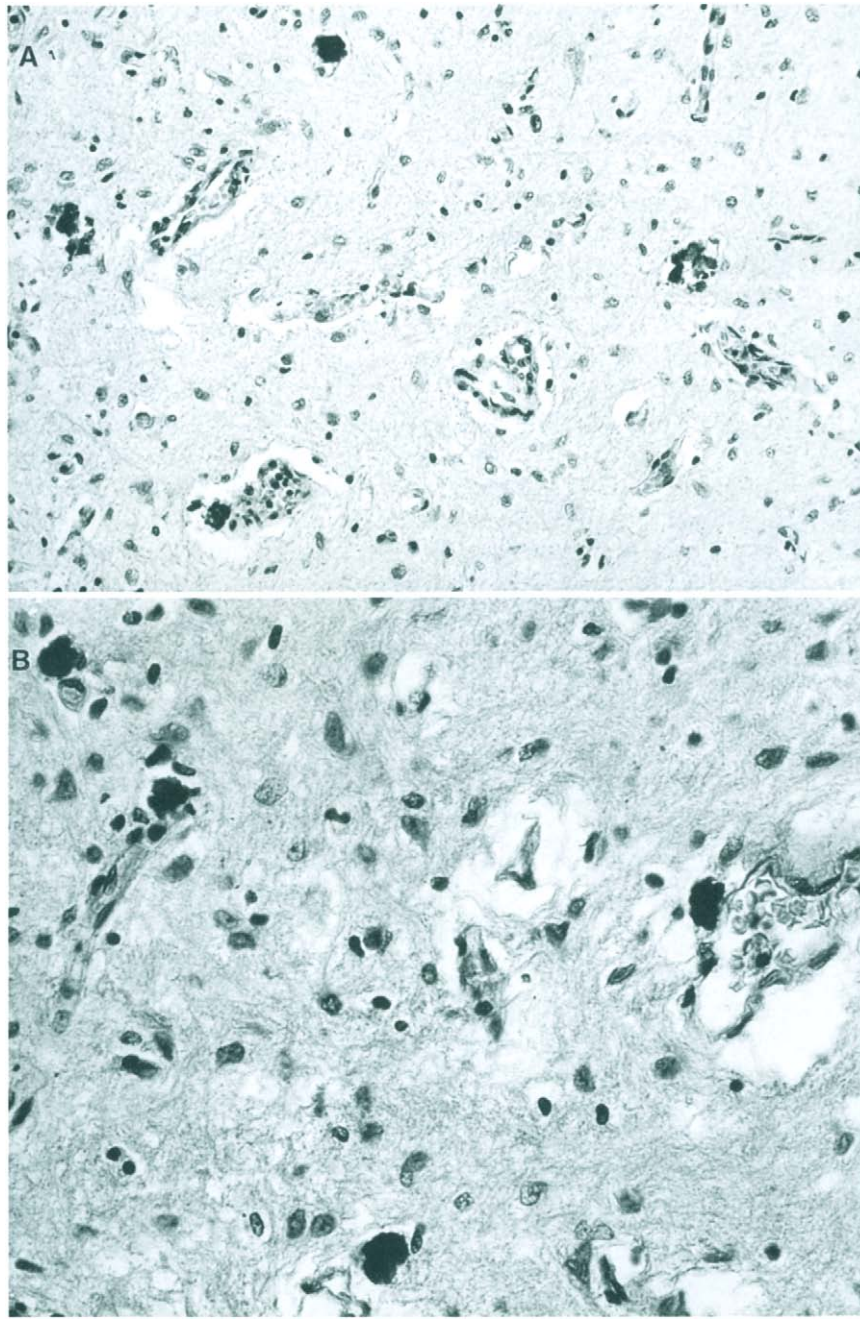


Fig. 53 Oculocerebrorenal syndrome. A basal ganglia, showing calcification in the walls of proliferated blood vessels. Nissl stain, (A) ×200 and (B) ×450. (Courtesy of R. Warzok, Greifswald, Germany.)

The long and short tracts in the spinal cord show a slight loss of myelin with prominent gliosis. Minor changes in peripheral nerves were interpreted as part of a "dying-back" process.

Pathogenesis None of the numerous metabolic disorders reported in this syndrome can be considered the primary cause of the disease. The possibility of a genetic defect leading to increased activity of the enzyme nucleotide pyrophosphatase and hence to inhibition of synthesis of glycosaminoglucans (Yano *et al.*, 1985) is incompatible with the observation of urinary excretion of chondroitin 4-sulfate, particularly in the acute stage of the disease (Kieras *et al.*, 1984; Wisniewski *et al.*, 1984).

The *ORCL* locus has been mapped to Xq25–q26 by Attree *et al.* (1992). Two different transcripts were found that map to the region around the Xq25–q26 breakpoint (Okabe *et al.*, (1992). The gene encodes a protein highly homologous to inositol polyphosphatase, suggesting that *ORCL* may be an inborn error of inositol phosphate metabolism (Attree *et al.*, 1992). Leahey (1993) detected by direct sequencing a candidate gene, *ORCL*, for the oculocerebrorenal syndrome a nonsense mutation at base 2746.

Several reports of affected females without obvious chromosomal abnormalities suggest genetic heterogeneity of the Lowe phenotype. Moraes *et al.* (1991) postulated that a defect of mitochondrial metabolism could be involved in the pathogenesis of the X-linked disease.

Mucolipidoses

Spranger *et al.* (1968) reported some "intermediate cases" between MPSs and the sphingolipidoses and demarcated them from other "intermediate" cases that they found difficult to classify. For these Spranger and Wiedemann (1970) coined the term *mucolipidosis I.* They added to this group I-cell disease (mucolipidosis II) and pseudo-Hurler polydystrophy (mucolipidosis III).

Spranger and Wiedemann defined the mucolipidoses as a group of diseases phenotypically resembling the MPSs, but without excretion of mucopolysaccharides in the urine. They showed storage not only of mucopolysaccharides, but also of glycolipids and/or sphingolipids in the viscera. Using this definition, a number of conditions can be included: GM_1 gangliosidoses I and II (see p. 302), multiple sulfatase deficiency (see p. 271), Farber's lipogranulomatosis (see p. 293), fucosidosis, and mannosidosis. In view of the deficiency of sialidase, Strecker *et al.* (1977) proposed the term *sialidosis.* Sialidase deficiency, however, appears in its pure form only in mucolipidosis I, while in mucolipidoses II and III it is only one of many hydrolases involved. The term *sialidosis* is therefore appropriate only for diseases in which a lack of sialidase is the primary defect (see p. 68).

We have included mucolipidosis I in the group of diseases characterized by sialidase deficiency and excretion of sialooligosaccharides in the urine (see p. 68). Fucosidosis and mannosidosis are also considered among the oligosaccharidoses. We have left GM_1-gangliosidosis, in view of the conventional terminology, among the gangliosidoses. Multiple sulfatase deficiency is associated with the urinary excretion of mucopolysaccharides and therefore does not belong to this group by definition. In view of the nature of the stored substances, it is described with the metachromatic leukodystrophies (see p. 271). Farber's disease belongs to the group of sphingolipidoses (see p. 293).

Mucolipidosis II (I-Cell Disease)

Mucolipidosis II was first described by Leroy and De Mars in 1967. The authors called it I-cell disease (inclusion cell disease) because of the peculiar appearance of cultured skin

fibroblasts under phase contrast microscopy, in which they are seen to be studded with coarse granular inclusions.

Clinical Picture The patients show a Hurler-like appearance soon after birth. Stunted growth, psychomotor retardation, and recurrent respiratory infections are the main symptoms. The tongue and the gingivae are hypertrophic, and multiple bony changes can be seen on X-rays. Hepatomegaly is inconspicuous. Epileptic seizures may occur.

Gilbert *et al.* (1973) distinguished three forms of the disease: a malignant infantile form, leading to death by the age of 3 years; a severe form, with prominent symptoms and death between the ages of 4 and 6 years; and a mild juvenile form, with longer survival and less obvious lingual and gingival hypertrophy.

Pathology *Gross appearances.* The heart is hypertrophic; the pericardium and the valves, thickened.

Light microscopy. The fibers of the heart muscle are vacuolated. The pericardium, endocardium, and heart valves contain vacuolated histiocytes. Apart from the vacuolated histiocytes, the lungs contain lipid granulomas (Gilbert *et al.*, 1973). The epithelial cells of the renal glomeruli are vacuolated and their basal membranes are thickened.

In the skin, skeletal muscles, and particularly the tongue one finds focal aggregates of foamy histiocytes. Endochondral osteogenesis is disturbed and both fibroblasts and chondrocytes show prominent vacuolation. An absence of hydrolase activity in the vacuoles is a striking feature of all affected cells. In contrast with the MPSs, the hepatocytes and Kupffer's cells are not significantly involved. The number of type I fibers in the skeletal muscles is reduced (Kula *et al.*, 1984).

Electron microscopy. The cytoplasm of chondrocytes contains abundant, electron-lucent, membrane-bound inclusions. These contain fine reticular and granular material. In cultured fibroblasts the inclusions are more pleomorphic (Terashima *et al.*, 1975). Some contain tightly packed, sometimes circular, osmiophilic membranes as well as some homogenous osmiophilic material, while others appear almost empty and are electron lucent. Fibroblasts, endothelial and perithelial cells, and macrophages in various organs show the same pleomorphic inclusions as cultured fibroblasts (Gilbert *et al.*, 1973). The heart muscle contains numerous inclusions with concentric lamellar structures, myelin figures, and multivesicular bodies. Some inclusions are electron lucent and contain floccular material. The epithelial cells of the renal glomeruli show clear electron-lucent inclusions, while in the endothelial cells electron-dense membranous inclusions predominate (Martin *et al.*, 1984). The prominent vacuolation of lymphocytes may be of additional help in making the diagnosis.

Neuropathology *Gross appearances.* The leptomeninges are thickened, cloudy, and gelatinous. The cerebral cortex and the cerebellar vermis are mildly atrophic.

Light microscopy. The leptomeninges are infiltrated with storage cells, particularly around the blood vessels. The adventitial cells of the blood vessels in the CNS and the

peripheral nervous system also show conspicuous changes. The cells of the cerebral cortex, as well as the Purkinje and granule cells in the cerebellum, are appreciably reduced in number. The neuronal cytoplasm of the dorsal root ganglia contains groups of osmiophilic granules.

Electron microscopy. The neurons of the cerebral cortex and the Purkinje cells contain scanty inclusions, if any. Those present show a fine, granular, homogenous matrix or contain lamellae with curvilinear and circular profiles. In the motor neurons of the spinal cord (Martin *et al.*, 1984) and the dorsal root ganglia, numerous inclusions are present, with electron-dense lamellar bodies, myelin figures, and zebra bodies. Similar structures may be seen in the pericytes of cerebral capillaries. In peripheral nerves multiple vacuolar inclusions are present in the Schwann cells, endoneurial fibroblasts, and perineurial cells (Kula *et al.*, 1984). The vacuoles are generally empty, except for a few granules or lamellar structures.

Pathogenesis The bony changes and the cardiac symptoms are easily explicable by the morphological findings. The mental retardation, on the other hand, is difficult to correlate with the neuropathology, except perhaps in long-term survivors.

Hickman and Neufeld (1975) held the view that enzymes restricted in their activity cannot enter the lysosomes and therefore cannot take part in lysosomal activity. This may be due to oversialization of the enzymes, caused by a lack of sialidase. It was also pointed out that faulty endocytosis can be due to lack of a recognition mechanism of the hydrolases (Hasilik and Kornfeld, 1993).

The unknown mutation eliminates or severely reduces the activity of phosphotransferase. As a result, newly synthesized lysosomal enzymes do not acquire mannose 6-phosphate residues and are quantitatively secreted by many cell types. This results in gross cellular deficiencies of most lysosomal enzymes (Glickman *et al.*, 1993).

Mucolipidosis III (Pseudo-Hurler Polydystrophy; I-Cell Disease Type 2)

Maroteaux and Lamy (1966) described four patients with "Hurler's pseudodystrophy" whose condition phenotypically resembled MPS I-H (see p. 112) but ran a slower clinical course and did not excrete mucopolysaccharides in the urine. They drew attention to other cases in the literature hitherto considered unclassifiable, but in their opinion representing the same clinical syndrome.

Clinical Picture Children with this disease attract attention at the age of 1–4 years, when slowing growth and stiffening of the joints become apparent (Brik *et al.*, 1993). In most cases coarsening of the facial features is obvious, but it may be minimal. The cornea frequently shows fine clouding. Occasionally, hypoplasia of the odontoid process and carpal tunnel syndrome may be found. Mental retardation may be slight or absent. The disease is slowly progressive up to the age of puberty and stabilizes thereafter. The prognosis is good.

Pathology So far no patient with an established diagnosis has died. Observations have been confined to biopsy material and fibroblast cultures.

Light microscopy. Using light microscopy, Maroteaux and Lamy (1966) found cells with empty vacuoles in the bone marrow. Fibroblast cultures from some of the patients show metachromatic staining of the cytoplasm with toluidine blue and alcian blue stains. Vacuolation of the peripheral lymphocytes is present in 30% of the cases.

Electron microscopy. Using electron microscopy on cultured fibroblasts, Quigley and Goldberg (1971) found membrane-bound vacuoles in the cytoplasm. They also found large amounts of lamellar material, similar to that seen in sphingolipidoses. They were left with the impression that vacuoles arise from the Golgi apparatus.

Pathogenesis Both mucolipidoses II and III show mutations of the enzyme *N*-acetylglucosamine-1-phosphotransferase. In mucolipidosis II this enzyme is significantly smaller than normal and is deficient against both natural and artificial substrates. In mucolipidosis III the enzyme is considerably larger than normal and is active against small substrates, but incapable of binding natural lysosomal glycoprotein substrates (Ben-Joseph *et al.*, 1987).

Mucolipidosis IV

Berman *et al.* (1974) described a new syndrome, which he called mucolipidosis IV. Further reports followed. All patients were children of Ashkenazi Jews. Adult cases were also reported (Zwaan and Kenyon, 1981), not all of the patients being of Jewish descent (Zwaan and Kenyon, 1981). The allocation of these cases to the group of mucolipidoses rests on purely morphological criteria and does not appear justified on enzymological grounds. Nevertheless, the condition is considered here in accordance with current terminology.

Clinical Picture The main symptom is corneal clouding, which may already be apparent at birth. Psychomotor retardation becomes obvious toward the end of the first year. Facial features are heavy, but without Hurler-like coarseness. There are no abnormalities of growth or skeletal deformities. No mucopolysaccharides are excreted in the urine.

Pathology *Light microscopy.* Vacuoles that stain intensely with toluidine blue are seen in the cytoplasm of conjunctival epithelia and in fibroblasts. In the majority of patients, vacuolation is observed in cells of the bone marrow, but this is not always present. Cultured skin fibroblasts contain inclusions 1–2 μm in diameter. They stain weakly with oil red O as well as toluidine blue, but do not stain metachromatically. In a 19-week fetus inclusions were present in epithelial and endothelial cells, as well as in parenchymal cells of the liver, kidneys, and placenta.

Electron miscroscopy. The vacuoles of the corneal and conjunctival epithelia, epidermis, and sweat glands (Fig. 54A) show a wide range of intracytoplasmic inclusions

(Cervós-Navarro and Goebel, 1989, Chitayat *et al.*, 1991). In most instances they form membranous bodies without a regular concentric structure. Granular material of low density and empty vacuoles (Fig. 54B) are also seen. Fetal tissues contained similar inclusions.

The exceptionally strong involvement of the conjunctival epithelium in mucolipidosis IV is a useful morphological criterion in the differential diagnosis between mucolipidoses II and III.

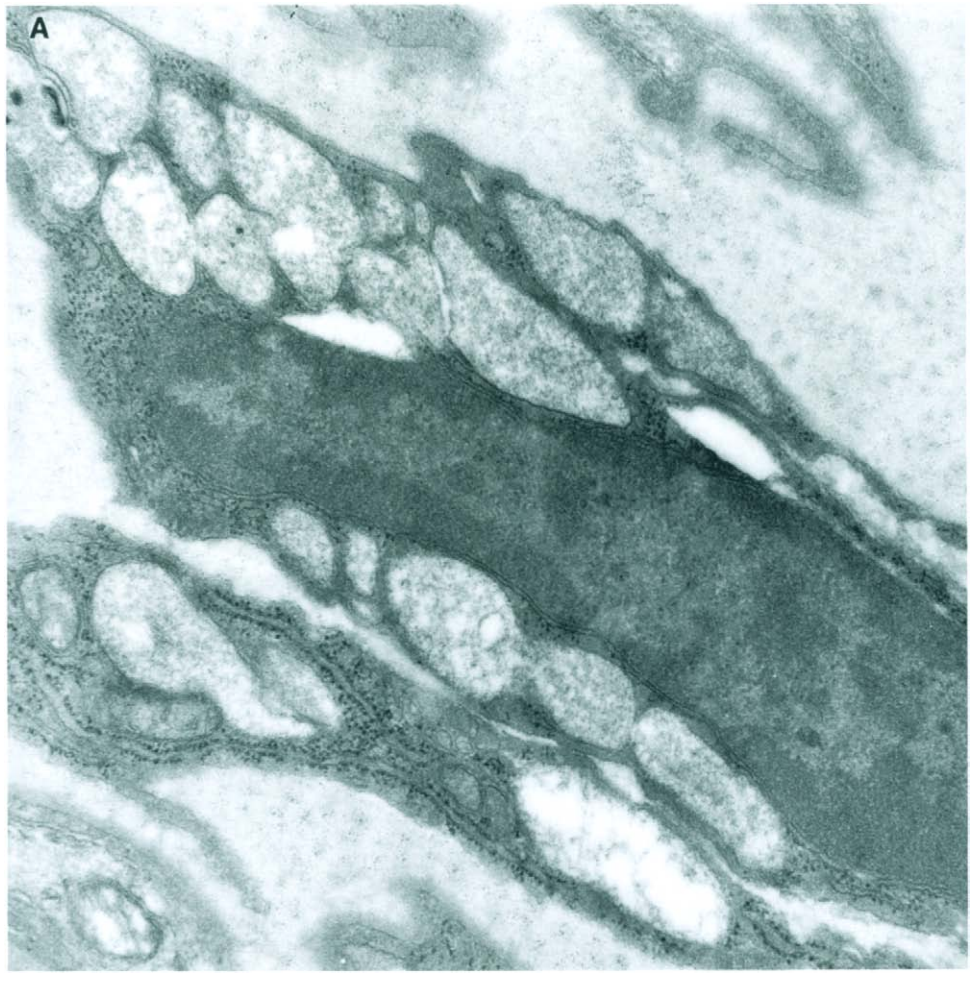


Fig. 54 Mucolipidosis IV in the skin. (A) Multiple vacuoles in the epithelium of a sweat gland, ×7600. (B) Vacuolar inclusion in Schwann cells, ×14,300. (Reproduced from Cervós-Navarro and Goebel, 1989.)

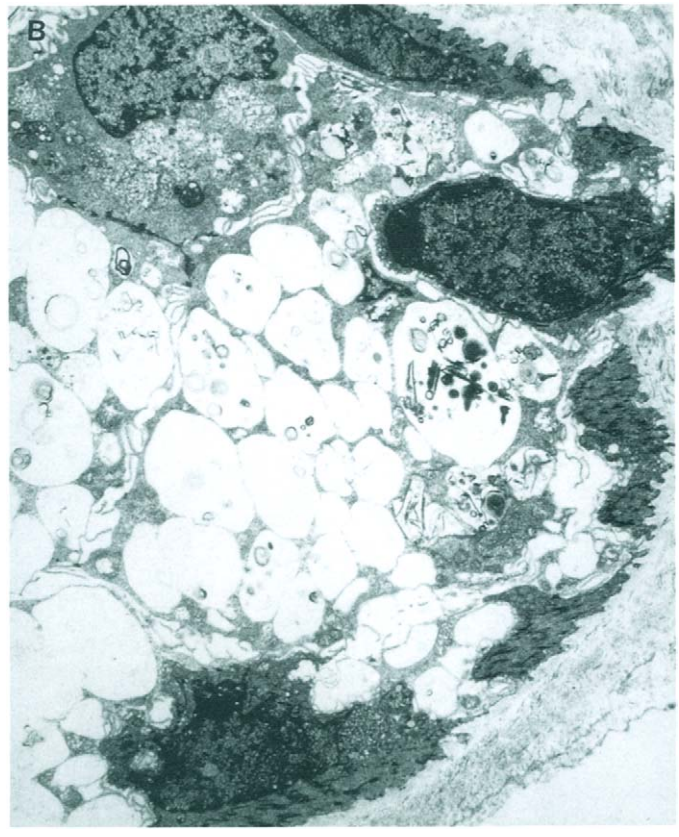


Fig. 54 Continued.

Neuropathology *Light microscopy*. In the CNS neuronal and axonal loss is marked by astrocytosis. In the brain and the spinal cord accumulations of granules are seen in some neurons. They stain weakly brown with H&E, stain intensely with PAS, and are Sudan black, and concanavalin A positive and autofluorescent. Similar material was found in the glial cells, particularly in the oligodendrocytes, and also in the pericytes (Folkerth *et al.*, 1994).

Electron microscopy. Numerous strongly osmiophilic granules are seen in the oligodendrocytes, as well as in the endothelial and perithelial cells. Their size ranges from 0.5 to 2 μm. Two types are recognized. One consists of granular and membranous components merging into each other. Stacks of 10–20 osmiophilic membranes with a periodicity of 5 nm are arranged around central cores, in which the granules form a crystal-like structure. The second type, found predominantly in the oligodendrocytes, Schwann cells, and peripheral cells (Fig. 55) has dense membranous contents, in some places, with fingerprint formations. In addition, some membranous cytoplasmic inclusions with curvilinear profiles are also seen.

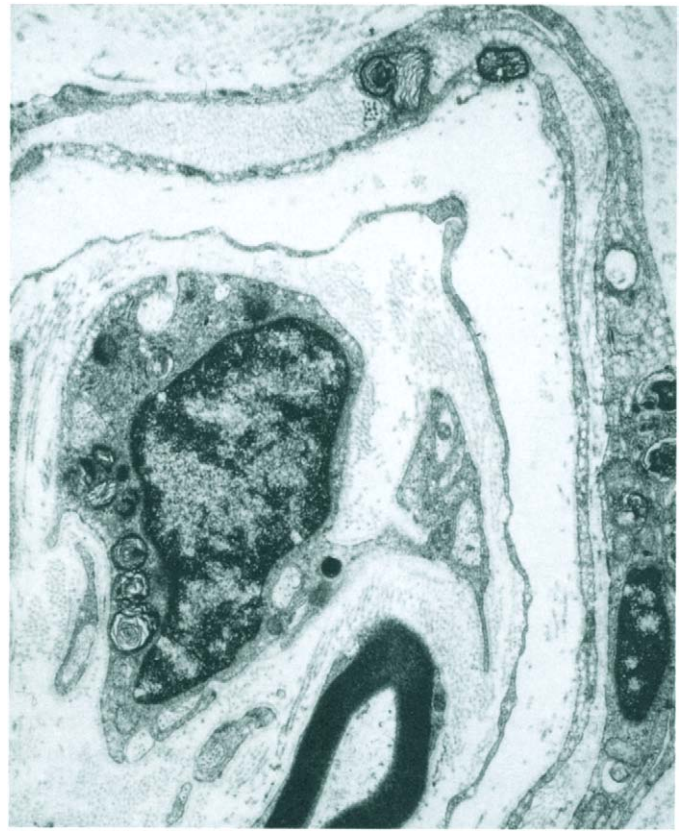


Fig. 55 Same case shown in Fig. 54. Lamellar inclusions in an endoneurial cell, ×14,300.

Pathogenesis From a biochemical point of view, the most important change is the increase in the total amount of gangliosides. The percentage of individual gangliosides is approximately normal, with perhaps a slight excess of GM_1 and GM_2.

In contrast with other mucolipidoses, no abnormalities could be found in the lysosomal hydrolases. A decrease in the activity of some ganglioside sialidases was considered a possible cause of the disease. Further studies on the distribution of ganglioside sialidases in cultured fibroblasts have been reported by Zeigler and Bach (1985).

Disorders of Amino Acid Metabolism

In reviewing the literature on metabolic disorders of amino acids, one is struck by the abundance of clinical and biochemical data compared with the paucity of morphological observations. This may be due to the large number of recently discovered entities with few deaths among the affected patients. In addition, in contrast with the disorders of lipid metabolism, the lesions, particularly those in the CNS, are scanty and largely nonspecific. The classification of these diseases is therefore based almost exclusively on clinical and biochemical criteria. We therefore consider here primarily aminoaciduria, the principal feature of these disorders, and the pathogenetic mechanisms leading up to it.

The pathological excretion of certain amino acids in the urine may be an overflow phenomenon, in which the high level of amino acids in the blood and the glomerular filtrate exceed the absorptive capacity of the renal tubules. It may also be due to an isolated impairment of the tubular amino acid transport mechanisms. A third possibility occurs in situations in which a generalized aminoaciduria is secondary to other metabolic disorders. Examples of this are fructose intolerance, galactosemia, and decompensated diabetes mellitus, which were dealt with in the chapter on carbohydrate metabolism. This may also occur in other generalized disorders of catabolism.

Disorders of Amino Acid Transport

Only traces of amino acids can be demonstrated in the urine of normal adults and children. On the other hand, the level of amino acids is high in neonates, and even more so in premature infants. It is probably a matter of immaturity of the transport mechanisms, since the blood level of amino acids remains normal. The excretion becomes normal in time.

The study of inborn errors of amino acid transport, carried out by methods of molecu-

lar genetics, has revealed that certain genes are responsible for the synthesis of carrier proteins, permeases, and other polypeptides that are essential for the penetration of amino acids through the cell membrane. This simple genetic framework is sufficient to explain most transport phenomena in microorganisms. In mammals the process of tissue differentiation leads to far-reaching changes in the transport mechanisms.

The tissue specificity of certain aminoacidurias (e.g., cystinuria) proves that the same amino acid is transported by different mechanisms in different tissues. This implies that certain systems are "switched on" and others are "switched off" in any particular tissue. Induction, repression, and feedback inhibition may all influence the transport systems.

The disturbances of amino acid transport may be confined to the kidneys or to the gut, but frequently both organs are simultaneously affected. If the resorption of essential amino acids is disturbed, nutritional deficiencies will arise, unless they are compensated for by other mechanisms. An impressive example is the pellagra-like symptoms in Hartnup disease, caused by a malabsorption of tryptophan from the gut.

Disturbances of Amino Acid Catabolism

Almost all disorders of amino acid breakdown are associated with aminoaciduria. In contrast with the transport abnormalities, this malfunction is due to overflow. In general, only the affected amino acid is excreted in the urine.

A total lack of an enzyme is rare in errors of amino acid metabolism, a quantitative reduction of enzymatic activity being far more common.

Enzyme deficiencies responsible for the impaired degradation of a specific amino acid may, in turn, lead to a variety of secondary disturbances. As a rule, an abnormality of the metabolism of a single amino acid will upset the amino acid balance. Furthermore, the synthesis of an important product may be inhibited, as, for instance, the synthesis of nicotinic acid in abnormal tryptophan metabolism. Finally, the excess of an amino acid may open metabolic pathways not normally in use, which may cause the production of harmful catabolites.

In many disorders of amino acid metabolism, mental retardation or psychotic symptoms dominate the clinical picture. Many of these disorders were first discovered during routine investigations of inmates of psychiatric institutions.

All those disturbances of amino acid metabolism that are associated with neurological symptoms have been considered in this chapter, even if their morphological substrate is still unknown.

Classification The disorders of amino acid metabolism can be classified on the basis of their pathophysiological mechanism into overflow, transport, and secondary aminoacidurias (Martin and Schlote, 1972). Although intracellular storage is rare, we have adopted a classification based on the principal amino acid affected, irrespective of the pathophysiological mechanisms involved. The metabolic highways and byways, however, are so interdigitated that a single enzymopathy may affect several amino acids, while several different enzyme defects may express themselves in an identical disturbance of the metabolism of a specific amino acid. It is therefore desirable to deal separately with diseases in which a series of interrelated enzymes is involved and several amino acids are affected.

Metabolic Disorders of the Urea Cycle

Allan *et al.* (1958) found a hitherto unknown substance in the urine of siblings in a London family, affected by psychomotor retardation and brittle hair. This substance was identified by Westall (1960) as argininosuccinic acid. It soon became apparent that this was only one of several inborn errors of metabolism in the urea cycle. Different enzymopathies have been described that lead to a primary disturbance of urea synthesis.

Clinical entities with available neuropathological findings are discussed in detail in this chapter; others are only briefly summarized. First, the effects of hyperammonemia, a constant feature of these disorders, are presented. This also occurs in other disorders, such as hepatic encephalopathy (see p. 407) and Reye's syndrome. The latter is discussed here in conjunction with the inborn enzymopathies.

Hyperammonemias

The digestion of proteins is incomplete, as a rule, and ammonia is formed in the colon by bacterial action on proteins and amino acids. The liver is the most important organ for the detoxification of ammonia. In severe loss of liver parenchyma or in portocaval shunts, in which the bloodstream from the gut bypasses the liver, hyperammonemic coma may develop. Hyperammonemia also occurs, at least at times, in all disturbances of the urea cycle. In all of these diseases, both clinical and pathological abnormalities are present in the CNS. The question therefore presents itself as to whether these changes are due to the accumulation of the amino acid, the metabolism of which has been impaired by the specific enyzme defect, or to the raised blood level of ammonia.

The hallmark of the effect of ammonia on the brain is the presence of Alzheimer's type II astrocytes, which are absent only if the hyperammonemia is slight or controlled by dietary measures.

The blood–brain barrier remains impermeable to large molecules in states of hyperammonemia, but ammonia in its non-ionized form (NH_3) easily passes the barrier, at a higher rate in the gray matter than would be expected from the capillary surface (Lockwood *et al.*, 1984). An excessive accumulation of ammonia in the brain may inhibit neurotransmission through the following mechanisms: (1) disturbance of the glutamine–glutamate balance, the higher concentration of glutamine inhibiting the liberation of neurotransmitters; (2) increased synthesis of 2-oxoglutaramide from 2-oxoglutarate and ammonia, producing EEG abnormalities; and (3) reduction of the amount of 2-oxoglutarate (β-ketoglutarate) available for oxidative breakdown, leading to diminished synthesis of phosphates rich in energy. This can also cause destruction of the microtubules and impairment of axonal transport. As a further factor in hyperammonemic damage to the brain, vasoparesis may be considered. Undoubtedly, the astrocytes play a central role in the multifactorial pathogenesis of brain damage. The metabolism of ammonia is compartmentalized in the brain and the astrocytic compartment appears to be responsible for it (Miyakawa *et al.*, 1982).

The appearances of Alzheimer's type II glia are a fixation artifact. They are, however, the equivalent of pathological changes produced by hyperammonemia. The effect of ammonia on astrocytes has been demonstrated in several animal species (Stastny *et al.*, 1992; Deshmukh *et al.*, 1993; Blei *et al.*, 1994) and in tissue cultures (Gregorios *et al.*, 1985). The spongy degeneration of nervous tissue in hyperammonemia could also be produced in experimental animals.

Carbamoyl-phosphate Synthetase Deficiency (Congenital Hyperammonemia Type I)

The first case of this deficiency was reported by Freeman *et al.* (1964). A partial or total enzyme defect may be distinguished.

Clinical Picture Children with a total lack of the enzyme die, with rare exceptions, within a few days of birth. Those with a partial defect show psychomotor retardation, frequently epileptic seizures, and EEG abnormalities even in the absence of seizures. Cortical atrophy and ventricular dilatation may be detected by CT. Patients with varying degrees of the enzyme deficiency or even without symptoms of metabolic disturbance (Verbiest *et al.*, 1992; Horiuchi *et al.*, 1993) may suffer coma after starting treatment with valproic acid. A late clinical presentation in adolescence has been reported (Lo *et al.*, 1993).

Pathology Apart from hemorrhages in the lungs and the gastrointestinal tract, no obvious lesions are seen. On electron microscopy of liver biopsies, abnormal mitochondria are found in the hepatocytes, as well as an increase in the number of peroxisomes and changes in the smooth endoplasmic reticulum (Zimmermann *et al.*, 1981).

Neuropathology *Gross appearances.* Ulegyrias are observed in the cerebrum and the cerebellum, as well as kernicterus (Minguillon *et al.*, 1990).

Light microscopy. Symmetrical bilateral spongy degeneration with gliosis (Fig. 56A and B) and vascular proliferation is seen, particularly in the basal ganglia and the brain stem (Zimmermann *et al.*, 1981).

Electron microscopy. The astrocytes show swelling and vacuolation of the cytoplasm (Zimmermann *et al.*, 1981).

Pathogenesis Carbamoyl-phosphate synthetase deficiency produces hyperammonemia only if combined with a reduced activity of ornithine carbamoyltransferase. Otherwise, it leads only to impaired production of urea. The high activity of ornithine carbamoyltransferase compared with carbamoyl-phosphate synthetase in the brain suggests a deficiency of the former also in the CNS and the possibility that the impairment of the urea cycle may be directly responsible for the brain damage. The gene for carbamoyl-phosphate synthetase (*CPS*) has been mapped to human chromosome 2q24.3–q31 (Tiller

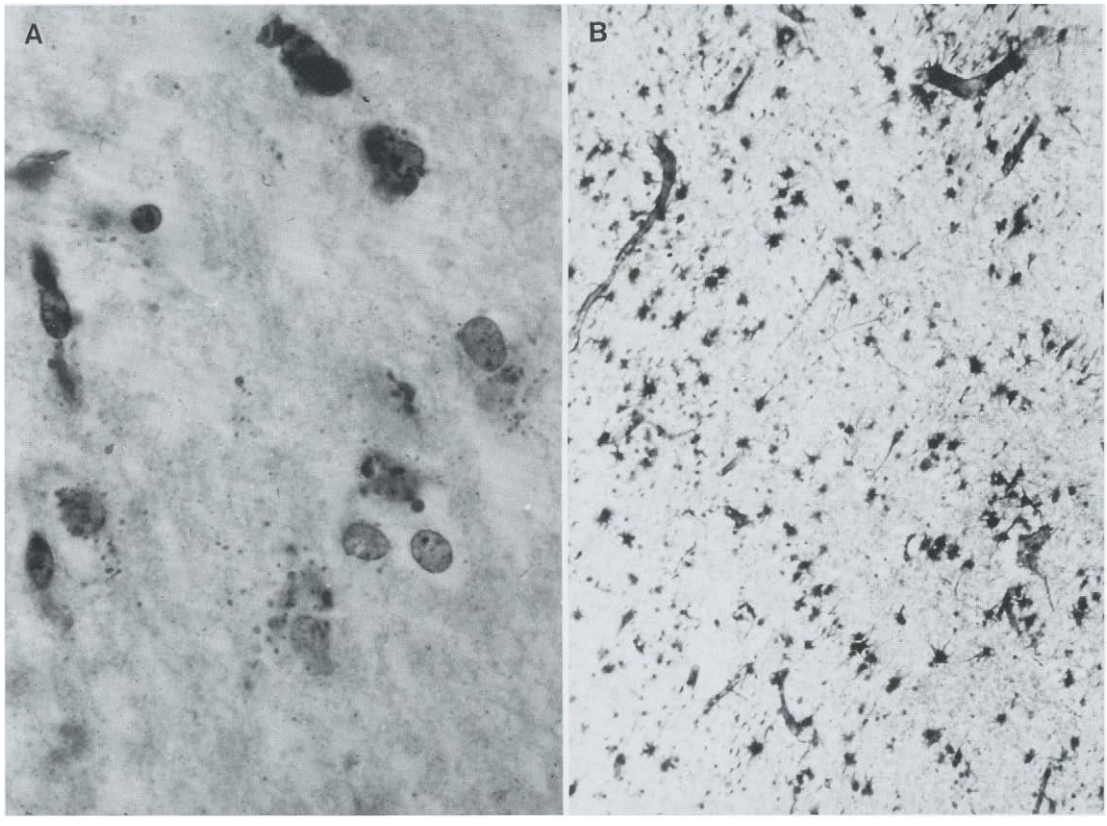


Fig. 56 Congenital hyperammonemia. (A) Spongiosis and glial proliferation. Nissl stain, ×400. (B) Prominent gliosis. Cajal's gold sublimate, ×80.

et al.,1994). One base substitution in an exon of the *CPS I* gene causes a 9-bp deletion due to aberrant splicing (Hoshide *et al.*, 1993).

Ornithine Carbamoyltransferase Deficiency (Ornithine Transcarbamylase Deficiency; Congenital Hyperammonemia Type II)

This enzymopathy, described by Russell *et al.*, (1962) is the most common disorder of the urea cycle. It is inherited as an X-linked dominant trait, fully expressed in male hemizygotes and partially in female heterozygotes. The enzyme is a nuclear DNA-coded mitochondrial compound and is apparently expressed only in the liver and the small intestine. It catalyzes the formation of citrulline from carbamoyl phosphate and ornithine (Christodoulou *et al.*, 1994).

Clinical Picture In male hemizygotes the symptoms usually appear a few days after birth. Most affected males die shortly after birth. In female heterozygotes they may also manifest themselves in the neonatal period or may be delayed to the end of the first decade, depending on the residual activity of the enzyme.

Somnolence, irritability, poor feeding, and vomiting are prominent symptoms. Spasticity or hypotonia, areflexia, and seizures may also be present. Long-term survivors commonly, but not necessarily, show severe psychomotor retardation. MRI spectroscopy shows increased brain glutamine (Connelly *et al.*, 1993). A girl with ornithine-carbamoyl transferase deficiency with a history of recurrent strokelike episodes was reported on by Christodoulou *et al.* (1993). In some cases of Rett syndrome (see p. 568), a defect of the urea cycle similar to that found in ornithine carbamoyltransferase deficiency has been detected (Thomas *et al.*, 1990; Sasaki *et al.*, 1991). Cases of adult women presenting with a symptomatic hyperammonemia precipitated by valproate therapy have been reported (Honeycutt *et al.*, 1992). Late onset of symptoms has also been observed in males. Older patients may also die of brain edema due to a hyperammonemic attack (Fukuizumi *et al.*, 1990) simulating Reye's syndrome (Mizoguchi *et al.*, 1990).

Pathology In patients with delayed onset of the disease, inflammatory foci, microvesicular fatty infiltration, and changes in the endoplasmic reticulum have been seen on liver biopsies. Crystalloid inclusions may be observed in the mitochondria (Fukuizumi *et al.*, 1990).

Neuropathology *Gross appearances.* No changes are seen in infants dying soon after birth. In patients with late onset of symptoms, the brain may also appear normal. In most long-term survivors cerebral edema, cortical atrophy, and ventricular dilatation are seen. In patients with early onset and long survival, destructive lesions in the cortex and the white matter are present, ranging from ulegyria (Kornfeld *et al.*, 1985) to hydranencephaly (Dolman *et al.*, 1988).

Light microscopy. Abundant Alzheimer's type II astrocytes are found in most cases. In cases with massive destruction of the cortex and the white matter, most neurons have disappeared (Dolman *et al.*, 1988). In cases with less severe damage, degenerative changes in the neurons and a loss of myelin with gliosis may be seen.

Pathogenesis The neuropathological changes are probably related to hyperammonemia (see p. 147), which is prominent in all cases and whose severity is correlated with the degree of enzyme deficiency. One can also detect an abnormal excretion of orotic acid, uracil, and uridine in the urine, for which an increased cytoplasmic synthesis of pyrimidines is probably responsible. This is the result of reduced utilization of carbamoyl phosphate in the urea cycle. MRI spectroscopy shows increased brain glutamine, consistent with the hypothesis that an intracerebral accumulation of glutamine contributes to the encephalopathy associated with hyperammonemia.

The restriction map of the entire human ornithine carbamoyltransferase (*OCT*) gene is about 73 kb long and contains 10 exons and 9 introns (Matsuda *et al.*, 1989).

Ornithine transcarbamylase deficiency shows an X-linked inheritance with frequent new mutations in the protein coding region. C-to-G, A-to-T, A-to-G, T-to-C, and C-to-T substitutions, deletions of variable size involving one or more exons, 29 different missense, nonsense, or frameshift mutations, and three polymorphisms have been found in patients with ornithine transcarbamylase deficiency. Ten to 15% of all molecular alterations associated with ornithine carbamoyltransferase deficiency are large deletions involving all or part of the *OTC* gene or contiguous genes on the short arm of the X chromosome. Ten percent of all point mutations involve the CpG dinucleotide codon 141 with a CGA-to-CAA transition (Guchmann *et al.*, 1993a).

Animal Models Sparse fur (spf) mice are congenitally hyperammonemic because of a defective hepatic ornithine carbamoyltransferase (Seiler *et al.*, 1994). Densities of (3H)PK 11195 binding sites are significantly increased in all tissues of *spf* mice compared with control animals. In view of the localization of PTBR on the mitochondrial membrane, changes in the PTBR in *spf* mouse tissues may modulate the altered mitochondrial function and oxidative metabolism in the brain and the peripheral tissues. Experimental work on the interpretation of reversible symptoms seems to demonstrate that the increased transport of tryptophan at the blood–brain barrier in the presence of an increased glutamine concentration in tissue appears to depend on intact γ-glutamyl transpeptidase in the brain microvessels (Bachmann, 1992).

Argininosuccinate Synthase Deficiency (Citrullinemia)

Citrullinemia is an autosomal-recessive disease caused by a deficiency of argininosuccinate synthase. McMurray *et al.* (1962) discovered this entity during systematic chromatographic investigation of a large cohort of mentally retarded patients. Three subtypes can be distinguished, based on age at onset and clinical course.

Clinical Picture In the familial type of this condition, the symptoms begin during the first few days after birth and consist of irritability, lethargy, poor food intake, and rapid respiration. Rigidity with opisthotonos soon follows; acne and seizures also occur (Engel and Buist, 1985). Pilus tortus (kinky hair) was found in one patient (Patel and Unis, 1985). One quarter of the patients die soon after birth, with signs of increased intracranial pressure (Wayenberg *et al.*, 1992), while some survive for months or even years. During

recovery from acute encephalopathy, EEG changes are observed (Clancy and Chung, 1991). In the subacute or infantile type the symptoms appear at the age of a few months in the form of episodic crises of hyperammonemia and psychomotor retardation. As a rule, these patients survive for several years and show few symptoms if kept on a restricted-protein diet. Elevated concentrations of argininosuccinic acid and its anhydrides can be found in all body fluids, but are most pronounced in the CSF (Gerrits *et al.*, 1993).

The adult type has been described almost exclusively in Japan, and is characterized by a paucity of symptoms. The onset varies from late childhood to adulthood. In younger patients some symptoms may be present, such as delayed onset of menstruation, insomnia, vomiting, and confusional states after meals. Some patients suffer from seizures (Origuchi *et al.*, 1984) and hallucinations. Over the years the symptoms become more severe, with manic episodes, echolalia, and psychotic manifestations. Paresis of the lower extremities, dysarthria, and skin lesions may appear. Neuroradiological findings include cerebral cortical atrophy seen on the CT scan and patchy abnormal myelinization visible on MRI (Brockstedt *et al.*, 1990). High values of citrulline, up to 100 times normal, are found in the plasma and the CSF. The triggering of episodic symptoms in otherwise asymptomatic patients may be caused by stress, liver dysfunction, alcohol, and drugs.

Pathology In the familial type, focal hepatocellular necroses have been repeatedly observed. Fatty changes in the liver are seen in older patients. Electron microscopy reveals changes in the endoplasmic reticulum of hepatocytes.

Neuropathology *Gross appearances.* Cerebral edema is the main feature of the familial type (Wick *et al.*, 1973). Other forms show a mild to moderate cerebral atrophy, ulegyria, and hemorrhages (Fig. 57A and B), as well as cortical and subcortical necroses leading to microcavitation (Kuhara *et al.*, 1985).

Light microscopy. Status spongiosus of the cortex is found in untreated congenital cases (Kuhara *et al.*, 1985), in addition to total or selective parenchymal necroses and numerous Alzheimer's type II glial cells. The latter may be absent in treated cases. In the white matter a loss of myelin with gliosis and lipid macrophages are seen, as well as disturbances of myelination. Glial scarring in the putamen and status marmoratus of the thalamus are observed. Shrunken neurons with pyknotic nuclei as well as circumscribed selective necroses may be seen, particularly in the cerebellar cortex, dentate nucleus, and inferior olives (Wick *et al.*, 1973). Small foci of total tissue necrosis have been reported in the dentate nucleus.

Pathogenesis Citrulline is an intermediate product of urea synthesis. When catalyzed by ornithine carbamoyltransferase, carbamoyl phosphate combines with ornithine to form citrulline. This is extruded from the mitochondrion and combined with aspartate in the cytosol through the action of argininosuccinate synthase to form argininosuccinate.

The expression of argininosuccinate synthase deficiency shows a wide range of variation suggestive of genetic heterogeneity (Kobayashi *et al.*, 1986). In particular, the enzyme kinetic constants undergo changes (the K_m may be increased 20- to 30-fold). Hyperammonemia is inconstant and may be absent in well-managed patients, which explains the absence of Alzheimer's type II glia in some cases.

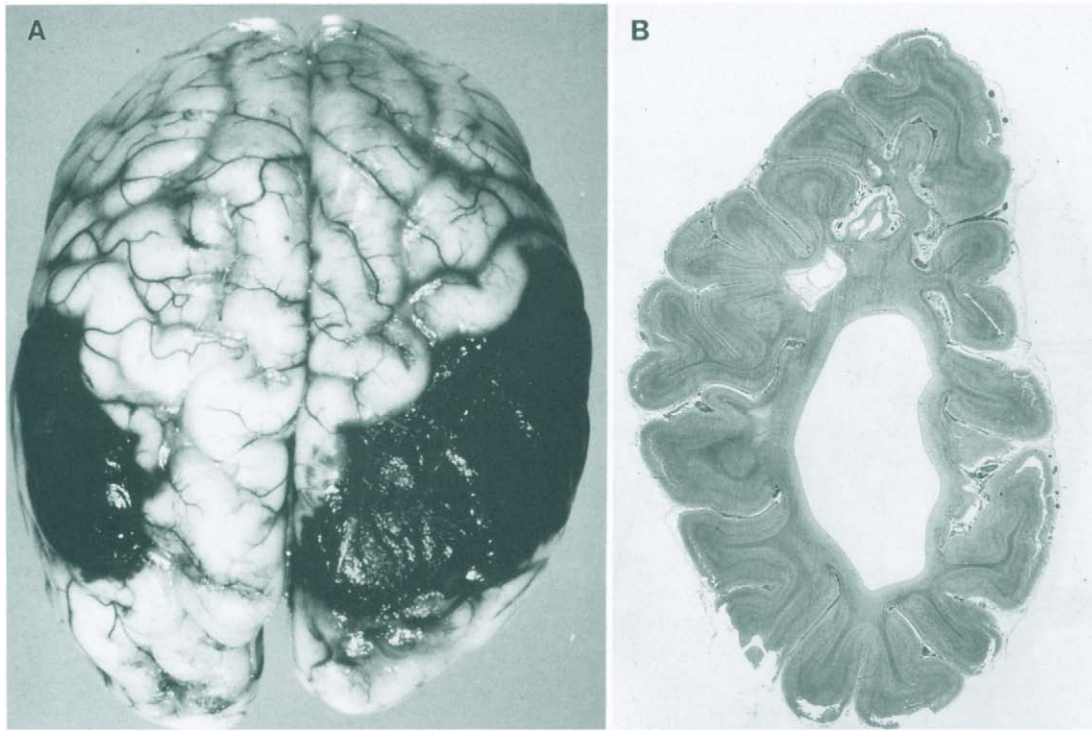


Fig. 57 Sporadic form of citrullinemia. (A) Moderate cerebral atrophy and extensive bilateral hemorrhages. (B) Loss of myelin and cyst formation in the white matter.

As a result of the enzyme deficiency, citrulline accumulates in the brain, where it may be held partially responsible for the neurological manifestations. Animal experiments indicate that high concentrations of citrulline inhibit the substrate phosphorylation in the glycolytic chain, thus impairing the intermediate and energy metabolism. An anoxic pathogenesis must be postulated for the ulegyrias and the tissue necroses, both selective and total. These are irreversible, as opposed to the glial changes of Alzheimer's type II and to the status spongiosus.

Kobayashi *et al.* (1990a) identified 10 mutations in the argininosuccinate synthase genes by the sequencing of amplified cDNA. Six of the missense mutations involve conversion of a CpG dinucleotide in the sense strand to TpG or CpA, and six of the seven mutations alter a restriction enzyme site on the cDNA. Two mutations have been observed in which the sequences encoded by a single exon (exon 7 or 13) were absent from the cDNA. There is an extreme heterogeneity of mutations causing citrullinemia. This heterogeneity of mutations may prove typical for less common autosomal-recessive human genetic diseases.

Citrullinemia in Animals Citrullinemia caused by argininosuccinate synthase deficiency has been reported in dogs (Strombeck *et al.*, 1975) and in Chinese guinea pigs

(Gonzalez-Noriega *et al.*, 1980). The mutant of *spf* mice presents an X-linked inherited defect. The brains contain a generalized up to two-fold increase of brain glutamine, consistent with their exposure to increased concentrations of ammonia (Ratnakumari *et al.*, 1994) and altered monoaminergic function (Raghavendra *et al.*, 1994).

Argininosuccinate Lyase Deficiency (Argininosuccinase Deficiency; Argininosuccinicaciduria; Argininosuccinate Retardation)

Argininosuccinase deficiency is the second most common— according to Perry *et al.* (1980), the most common—of the metabolic errors of the urea cycle. It was the first condition recognized in this group of disorders, having been described by Allan *et al.* in 1958.

Clinical Picture This disease may manifest itself at birth or during the first or second year of life. The congenital form presents with respiratory and nutritional difficulties, vomiting, lethargy, hypotonia, and seizures. Jaundice and hepatomegaly soon follow. The majority of untreated patients die soon after birth, occasionally after a few months. In cases of later onset, prominent features include more or less severe psychomotor retardation, sparse brittle hair (trichorrhexis nodosa), and hepatomegaly. Tonic–clonic seizures with corresponding EEG changes and intermittent ataxia are observed in some patients. Some patients with disease of late onset suffer only from mild symptoms (Schutgens *et al.*, 1979), and occasional asymptomatic cases are found during routine examination. Early treatment of partial argininosuccinate acid lyase deficiency with an arginine supplement results in normal intellectual and psychomotor development (Widhalm *et al.*, 1992). Irrespective of the clinical course, a large amount of argininosuccinate is found in the blood, urine, and CSF in all cases.

Pathology Focal hepatic necroses, sometimes with fatty infiltrations, are found in acute cases. Casts may be found in the collecting tubules of the kidneys. Pulmonary hemorrhages also occur.

Neuropathology *Gross appearances.* Moderate edema is the only finding (Glick *et al.*, 1976).

Light microscopy. A delay in myelination may be seen in acute and subacute cases. The cerebral cortex, basal ganglia, and sometimes also the white matter show spongy rarefaction (Perry *et al.*, 1980). Alzheimer's type II glia is seen in the cerebral cortex, basal ganglia, and dentate nuclei in patients with longer survival (Perry *et al.*, 1980), but not in neonates. Acute ischemic nerve cell changes have also been observed (Glick *et al.*, 1976).

Pathogenesis A lack of activity of the enzyme argininosuccinate lyase was demonstrated by Tomlinson and Westall (1964) in erythrocytes and liver biopsies. This cytosolic enzyme splits argininosuccinate into fumarate and arginine. In insufficient activity of the enzyme, argininosuccinate accumulates and exerts a "toxic" influence on intermediate metabolism. The fact that the concentration of this metabolite is, as a rule, higher in the

CSF than in the blood can be explained by a higher synthesis in nervous tissue as a consequence of increased citrulline uptake.

The fact that the defective enzyme activity varies from organ to organ may be explained either by the availability of isoenzymes (Perry *et al.*, 1980) or by a defect in gene regulation. Barbosa *et al.* (1991) identified three single-base mutations, one within exon 13 and one in which exon 2 was deleted from the mature RNA.

Arginase Deficiency (Argininemia)

Arginase deficiency is the rarest enzymopathy in the urea cycle. The first case was probably recorded by Peralta Serrano (1965). The defective enzyme was demonstrated by Terheggen *et al.* (1970) in three members of a family. Arginase deficiency, although rare, is a heterogenous disorder at the genotypic level, transmitted as an autosomal-dominant trait and generally encompassing a variety of point mutations rather than substantial structural gene deletions (Grody *et al.*, 1992).

Clinical Picture Apart from a high level of arginine in the blood and the CSF and its excretion in the urine, lysine and ornithine, and sometimes cystine, are also excreted in increased amounts. This is caused by competitive reabsorption in the renal tubules, the various amino acids competing with arginine for the same transport mechanism. Symptoms include seizures (Patel *et al.*, 1994), vomiting, psychomotor retardation, spastic paresis, choreoathetosis, and tremor. Ventricular dilatation due to cerebral atrophy was demonstrated in a pneumoencephalogram.

Christmann *et al.* (1990) reported a case of homozygous arginase belatedly diagnosed at the age of 18 years, when treatment with valproate sodium was instituted.

Neuropathology In the two fatal cases reported by Scheuerle *et al.* (1993), postmortem examination revealed severe global cerebral edema.

Pathogenesis The mechanisms responsible for neurological damage are unknown, but are unlikely to be due to hyperammonemia alone. Arginine and its guanidine metabolites are candidate neurotoxins (Lambert *et al.*, 1992).

Reye's Syndrome

In 1963 Reye *et al.* described a syndrome in children, consisting of metabolic changes in the liver, hyperammonemia, and an encephalopathy of obscure pathogenesis.

Clinical Picture This condition occurs between the ages of 5 months and 16 years. Several cases have also been described in adults (Van Coster *et al.*, 1991). After a prodromal illness, most commonly an upper respiratory infection, vomiting, rapidly developing coma, seizures, and fever supervene. Hyperventilation leads to a respiratory alkalosis. The blood levels of transaminases and ammonia are high, particularly near the onset of the disease. Focal CT lesions of the thalamus and the brain stem have been detected in

cases associated with influenza A virus infection (Nagai *et al.*, 1993). Occasionally, in children with sudden death the diagnosis was first made during medicolegal autopsy.

Mortality is variable and ranges from nil (Lansky *et al.*, 1977) to 81% (Reye *et al.*, 1963), presumably depending on the efficacy of therapeutic measures. Nevertheless, it remains fairly high (Manz and Colon, 1982). Of the survivors 39% suffer from significant psychomotor disabilities, ranging from a reduction in scholastic performance or manual dexterity to a severe neurological deficit, major seizures, mental retardation or dementia, quadriplegia, and a neurovegetative state (Manz and Colon, 1982).

Margosa oil, a long-chain fatty acid compound, has been shown to cause a Reye-like syndrome with death from hepatoencephalopathy in children in Malaysia and India (Sinniah *et al.*, 1989). Recurrent familial Reye-like syndrome in five siblings from an Ashkenazi Jewish family with a complex aminoaciduria and organic aciduria has been reported by Elpeleq *et al.* (1990). Carnitine deficiency can mimic Reye's syndrome (Kimura *et al.*, 1990).

Pathology Diffuse fatty infiltration, consisting of fine droplets, is typically present in the liver ("white liver disease"). The glycogen stores are severely depleted. There is no inflammatory reaction, but occasionally spotty necroses have been reported (Kimura and Anemiya, 1990) Fatty infiltration is also present in the renal tubules, pancreas, and myocardium. Muscle biopsies reveal focal, noninflammatory myolysis as well as fatty infiltration. In electron microscopy of the liver and the skeletal muscle, there are striking mitochondrial changes (Fig. 58A), consisting of swelling and alterations in both the matrix and the membranes (Daugherty *et al.*, 1987).

Neuropathology The lesions in the CNS have been studied in autopsy cases of patients who died in the acute stage, in brain biopsies of survivors with a neurological deficit, and in one long-term survivor in a neurovegetative state (Manz and Colon, 1982).

Gross appearances. Cerebral edema with a considerable increase in brain weight and volume is seen in the acute cases, particularly in young infants. Tentorial and tonsillar herniation have been present in several cases.

Light microscopy. Acute, multifocal, or diffuse, ischemic changes, often in a laminar distribution, are seen in the cerebral cortex, as well as in the basal ganglia, diencephalon, and brain stem. Foci of hemorrhagic infarction and microhemorrhages may be present in some cases. Resolving microinfarcts with a proliferation of macrophages and astrocytosis are seen on cerebral biopsies. Old microinfarcts have been seen in the cerebral cortex, basal ganglia, and thalamus of a long-term survivor. In addition, a large area of old necrosis occupied the pontine tegmentum. A diffuse loss of Purkinje and granule cells with Bergmann's gliosis was seen in the cerebellar cortex.

Electron microscopy. Expansion of astrocytic footplates and endothelial cells is seen in acute cases (Blisard and Davis, 1991), as well as delamination of myelin and ballooning of the neuronal mitochondria. The mitochondrial changes resemble those seen in the liver (Fig. 58 B and C).

Pathogenesis The metabolic consequences of mitochondrial damage in hepatocytes and of the massive catabolism of proteins, fats, and carbohydrates are reflected in the

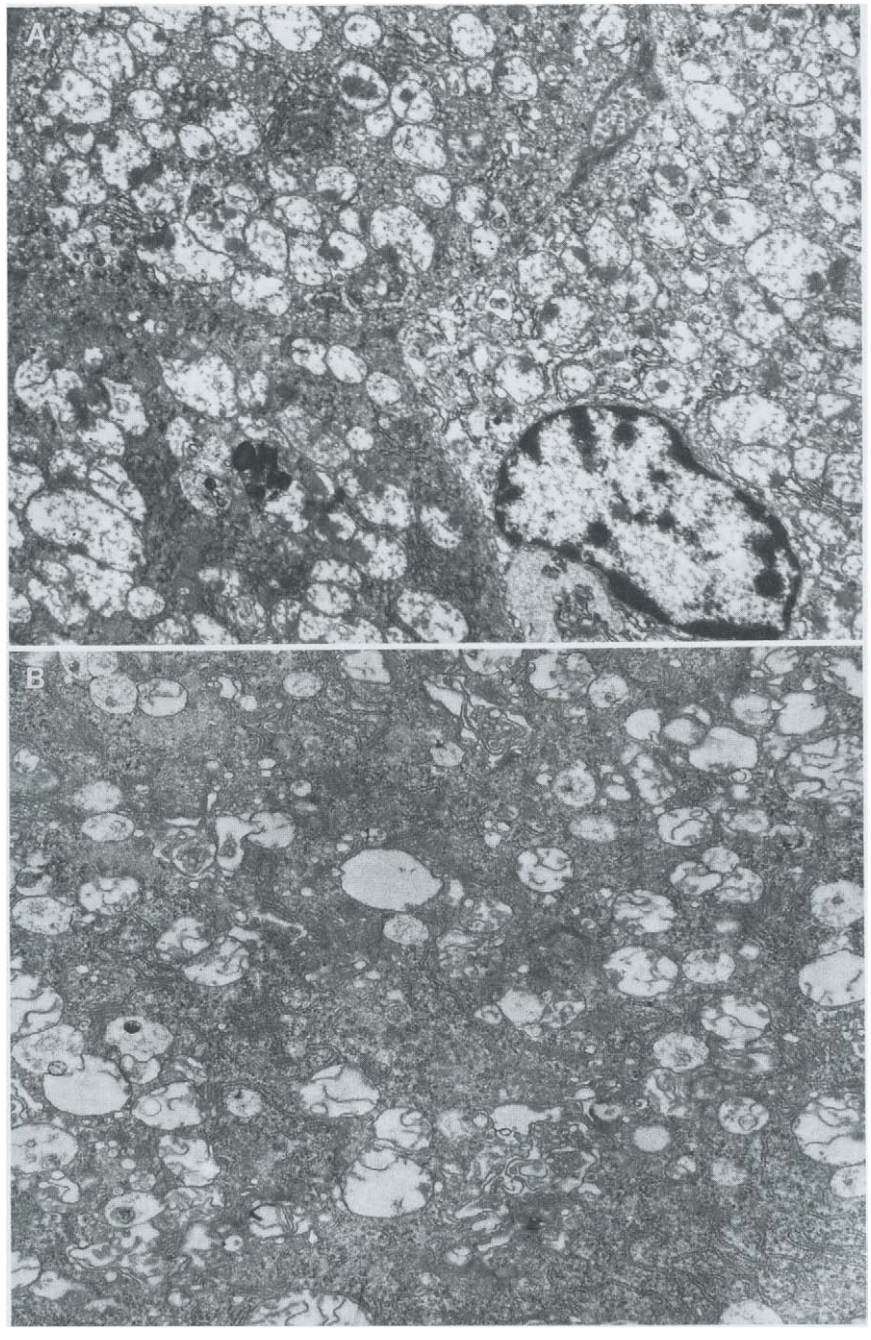


Fig. 58 Reye's syndrome. Mitochondrial abnormalities of (A) a liver cell, (B) a parietal cortical neuron, and (C) a cerebellar granule cell.

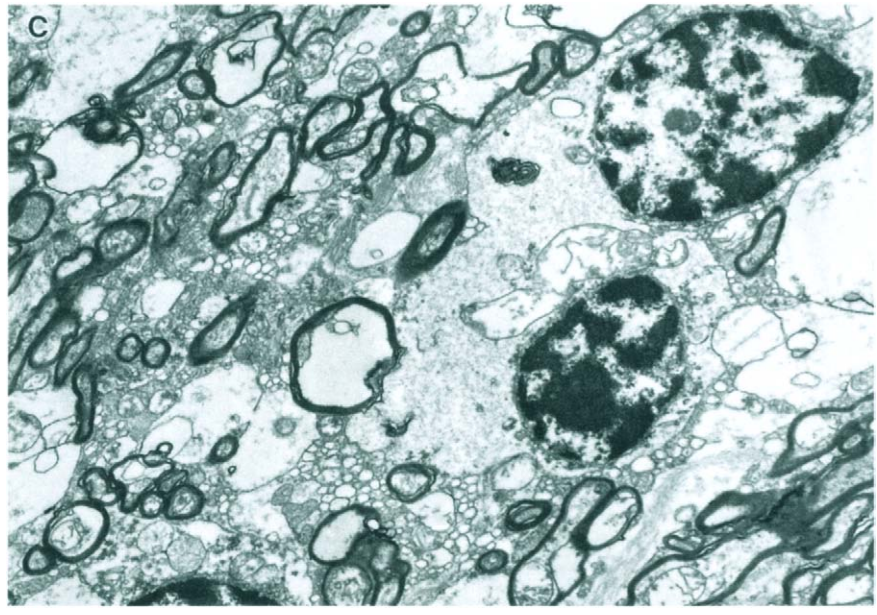


Fig. 58 Continued.

raised levels of ammonia, free fatty acids, and lactate, as well as in hypoglycemia, which develops in up to 40% of the children with Reye's syndrome (Davis *et al.*, 1993).

The massive proteolysis in skeletal muscles is one of the factors leading to hyperammonemia. Adrenaline may play a part in the origin of the lactic acidosis and the encephalopathy (Arcinue *et al.*, 1986). Three-week-old astrocytes exposed to the serum of children with Reye's syndrome for the final 7 days of culture exhibited minor mitochondrial pleomorphism and inhibited fatty acid oxidation (Murphy *et al.*, 1992).

The etiology of this condition remains obscure, since many causes can be considered (Brown and Imam, 1991), but the interaction of several factors has been postulated. The onset of the disorder is usually preceded by a respiratory infection or, less commonly, by varicella or infantile gastroenteritis. Clustering of outbreaks of Reye's syndrome is observed, particularly during influenza B epidemics. Viral infection as well as acetylsalicylate-induced mitochondrial aberration has been reported to play an important role in the pathogenesis of Reye's syndrome (Tomoda *et al.*, 1992). A number of environmental toxins have been suggested on slender evidence, particularly hypersensitivity to salicylates (Khan *et al.*, 1993). Finally, the possibility of underlying genetic factors, such as subclinical abnormalities in the urea cycle, should be considered. Ten percent of the patients in the British Isles initially reported with Reye's syndrome have subsequently been found to have an underlying inherited metabolic disorder. There is evidence to suggest that other cases may not have been recognized (Green and Hall, 1992; Glasgow and Moore, 1993). The results of β-oxidation of palmitic acid in mice by astrocyte culture exposed to the serum of children with Reye's syndrome suggest that some of the "toxins" implicated in this disorder inhibit fatty acid oxidation in the astrocytes and produce other lipid-related abnormalities that could be related to encephalopathy (Murphy *et al.*, 1992).

Molecular studies have revealed a nonuniform decrease in several mitochondrial residual enzyme activities in the liver and the brain (Van Coster *et al.*, 1991). Corkey *et al.*, (1991) found elevated concentrations of cytokines in the plasma of patients acutely ill with Reye's syndrome and proposed that the increased response reflects a genetic defect in cytokine- and receptor-modulated signal transduction.

Animal Models Mice intravenously inoculated with influenza A/PR8 virus developed lethargy, seizures, and coma, and subsequently died. Blisard and Davis (1990) demonstrated that changes occurred simultaneously and postulated that influenza B virus caused a simultaneous primary insult to the liver and the brain. Clinical, biochemical, and pathological features of the mouse illness resemble those seen in Reye's syndrome (Sanchez-Lanier *et al.*, 1991).

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (Familial Reye-like Syndrome)

Medium-chain acyl-CoA dehydrogenase deficiency is an autosomal-recessive disorder of fatty acid oxidation similar to Reye's syndrome because of its associated features of pernicious vomiting, coma, hyperammonemia, and fatty infiltration of the liver. Sudden infant death syndrome is another recognized phenotype of medium-chain acyl-CoA dehydrogenase deficiency. Two fatty acyl glycine conjugates, hexanoylglycine and suberylglycine, also appear in the urine and are believed to be pathognomonic of medium-chain acyl-CoA dehydrogenase deficiency. The patient's age at the time of presentation is usually less than 2 years. Many reported cases of supposed Reye's syndrome in children less than 2 years old read suspiciously more like medium-chain acyl-CoA dehydrogenase deficiency. In contrast to Reye's syndrome, a lack of abnormal posturing and signs of increased intracranial pressure have not been reported. Because fat-derived acetyl-CoA and ketone bodies constitute the major metabolic fuels during prolonged fasting, children with medium-chain acyl-CoA dehydrogenase deficiency are most likely to become symptomatic when they have an illness that limits caloric intake.

Changes uncharacteristic of Reye's syndrome are a large-droplet steatosis and the presence of distinctive mitochondrial abnormalities on electron microscopy. The detection of electron-dense mitochondrial membranes rules out Reye's syndrome and is suggestive of a disorder of mitochondrial fatty acid oxidation (Santer *et al.*, 1990).

Although liver histology in medium-chain acyl-CoA dehydrogenase deficiency characteristically demonstrates a heterogenous macrovesicular pattern of fatty infiltration, the classic microvesicular fatty changes of the liver in Reye's syndrome can also be seen. Sudden death associated with fatty liver and encephalopathy in a 4-year-old boy with medium chain acyl-CoA dehydrogenase deficiency was described by Perper and Ahdab-Barmada (1992).

A point mutation of K-to-E substitution at position 329 in the gene for this deficiency (*MCAD*) was identified as the most common mutation in patients with medium-chain acyl-CoA dehydrogenase deficiency (Matsubara *et al.*, 1992).

In a 13-year-old girl with hyperammonemic encephalopathy and orotic aciduria, the diagnosis was confirmed by DNA analysis, which revealed homozygosity for the prevalent muta-

tion of medium-chain acyl-CoA dehydrogenase deficiency (the adenine-to-guanine transition at position 985) (Marsden *et al.*, 1992). The diagnosis can be confirmed by a positive 3-phenylpropionic acid test and molecular genetic proof of the adenine-to-guanine mutation at position 985 in the *MCAD* cDNA (G985) with the polymerase chain reaction (Wilken *et al.*, 1991).

Hyperornithinemias

Three metabolic disorders lead to hyperornithinemia: gyrate chorioretinal atrophy, hyperornithinemia–hyperammonemia syndrome, and ornithine–keto acid transaminase deficiency. The first of these does not involve the nervous system, even though occasional slowing of the EEG has been reported. The frequently mentioned changes in type II muscle fibers are non-specific.

Ornithine-aminotransferase Deficiency (Hyperornithinemia–Hyperammonemia–Homocitrullinuria Syndrome)

The first patient with this enzyme deficiency was described by Shih *et al.* (1969). The syndrome can be associated with widespread manifestations in the CNS and the peripheral nervous system (Lemay *et al.*, 1992).

Clinical Picture The manifestations of the disease differ, depending on whether the infants are breast fed or bottle fed a high-protein diet. Aside from a failure to thrive, mental retardation may also be present. Seizures are common. Some patients develop ataxia and choreoathetoid movements and buccofaciolingual dyspraxia and episodic confusion during acute hyperammonemic episodes (Tuchmann *et al.*, 1990). Rodes *et al.* (1987) reported three siblings with a progressive spastic paresis.

Pathology The liver biopsy typically reveals vacuolated hepatocytes that are distended with glycogen (Smith *et al.*, 1992). Electron microscopic examination of the liver cells and cultured fibroblasts revealed pleomorphism of the mitochondria, some of which contained paracrystalline inclusions (Gordon *et al.*, 1987). No neuropathological findings are available.

Pathogenesis Ornithine aminotransferase is a key enzyme of the Arg–Orn–Glu–GABA (γ-aminobutyric acid) pathway (Seiler *et al.*, 1993). The disorder is characterized by a genetic defect of ornithine transport in the mitochondrial membrane (Shimizu *et al.*, 1990).

Ornithine–oxo-acid Aminotransferase Deficiency

Few patients have been reported to date (Bickel *et al.*, 1968; Kekomäki *et al.*, 1969). These patients suffer from prolonged neonatal jaundice in the absence of blood group incompatibility, followed by delayed psychomotor development, failure to thrive, retardation of speech development, and EEG abnormalities with a latent epileptic pattern. Aminoaciduria is also present.

The liver biopsy revealed a disintegration of the lobular pattern with fibrous replacement of damaged parenchyma. The hepatocytes showed vacuolar degeneration.

Metabolic Disorders of Branched-Chain Amino Acids

In 1954 Menkes *et al.* described a new disease with severe neurological involvement, accompanied by a peculiar odor of the body and the urine, reminiscent of maple syrup. In a similarly affected patient Westall *et al.* (1957) found an excessive urinary excretion of the branched-chain amino acids leucine, isoleucine, and valine. Their concentration in the plasma was similarly raised. Menkes (1959) isolated three keto acids from the urine—2-oxoisocaproate, 3-methyl-2-oxovalerate, and 2-oxoisovalerate—arisen from the transamination of leucine, isoleucine, and valine, respectively.

Through the application of gas chromatography and mass spectrometry to the identification of organic acidemias, further enzymopathies were demonstrated affecting the metabolism of branched-chain amino acids. Most of these form entities consisting of only a few patients, perhaps only members of a single family. As most of these patients are still alive, morphological observations are scanty. An entity that, clinically and biochemically, resembles the branched-chain amino acid disorders, propionyl-CoA carboxylase deficiency, is considered later in this chapter.

Maple Syrup Urine Disease (Branched-Chain Ketoaciduria)

Clinical Picture At the age of 3–18 days, occasionally later, infants with maple syrup urine disease (MSUD) present with feeding difficulties, irregular respirations with periods of apnea, lethargy, seizures, spasticity, and opisthotonos. These symptoms rapidly become life threatening. The typical maple syrup odor of the body and the urine is detectable either immediately or a few days after the onset of symptoms. It can be intense, in which case it is pathognomonic for the disease, or weak, and in some cases is even undetectable. A hyperchloremic metabolic acidosis and hypoglycemia may develop in the course of the illness. Children can die of cerebral edema during an intercurrent infection with severe dehydration and acidosis. If untreated, all patients with onset of symptoms before 16 weeks of age die within 20 months.

In rare cases with a less fulminating course, the patients end up with psychomotor retardation and spastic paresis. The length of time after birth in which the plasma leucine concentration remained above 1 m*M* and the quality of long-term metabolic control have important influences on the patient's IQ (Hilliges *et al.*, 1993). Ocular complications in untreated or late-diagnosed patients include optic atrophy, gray optic papilla, nystagmus, ophthalmoplegia strabismus, and cortical blindness (Burke *et al.*, 1991). In older patients with a subacute course, the increased intracranial pressure leads to the symptoms of pseudotumor cerebri (Levine *et al.*, 1993).

Muller *et al.* (1993) could not find major abnormalities in the MRI of treated patients, yet the chronic accumulation of branched-chain 2-oxo acids in treated patients is associated with chronic demyelinating changes in the CNS visible by imaging. CT and MRI, have shown diffuse symmetrical involvement of the cerebral and deep cerebellar white

matter, basal ganglia, especially of the pallidi, thalami, brain stem, and internal and external capsules in treated patients (Della Puppa *et al.*, 1994). Signs of brain stem compression occurred in some cases after treatment, when biochemical abnormalities were improving (Riviello *et al.*, 1991).

Pathology Death is usually caused by intercurrent infections, most commonly bronchopneumonia (Menkes *et al.*, 1954). Focal fatty infiltration of the liver and deposition of a granular eosinophilic material in the hepatocytes was found in some of the children.

Neuropathology *Gross appearances.* Occasionally, there is evidence of cerebral edema, sometimes especially conspicuous in the brain stem. Cystic lesions and a spongy consistency of the white matter have been mentioned by various authors. Lane (1961) found a cerebral hemorrhage in a child who died at 12 days of age.

Light microscopy. The striking feature is an absence of myelinization in young infants (Menkes *et al.*, 1954). In children surviving to the age of a few months, hypomyelinization, status spongiosus, loss of oligodendrocytes, and proliferation of astrocytes are the main lesions in the white matter. Diezel and Martin (1964) drew attention to minor changes in the cellular organization of the phylogenetically younger parts of the cerebrum and the cerebellum. This is particularly apparent at the border between the cortex and the white matter. Occasionally, one finds a slight deposition of neutral fat in the adventitia of the cerebral blood vessels. Crystalline deposits may be recognized in the astrocytes, and occasionally in the vacuoles of the status spongiosus, in sections of unfixed or alcohol-fixed material (Diezel and Martin, 1964). All of these findings vary with the age of the patient and the effects of therapy. In treated patients who died during the treatment, autopsy revealed cerebral edema with herniation and subarachnoid hemorrhage.

Disorders of amino acid metabolism may be associated with alterations in the terminal stages of neuronal migration and maturation (Kamei *et al.*, 1992). Golgi studies demonstrate an aberrant orientation of neurons together with abnormalities of the dendrites and the dendritic spines. Similar changes have been observed in patients with dihydropteridine reductase deficiency.

Pathogenesis MSUD is due to defective oxidative decarboxylation of the branched-chain α-keto acids derived from transamination of the three branched-chain amino acids—valine, leucine, and isoleucine—catalyzed by the branched-chain α-ketoacid dehydrogenase. As a result of the impaired breakdown of the branched-chain keto acids, the amino acids leucine, isoleucine, and valine, ingested with food, cannot be catabolized. They are retained in the blood, CSF, and tissues and their corresponding keto acids are excreted in the urine.

Acute metabolic decompensation in MSUD during an otherwise minor illness results from the massive release of leucine from protein catabolism. The cause of disturbances of glucose metabolism may be sought in the stimulation of insulin secretion by leucine and 2-oxoisocaproate, on one hand, and in diminished gluconeogenesis, on the other. The morphological changes in the brain are not characteristic of leucinosis, and a diagnosis of MSUD cannot be made based on neuropathological findings. The latter are probably the result of a nutritional protein deficiency. Even the protein crystals described by Diezel and Martin (1964), which may be absent in treated cases, are only suggestive. The abnor-

malities in the oligodendroglia point to a primary impairment of myelinization and not to myelin breakdown as a cause of the observed hypomyelinization (Menkes *et al.*, 1965; Sander *et al.*, 1968).

The mitochondrial branched-chain α-ketoacid dehydrogenase complex is a macromolecule (M_r 4×19^6 consisting of at least six distinct subunits. The human *E1β* gene is over 100 kb long and is split into 10 exons (Mitsubuchi *et al.*, 1991b) and is mapped to human chromosome 6 and regionally assigned to bands 6p21–22. The *E2* gene is localized to chromosome 1 and is regionally assigned to 1p31 (Zneimer *et al.*, 1991).

The concurrent expression of both *E1α* and *E1β* subunits in the same cellular compartment is important for the assembly of both subunits into a functional $E1\alpha_2\beta_2$ heterotramer.

A variety of genetic changes, mainly mutation in the *E1α* and *Eβ* genes, may produce the MSUD phenotype by affecting the function of any of the three complex-specific subunits. Regarding the *E1α* subunit gene, four single-base missense mutations, *R115W*, *Q156K*, *A209T*, *A209T*, *I282T* (Nobukuni *et al.*, 1993), and *T368C* (Hayashida *et al.*, 1994) were detected. MSUD in Mennonites is associated with homozygosity for a T-to-A transversion in this *E1α* gene of the branched-chain α-ketoacid dehydrogenase complex. This causes a Y-to-N substitution at position 393. This mutation impedes the assembly of *E1α* with *E1β* into a stable $\alpha_2\beta_2$ structure, resulting in the degradation of the free *E1β* subunit (Matsuda *et al.*, 1990; Fisher *et al.*, 1991a,b). In a large Mennonite kindred of MSUD studied in Pennsylvania, the *E1α* gene of branched-chain α-ketoacid dehydrogenase, a T-to-A substitution generates an asparagine in place of a tyrosine at amino acid 394 of the mature *E1α* subunit (Mitsubuchi *et al.*, 1992c).

In the *E1β* subunit gene a single-base missense mutation, *H156R*, and three frameshift mutations to generate stop codons downstream, including an 11-bp deletion of the tandem repeat in exon 1, a single-base (T) deletion, and a single-base (G) insertion, were identified. Furthermore, the *E1β* gene revealed a single-base substitution from G to T of the invariant GT dinucleotides at the 5′ splice site of intron 5, and both exons 5 and 6 were absent. This is an example of exon skipping in the *E1β* gene as the cause of MSUD and the mutation of the invariant G at the 5′ splice site, which results in two alternatively spliced mRNAs due to the skipping of the preceding exon as well as both the preceding and following exons (Hayashida *et al.*, 1994).

Within this wide group of mutations is a subset that results in antigenetic absence of the acyltransferase protein of the complex in a compound heterozygote with one allele lacking 15–20 kb of genomic DNA and another allele containing a single-base substitution in the −1 position of the 5′ splice junction following exon 8. All mRNAs for the acyltransferase found have the potential to produce proteins, the largest being 26 amino acids short of a full-length acyltransferase. The potential of these transcripts to produce protein is of interest, since the patient is clinically responsive to thiamine (Herring *et al.*, 1992).

Regarding the *E2* gene, Fisher *et al.* (1993) identified a 2-bp (A-to-T) deletion in exon 2 that causes a frameshift downstream of residue −26 in the mitochondrial targeting presequence. A G-to-T transversion in exon 6 of the *E2* gene produces a premature stop codon at E163.

Fisher *et al.* (1991b) showed a 17-bp insertion in the *E2* gene, apparently resulting from an aberrant splicing of the gene and a missense (T-to-G) mutation that changes F215

to C. This supports the thesis that the thiamine-responsive MSUD patient (*WG34*) is a compound heterozygote at the *E2* locus.

A 78-bp deletion in the mRNA of the *E2* subunit was caused by an exon skipping due to a single base deletion in the 5′ splicing donor site. As a result of the mutation, part of the inner *E2* core domain was omitted (Mitsubuchi *et al.*, 1991a).

Variants of Maple Syrup Urine Disease

Aside from the classical form of the disease, several variants have been described: the intermittent (Morris *et al.*, 1961), intermediate (Schulman *et al.*, 1970), thiamine-dependent (Scriver *et al.*,1971), and ophthalmoplegic forms (Zee *et al.*, 1974). All of these variants are heterogeneous, and the number of biochemically definable entities is probably much greater.

Intermittent Form

Clinical Picture Attacks of the intermittent form can occur at any time in infancy or childhood. They are often preceded by upper respiratory or middle ear infections or may be precipitated by a high-protein meal. They begin with ataxia, followed by disturbances of consciousness, leading to coma. Opisthotonos, choreiform movements, and seizures may also occur. The EEG shows general slowing or dysrhythmia without focal signs. The characteristic maple syrup body odor appears during the attack. A slight to severe metabolic acidosis may be present. An attack may end in death from respiratory failure.

Neuropathology In two autopsy cases (Morris and Fisher, 1966) the findings consisted of cerebral edema, spongy degeneration of the deeper cortical layers, a loss of pontine and nigral neurons, and total necrosis of the granular layer of the cerebellum with preservation of the molecular and Purkinje cell layers. In a pair of siblings, Valman *et al.* (1973) found cerebral edema in one and no abnormalities in the other.

Intermediate and Thiamine-Dependent Forms

Thiamine pyrophosphate is necessary for α-ketoacid dehydrogenase complex activity, and a thiamine-responsive form of MSUD is known. A few cases have been observed (Schulman *et al.*, 1970; Van Der Horst and Wadman, 1971). Aside from delayed motor development and the characteristic odor the patients have no significant symptoms apart from occasional bouts of ataxia. In spite of the benign course of the disease, death may occur during acute episodes of acidosis.

Some patients with MSUD respond to thiamine administration with a reduction in ketoaciduria and an increase in the activity of branched-chain α-ketoacid dehydrogenase. The biochemical mechanism underlying this effect is unknown, but may result from a decreased affinity of the mutant enzyme for thiamine or from stabilization of the abnormal enzyme by thiamine. The *E1*α subunit of the complex participates in the thiamine-dependent decarboxylation of branched-chain α-keto acids. The amino acid sequence of this subunit is identical to that in normal controls, suggesting that in these patients the thi-

amine binding site is abnormal because of a mutation in the *E1β* subunit. Another possible explanation is that a mutation in the *E1β* or *E2* subunit alters thiamine binding by *E1α* because allosteric interactions cause the complex to be unstable, and thiamine stabilizes the complex. A lack of response in cultured cells (Ellerine *et al.*, 1993) suggests that the observed whole-body response to thiamine must be a tissue-specific effect in the liver, muscle, or kidneys.

In a patient with the intermediate form of the disorder, a mutation due to a deletion of exon 5 causing a mutation of the translational stop codon to codon **534Q* was detected. **534Q* mutant polypeptide escapes with degradation, is sorted to dense lysosomes, and has a ninefold higher catalytic efficiency than the wild type (Arlt *et al.*, 1994).

Ophthalmoplegic Form

Shortly after birth cranial nerve palsies become apparent, particularly external ophthalmoplegia. The diagnosis of MSUD is usually delayed by a few months. A residual activity of 10–20% of the branched-chain ketoacid decarboxylase has been established. The ophthalmoplegia and other cranial nerve palsies regress when the patient begins dietary treatment. So far there have been no deaths.

Dihydrolipomide Dehydrogenase Deficiency

Robinson *et al.* (1981) found an increase in branched-chain keto acids in a patient with lactacidosis due to dihydrolipoamide dehydrogenase (E3) deficiency. This is in accordance with the observation by Petit *et al.* (1978) that E3 is a component of the pyruvate and branched-chain ketoacid dehydrogenase complex.

Disturbances of pyruvate or fatty acid metabolism are examples of substrate utilization defects. Dihydrolipoamide dehydrogenase deficiency is one of the four defects of Krebs' cycle. Exon 9 contains the Y393N mutation identified in the *E1α* subunit of Mennonites and other MSUD patients (Dariush *et al.*, 1991).

Liu *et al.* (1993) found two substitution mutations changing a single nucleotide from A to G, resulting in the substitution of E for K at position 37. The other point mutation was a nucleotide change from C to T, resulting in the substitution of L for P at position 453.

Animal Models An animal model of MSUD may be developed by feeding the animals branched-chain amino acids along with treating them with β-chloroalanine (Dwivedi *et al.*, 1992). The only naturally occurring animal models for this disease (i.e., cattle) have also been characterized in polled Hereford calves with clinically confirmed MSUD and neonatal Holstein–Friesian calves with clinically confirmed citrullinemia. Encephalopathy in the former appears to be driven by a diminution of GABA-mediated inhibitory neurotransmission, whereas in citrullinemia the equivalent proconvulsive state may be driven by a relative increase in glutamate-mediated excitatory activity (Dodd *et al.*, 1992). The mutation in polled Hereford calves consists of a single base substitution at codon 6 (C/AG to T/AG) (Zhang *et al.*, 1990), which introduces a stop codon in the leader peptide of the *E1α* subunit, resulting in a premature termination of translation.

Rats fed a diet containing high levels of individual amino acids and α-keto acids show increased concentrations of aromatic amino acids in the brain but not in the plasma.

Conditions Related To Maple Syrup Disease

Hypervalinemia

Only one patient with this deficiency has been described so far. Before treatment he failed to thrive, vomited, and was hypotonic and hyperkinetic (Tada *et al.*, 1967). All symptoms regressed on a valine-free diet. No morphological data are available.

Hyperleucine-isoleucinemia

This biochemical abnormality was reported in two siblings (Jeune *et al.*, 1970). The first symptoms appeared 2–3 months after birth and consisted of seizures, failure to thrive, and mental retardation. The defective enzyme is a branched-chain amino acid transaminase specific for leucine and isoleucine.

Isovalinacidemia

The first two cases were described by Tanaka *et al.* (1966). This variant cannot be diagnosed clinically or by routine biochemical tests, and can only be identified by gas chromatography. While more cases are being reported, insufficient information is available to estimate the incidence of this variant.

Clinical Picture In the acute form of this condition (Newman *et al.*, 1967), hypotonia and poor mobility are evident soon after birth. A striking feature is a penetrating "sweaty feet" body odor. Hypertrophic pyloric stenosis is present in some patients (Lehnert *et al.*, 1979). Most infants die within the first month.

The chronic form consists of episodic phases of vomiting, lethargy, acidosis, and characteristic body odor, all of which regress on a restricted-protein diet. Physical and mental development is usually normal, although in a few cases mental retardation and microcephaly have been recorded.

Pathology Hepatomegaly and polycystic kidneys may be present. Hemorrhages have been repeatedly observed in the lungs, kidneys, adrenals, and pericardium. Light microscopy may reveal fatty infiltration of the liver (Tanaka and Rosenberg, 1983).

Neuropathology *Gross appearances.* Gross cerebral edema is seen.

Light Microscopy. Under light microscopy focal demyelination and gliosis were observed in one patient (Sweetman *et al.*, 1980).

Pathogenesis These patients suffer from an inactivity of all dehydrogenases for different acetyl-CoA complexes. A deficiency of an electron-transferring flavoprotein may

be the common factor responsible for all of these enzyme defects (Tanaka and Rosenberg, 1983).

β-Methylcrotonoyl-CoA Carboxylase Deficiency

β-Methylcrotonoyl CoA is an intermediate product in the catabolism of leucine. Further carboxylation and hydratization produce β-hydroxy-β-methylglutarate-CoA, which, in turn, splits into acetyl-CoA and acetoacetate. In carboxylase deficiency a syndrome is produced resembling infantile spinal muscular atrophy (Werdnig–Hoffmann disease; see p. 654). Other clinical manifestations with metabolic acidosis have also been reported in this enzymopathy (Tuchmann *et al.*, 1993).

Bannwart *et al.* (1992) reported a child who presented from the first day of life with epileptic seizures, a severe generalized muscular hypotonia, progressive psychomotor retardation, and marked EEG abnormalities. Treatment with leucine did not significantly improve these conditions, and the patient died after a prolonged epileptic attack. A severe neonatal variant of this otherwise rather benign genetic enzyme deficiency must be considered. None of the reported cases were subjected to pathological or neuropathological investigations.

β-Hydroxy-β-methylglutaryl-CoA Lyase Deficiency

Patients with this deficiency suffer from episodes of extreme hypoglycemia and metabolic acidosis with vomiting, cyanosis, and hypotonia, resembling Reye's syndrome (Dekremer *et al.*, 1992). Hemiplegia and choreoathetosis may follow these episodes, as well as severe psychomotor delay, seizures, microcephaly, and generalized hypotonia.

Although several of these patients died, necropsy showed signs of neither hepatic nor cardiac derangement (Vilaseca Busca *et al.*, 1990), and no pathological or neuropathological observations have been reported. MRI of the brain shows images suggestive of marked cerebral atrophy, hyperintensive images predominating in the frontal and posterior parietal areas, and punctiform lesions in the basal ganglia. Dekremer *et al.* (1992) considered these findings to be signs of gliosis or demyelination of the white matter and neuronal necrosis of the gray matter. In spite of its rarity, this syndrome may account for the death of some neonates due to hypoglycemia and acidosis.

A 2-bp deletion within the S69 codon results in a truncated nonfunctional hydroxymethylgutaryl-CoA lyase (HL) peptide, present in some patients but not in others, HL-deficient ones showing that HL deficiency is genetically heterogenous (Mitchell, 1993).

Propionyl-CoA Carboxylase Deficiency (Propionic Acidemia)

This condition was identified by Hommes *et al.* (1968) as an independent entity . Similar cases have been reported under the generic term *ketotic hyperglycinemia* (Nyhan *et al.*, 1963; Anderson, 1968; Rushton, 1968; Shuman *et al.*, 1978).

Clinical Picture The disease usually presents during the first week of life with neurological dysfunction, including lethargy or coma, poor feeding, vomiting, hypotonia, respi-

ratory distress, and seizures (Kalloghlian *et al.*, 1992). Other features include neutropenia, thrombocytopenia, hypoglycemia, ketoacidosis, and hyperammonemia. Osteoporosis and spontaneous fractures have also been observed (Lehnert *et al.*, 1994). Most patients die in early infancy, but some may survive up to an age of 2 years (Steinman *et al.*, 1983). A case with late (adult) onset has been reported, presenting with chorea and dementia (Sethi *et al.*, 1989).

Neuropathology The appearances in neonates are different from those seen in older children (Steinman *et al.*, 1983).

Gross appearances. An infant who survived for 12 days was microcephalic, but showed no obvious malformations. There was a localized subarachnoid hemorrhage over the right cerebellar hemisphere. In a child who died at 23 months, the only obvious abnormality was a subdural hematoma over the right cerebral hemisphere.

Light microscopy. The younger infant showed spongy rarefaction at the interface of the gray and white matter of the temporal lobe and neuronal loss in the dentate fascia, end plate, and Sommer's sector of Ammon's horn. Status spongiosus was present in the myelinated tracts of the globus pallidus, internal capsule, medial longitudinal bundle, medial lemnisci, tectospinal tracts, restiform bodies, hila of the inferior olives, and intracerebral fibers of several cranial nerves. The cerebellum showed a striking depletion of the external granular layer and a patchy loss of Purkinje cells. Numerous Alzheimer's type II astrocytes were seen in the basal ganglia.

No status spongiosus was seen in the older child, which showed only some ill-defined pallor the of the myelin. Similar disturbances of myelinization were subsequently reported by Behbehani *et al.* (1984).

Pathogenesis This enzyme defect has been demonstrated in lymphocytes (Hsia *et al.*, 1969) and in cultured fibroblasts (Steinman *et al.*, 1983). It is a deficiency of propionyl-CoA carboxylase that converts propionyl-CoA to D-methylmalonyl-CoA. As a result, increased amounts of propionate are present in the serum and the urine, and increased methylcitrate and 3-hydroxypropionate are found in the urine, while methylmalonate is considerably reduced or absent.

Propionyl-CoA carboxylase is a biotin-dependent mitochondrial carboxylase. It is a dodecamer composed of six α- and six β-subunits. The α-chain is coded by a gene located on chromosome 13; the β-chain on chromosome 3 (Lamhonwah *et al.*, 1986, 1990). The defects on the α-chain (*pccA*) and those on the β-chain (*pccB*) complement each other on human fibroblast cultures (Gravel *et al.*, 1977). Several abnormalities have been detected in the genes. The common defect in white patients is an insertion or deletion in the β-subunit gene, replacing 14 nucleotides with 12 others of unrelated sequence (Tahara *et al.*, 1993). In Japanese patients the common abnormality is the deletion of an entire exon consisting of 101 nucleotides from the β-chain gene (Ohura *et al.*, 1993). A few Japanese patients had neither α- nor β-subunits (Ohura *et al.*, 1991). There is apparently no correlation between the genetic heterogeneity and the clinical presention of propionic acidemia.

As in other aminoacidurias, the excess of one amino acid interferes with the competitive entry of other amino acids into the brain, leading to defective synthesis of myelin

proteins. This manifests itself as status spongiosus of recently myelinated tracts, which disappears with time, leading to generalized hypomyelinization.

Ketothiolase Deficiency (Acetoacetyl-CoA Thiolase Deficiency)

Ketothiolase deficiency is an inborn error of isoleucine and ketone body catabolism that shows autosomal-recessive traits, caused by a deficiency of mitochondrial acetoacetyl-CoA thiolase.

Clinical Picture Statomotor disturbances may be present at birth or may become apparent later. Some children show normal development despite episodic ketoacidosis. RP, amaurosis, and seizures have been reported (Jänisch et al., 1993). These patients present with intermittent ketoacidotic episodes and urinary excretion of 2-methylacetoacetate, 2-methyl-3-hydroxybutyrate, and tiglylglycine.

Pathology Cardiac hypertrophy with vacuolation of the muscle fibers was observed in the only autopsy report available (Jänisch et al., 1993).

Neuropathology The brain pathology consisted of a loss of neurons, spongiosis, and slight reactive astrocytosis affecting the parasagittal areas of the parietal and occipital cortices, visual cortex, putamen, caput nuclei caudati, and claustrum. Furthermore, demyelination of the visual pathways, including the optic chiasm, was seen (Jänisch et al., 1993).

Pathogenesis Three mutant alleles of the gene for mitochondrial acetoacetyl-CoA thiolase have been reported (Fukao et al., 1992): a point mutation of G to A at position 547 on the T_2 cDNA, causing a G150-to-R substitution of the mature T_2 subunit, exon 11's skipping of the T_2 cDNA, and exon 8 skipping.

Hyperphenylalaninemias

The first description of hyperphenylalaninemia goes back to Følling (1934) under the name *imbecilitas phenylpyruvica*. It is the most common disorder of amino acid metabolism. Penrose and Quastel (1937) proposed the term *phenylketonuria* in view of the characteristic excretion of phenylpyruvate in the urine.

The development of a simple method for the estimation of phenylalanine in the blood and the consequent wide use of a screening test led to differentiation of various forms of the disease, differing in their clinical manifestations and their underlying enzyme defects. Of the eight types described so far (Tourian and Sidbury, 1983) four present with prominent neurological symptoms. The other four correspond to that group of patients in whom Jervis (1939) found no neurological symptoms and who account for about one third of all cases of PKU. Another one third suffers from mild, and the last third, from severe, neurological involvement.

Type I: Phenylketonuria (Phenylalanine Hydroxylase Deficiency; Phenylalanine 4-Monooxygenase Deficiency; Oligophrenia Phenylpyruvica; Følling Disease)

Clinical Picture In some patients the symptoms appear during the first few months of life. These include spitting and vomiting, irritability and excitability, deviation from normal reflex behavior, unpleasant body odor reminiscent of mouse droppings or stables, and skin lesions on the trunk.

Most patients show a generalized poverty of pigmentation: pale skin, blue eyes, and very fair hair. Skeletal and dental abnormalities are common. Aside from microcephaly, which develops in about one half of the untreated patients, prominence of the upper jaw with widely spaced teeth has been recorded. Mental retardation varies in severity in the untreated patients (Harper and Reid, 1987).

Severe neurological manifestations include spastic paraplegias and diplegias, pyramidal signs, contractures, and choreoathetoid dyskinesias of the hands and fingers. In about one quarter of all patients, seizures occur, most commonly between the ages of 6 and 18 months. Besides grand mal seizures, lightning, jackknife, and salaam attacks occur in infancy and myoclonic–astatic ones occur in childhood. Abnormalities in the EEG are observed even more frequently than actual seizures. A marked regression of MRI abnormalities as early as 3 months after strict diet control suggests that the observed white matter changes in treated PKU probably represent reversible structural myelin changes rather than permanent demyelination (Bick *et al.*, 1993). Treated adolescent patients with hyperphenylalaninemia show neurological dysfunction that may be related to morphological as well as pharmacological changes (Ludolph *et al.*, 1992).

Maternal Phenylketonuria

Maternal PKU is a syndrome of congenital anomalies and mental retardation that appears in offspring of PKU mothers as a result of fetal exposure to the high phenylalanine level in the maternal blood (Smith, 1993). Children of mothers with PKU may suffer from prenatal malformations with microcephaly and cerebral lesions (Bode *et al.*, 1987; Rohr *et al.*, 1987). The transport of L-phenylalanine and related neutral amino acids is known to be mediated by a stereospecific, sodium-independent, saturable carrier. There is insufficient information concerning the blood–brain barrier transport of amino acids in the fetal brain to allow firm conclusions to be drawn concerning implications for the treatment of maternal PKU. It has been suggested that an inhibition of neutral amino acid influx into the brain by hyperphenylalaninemia contributes to the pathophysiology of brain damage in this condition.

Neuropathology Early neuropathological investigations have yielded negative results. Alvord *et al.* (1950) were the first to demonstrate lesions in the CNS. Since the introduction of screening tests and dietary treatment, few cases have come to autopsy.

Gross appearances. The brain weights are slightly reduced, usually to just under 90% of normal values. Severe reductions are exceptional (Alvord *et al.*, 1950). Slight abnormalities of the convolutional pattern have been repeatedly recorded. The white matter is more severely reduced in comparison with the gray matter.

Light microscopy. Lesions in the white matter may range from spongy rarefaction to extensive demyelination (Fig. 59A, B) (Malamud, 1966; Joshua *et al.*, 1978). Spongy changes (Fig. 60) are more common in younger patients (Malamud, 1966). Neuronal loss in the cerebral cortex is relatively slight (Fig. 61).

The site of predilection of the white matter changes shows a wide range of variation. The optic tracts and radiation are commonly affected, particularly in their central parts (Alvord *et al.*, 1950). Changes may be prominent in the posterior and central parts of the centrum ovale, in the subependymal white matter, in the corpus callosum and other commissures, and in the globus pallidus. The U-fibers are generally spared (Malamud, 1966). In the spinal cord the cervical segments are predominantly affected. In all of these areas, particularly in the subependymal layer, the lesions are accompanied by gliosis. Gliosis was present in the white matter of successfully treated children. Fat granule cells may be present in variable numbers in different cases or in different regions in the same patient.

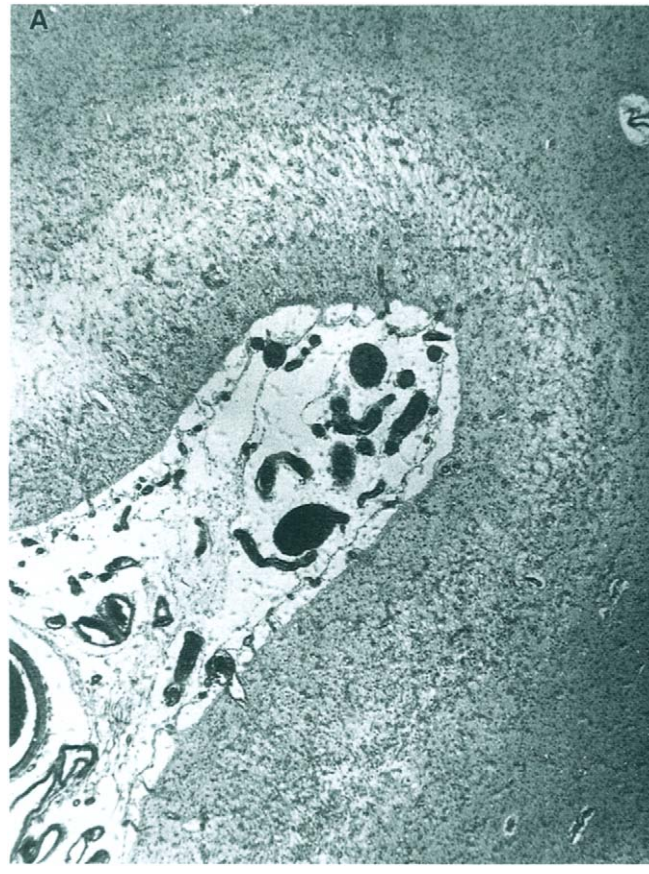


Fig. 59 (A) Area 17, showing spongiosis in the middle layers of the cortex. Hematoxylin–eosin stain, ×24. (B) The putamen, showing a total loss of nerve cells and spongiosis. (Reproduced from Jänisch *et al.*, 1993.)

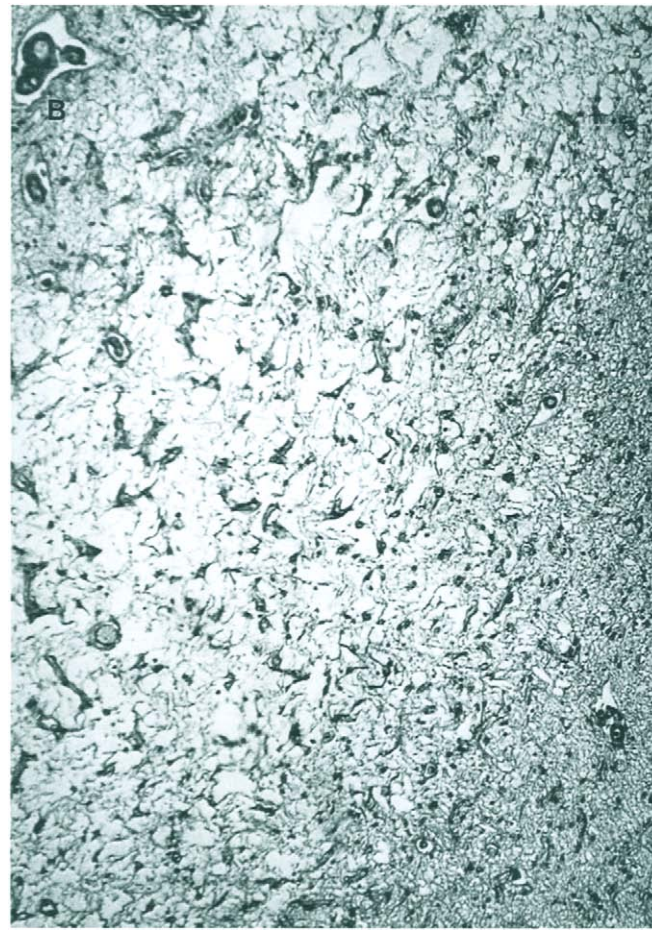


Fig. 59 Continued.

Scholz (1957) found changes in the neuronal cytoplasm and nuclei in one half of the cortical pyramidal cells, in most thalamic and pallidal neurons, and in a few Purkinje cells of a 23-year-old patient. Hypopigmentation of the substantia nigra has been reported. In Golgi preparations an increased development of the dendrites and the dendritic spines as well as a reduction of the same structures has been observed. Robain *et al.* (1981) recorded migration disorders in the cerebellum; Bauman and Kemper (1982), in the cerebral cortex.

Electron microscopy. The spongy vacuoles were seen to be surrounded by laminated myelin (Joshua *et al.*, 1978). Laminar and granulomembranous inclusions were found in the oligodendrocytes, reminiscent of zebra bodies, but more complex (Oteruelo, 1976).

Biochemically, a reduction of the cerebroside and cholesterol fractions has been demonstrated. This is not specific for PKU but has been observed in other disorders of amino acid metabolism, for example, in MSUD (see p. 160).

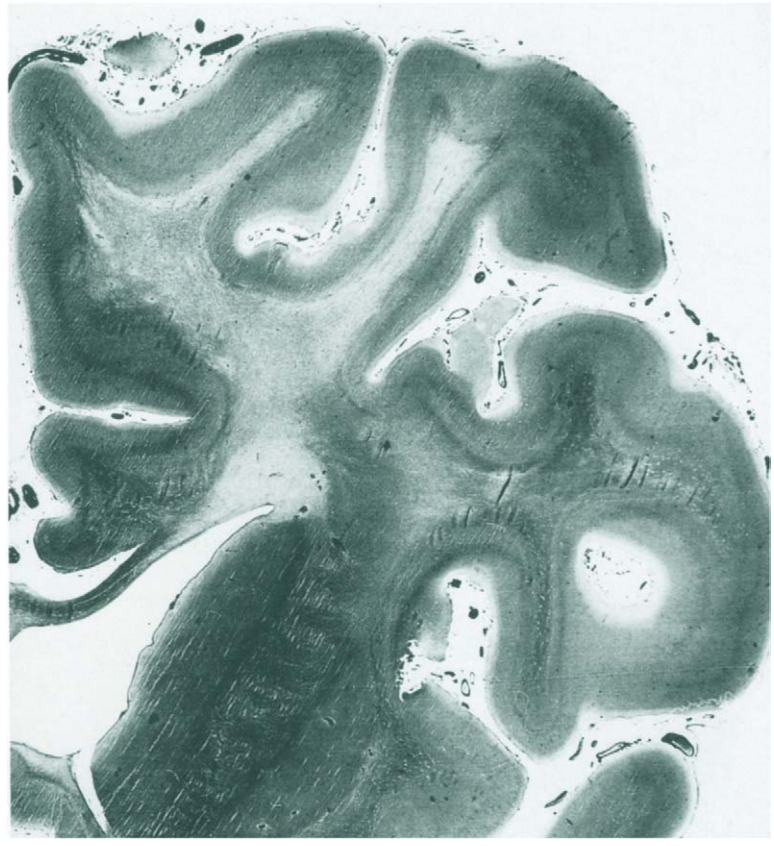


Fig. 60 Phenylketonuria. Extensive demyelination of the centrum ovale. Heidenhain–Wölcke stain. (Courtesy of R. Warzok, Greifswald, Germany.)

Pathogenesis Følling and Closs (1938) were aware of the connection between the excretion of phenylpyruvate and the metabolism of phenylalanine. Jervis (1939) established that the condition was inherited as an autosomal-recessive trait. He demonstrated that the metabolic defect operated at the stage of transition from phenylalanine to tyrosine. In 1953 he succeeded in demonstrating the lack of activity of phenylalanine 4-hydroxylase in the patient's liver.

The differences in neuropathological findings reported by various authors reflect the wide range of clinical symptoms. The metabolic disturbance in PKU does not reside in the brain. There is no correlation between the blood levels of the retained metabolites and the intelligence of the untreated patients. Similarly, the concentration of phenylalanine in the CSF is not an indicator of the severity of the impairment of cerebral functions. Winkler *et al.* (1972) postulated a transport disturbance in the competitive entry of aminoacids into the brain cells, the excess of one amino acid inhibiting the entry of others and leading to reduced protein synthesis.

Fig. 61 Same case shown in Fig. 60. Status spongiosus of the cortex and a loss of myelin in the subcortical white matter, with partial sparing of the unmyelinated fibers. Heidenhain–Wölcke stain, ×12.

Phenylalanine inhibits the absorption of tryptophan in the gut, where both amino acids use the same transport mechanism. Amino acid imbalance in the brain leads to an inhibition of protein, DNA, and lipid syntheses. This is probably enhanced by a specific effect on phosphorylation mechanisms and a competitive influence on various glycolytic and oxidative enzymes. Glutamine concentrations in the CSF of 31 untreated patients were increased to 131% of normal values, on average. Similarly, glutamine values were raised in the white matter of patients compared with normal controls (155%). Levels of phenylalanine and glutamine in the CSF were lower in patients with a low IQ than in high-grade IQs, in spite of similar blood levels. Winkler *et al.* (1972) concluded that in children with PKU with normal intelligence, there was an undisturbed outflow of amino acids from the brain.

A reduced amount of unsaturated long-chain fatty acids found in patients' myelin suggests a disturbance of lipid metabolism limited to the oligodendrocytes.

A high proportion of affected subjects are compound heterozygotes rather than homozygotes, although particular mutations may occur with a frequency of over 60% in certain populations (MRC Working Party on Phenylketonuria, 1993).

The phenylalanine hydroxylase gene (*PAH*) located on chromosome 12 has been cloned, sequenced, and mapped; it is a single-copy gene. PKU and hyperphenylalaninemia are caused mostly by an inherited (autosomal-recessive) deficiency in hepatic PAH activity. More than 50 *PAH* mutations have been reported. Three mutations—*R408W*, *Y414C*, and *IVS12*—together accounted for 56% of all mutant alleles, and 10 relatively infrequent mutations were found on another 17%. Patients from 50 of the 88 families (57%) had mutations identified in both *PAH* genes, which allowed the comparison of the clinical effects of different combinations of *PAH* mutations (Svensson *et al.*, 1993). Disease phenotype is a consequence of the nature of the mutations at the *PAH* locus and is not significantly influenced by other loci.

Molecular studies do not help to predict either the phenotype or the long-term outcome. However, a description of the biochemical changes combined with identification of the mutation should lead to a better understanding of the consequences of mutation for PAH activity (Rey *et al.*, 1992). Fifty to 60 mutations have been reported in white patients, and these are reflected in a wide range of clinical severities. Most mutations are linked to specific haplotypes, as defined by eight polymorphic restriction sites in the *PAH* gene (Svensson *et al.*, 1992). Mutations in the human gene exhibit a high degree of association with specific RFLP haplotypes at the *PAH* locus. About 50 of these mutations are single-base substitutions, including six nonsense mutations and eight splicing mutations, the remainder being missense mutations. One splicing mutation results in a 3-amino acid in-frame insertion. Two or three large deletions, two single-codon deletions, and two single-base deletions have been found (Eisensmith and Woo, 1992).

Nonphenylketonuria hyperphenylalaninemia is defined as PAH deficiency with blood phenylalanine levels below 600 μmol/liter. It has been demonstrated that the identified mutations in this condition have less of an impact on the heterozygote's ability to hydroxylate phenylalanine to tyrosine compared to the patients carrying a *PKU* mutation (Economou-Peterson *et al.*, 1992).

Type IV: Dihydropteridine Reductase Deficiency (Malignant Hyperphenylalaninemia)

Malignant PKU is a rare disease caused by a deficiency in dihydropteridine reductase that induces a hyperphenylalaninemia and a deficiency of neurotransmitters such as 3,4-dihydroxyphenylalanine (Dopa) and 5-hydroxytryptophan. Phenylalanine 4-monooxygenase requires tetrahydrobiopterin as cosubstrate. The latter is oxidized to dihydrobiopterin during the hydroxylation of phenylalanine. Subsequently, dihydrobiopterin is reconverted into tetrahydrobiopterin by the action of dihydropteridine reductase with utilization of NADPH. Three enzymatic defects have been identified so far as leading to tetrahy drobiopterin deficiency: GTP cyclohydrolase deficiency, pyruvoyl-tetrahydropterin synthase deficiency, and dihydropteridine reductase deficiency (Giovannini *et al.*, 1991).

Clinical Picture Symptoms appear soon after birth and consist primarily of a failure to thrive that cannot be controlled by a diet low in phenylalanine. Seizures can be of the grand mal type or, more frequently, in the form of myoclonic attacks. Mental retardation can be diagnosed a few weeks after birth (Danks *et al.*, 1978). The urinary concentration of neurotransmitter metabolites is low. MRI and CT demonstrate diffuse cerebral atrophy and a cystic loss of parenchyma with surrounding white matter changes. T_2-weighted MRI demonstrates the white matter changes better than CT. However, CT demonstrated conspicuously the characteristic calcifications in the basal ganglia and the subcortical region bilaterally (Sugita *et al.*, 1990). MRI demonstrated areas of hypersignal on T_1-weighted images in the basal ganglia, subcortical frontal and occipital white matter, and cortex, probably corresponding to calcifications (Gudinchet *et al.*, 1992).

Neuropathology Diffuse demyelination throughout the white matter and spongy vacuolation in the long tracts of the brain stem are common. Extensive neuronal loss, calcification, and abnormal vacuolar proliferation have been noted in the cerebral cortex, white matter, basal ganglia, and thalamus. Golgi studies demonstrated an abnormal orientation of the neurons together with abnormalities of the dendrites and the dendritic spines (Takashima *et al.*, 1991a).

Pathogenesis The pathogenesis of this condition is unknown, although folate deficiency may be involved. The secondary deficiency of serotonin and dopamine occurring during neuronal growth and differentiation may also affect the terminal stages of neuronal maturation (Takashima *et al.*, 1991a).

Dihydropteridine reductase is necessary for the biosynthesis of tyrosine, dopamine, norepinephrine, and serotonin. The lack of this enzyme interferes with the neurotransmitter balance and hence with the function of the nervous system. The functional relationships between dihydropteridine reductase and folate metabolism (see p. 181) suggest a common pathogenesis of the neurological disturbances in both conditions.

Dianzani *et al.* (1993) identified within the dihydropteridine reductase gene in chromosome 4p15 a mutation that causes a G-to-D substitution at codon 23 and seems particularly frequent in Mediterranean patients. A second change involves a W-to-G substitution at codon 108.

Mutations in genes necessary for the synthesis and regeneration of the cofactor tetrahydrobiopterin also have serious consequences, since this cofactor is absolutely required for all aromatic amino acid hydroxylations and nitric oxide production from L-arginine (Citron *et al.*, 1993).

Type V: Dihydrobiopterin Synthetase Deficiency

6-Pyruvoyl-tetrahydropterin synthetase is the second enzyme in the biosynthetic pathway for tetrahydrobiopterin (BH_4). Lemming *et al.* (1976) described a child with high blood levels of phenylalanine and a progressive neurological illness from birth. Myoclonus, athetoid movements, and difficulty in swallowing were prominent features. Quadriplegia supervened at the age of 1 year. A deficiency of dihydrobiopterin synthetase was demonstrated by Bartholome *et al.* (1977).

Direct cDNA sequence analysis using reverse transcriptase–polymerase chain reaction shown for the central form a homozygous G-to-A transition at codon 25, causing an R-to-Q replacement (*R25Q*) for compound hererozygosity, having on one allele a C-to-T transition, resulting in the substitution of R16 for C (*R16C*) in the enzyme, and on the second allele a 14-bp deletion (*Delta 14bp*), leading to a frameshift at K120 and a premature stop codon (*K120Stop*) (Thony *et al.*, 1994).

Type VI: Hyperphenylalaninemia and Tyrosinemia

Raised blood levels of phenylalanine and tyrosine were described by Rennert *et al.* (1971) in patients with progressive ataxia and seizures that appeared between the ages of 12 and 18 months. This type is probably due to the lack of a PAH cofactor.

Experimental Phenylketonuria Animal models were developed to obtain better insight into the pathogenetic mechanisms by which PKU leads to brain damage. Hypomyelinization was achieved by treating newborn rats with phenylacetate (Loo *et al.*, 1978). Working with the same model, a variety of the lesions were obtained: aggregations of external granule cells in the cerebellum and of neuroblasts in the retina, a reduction in the number of axons in the optic nerve (Wen *et al.*, 1980), and alterations in the development of dendrites in pyramidal and Purkinje cells (Robain *et al.*, 1981, 1983; Cordero *et al.*, 1983).

McDonald *et al.* (1990) described one mutant in which PAH activity is severely deficient. Genetic mapping has localized the mutation to murine chromosome 10 at or near the *PAH* locus, the structural gene for PAH. Shedlovsky *et al.* (1993) isolated three mutants deficient in PAH activity and cross-reactive protein.

If one translates the results of animal experiments to the problems of PKU, it becomes apparent that the high levels of phenylalanine lie in the center of the biochemical abnormalities. The excess of this amino acid interferes with the transport of other amino acids into the brain, leading to an amino acid imbalance that inhibits the synthesis of proteins and lipids, particularly during the stage of active myelinization (Reynolds *et al.*, 1993). In experiments with monkeys and rats, disturbances in amino acid balance cause impairment of learning capacity, but, in contrast with the case of PKU, these disturbances are reversible.

Disorders of Sulfamino Acid Metabolism

This group consists of homocystinuria and methylmalonic aciduria, closely linked with each other and sometimes appearing together, and also includes cystinosis and disorders of folate metabolism.

Homocystinuria (Cystathionine β-synthase Deficiency)

Homocystinuria was first discovered in retarded children in Northern Ireland (Carson and Neill, 1962) and in the United States (Gerritsen *et al.*, 1962). After PKU it is the most common metabolic disorder causing mental retardation. Its exact incidence is not known, but is estimated to be between 1 in 10,000 to 1 in 100,000 live births. The disease is not

genetically homogeneous and may be caused by several enzymatic abnormalities. Some of the patients presenting with homocystinuria suffer from disorders of folate or cobalamin (vitamin B_{12}) metabolism.

Clinical Picture All grades of mental retardation may be observed; about one half of the patients have normal intelligence. Failure to thrive, retarded motor and intellectual development, and occasional seizures may become apparent during the first few years of life. Dislocation of the lens is a common finding (Kraus *et al.*, 1993), usually occurring between the ages of 2 and 3 years and leading to myopia and, occasionally, glaucoma. At puberty the patients often present with a marfanoid appearance (Müller *et al.*, 1983). Other features are sparse, light, dry hair and livedo reticularis. A marked tendency to atherosclerosis and thromboembolism, even in young children, may lead to life-threatening complications, such as stroke, myocardial infarction, or pulmonary embolism (Liebermann *et al.*, 1993). High blood pressure is the rule. Even in heterozygotes, there is an increased risk of cerebrovascular accidents (Minkhorst *et al.*, 1991; McCully, 1993). Mild homocystinemia occurs surprisingly often in patients with premature vascular disease (Dudman *et al.*, 1993).

Aside from neurological symptoms due to vascular accidents, other manifestations include epilepsy, EEG abnormalities, dystonias (Berardelli *et al.*, 1991), and schizophrenia-like disturbances (Bracken and Coll, 1985) with excessive irritability. CT scans may reveal sinus thrombosis and multifocal infarcts in young patients (Schwab *et al.*, 1987).

Pathology *Gross appearances.* One frequently finds thrombi in various veins and pulmonary emboli. In the aorta corrugations have been observed, running transversely to the long axis of the vessel. The liver and the heart may be slightly enlarged.

Light microscopy. Vascular lesions predominate in the form of intimal thickening, splitting of the internal elastic lamina, deposition of a metachromatic substance in the media, and narrowing of the lumen. The thrombotic tendency may be observed in both arteries and veins. Old and recent infarcts may be present in all organs. The liver shows centrilobular fatty changes, but no cirrhosis. Apart from the frequent dislocation of the lens, other findings in the eye include atrophy and fibrosis of the ciliary body, keratitis, and corneal scarring.

Electron microscopy. Electron microscopy confirmed intimal hyperplasia in the renal arteries.

Neuropathology *Gross appearances.* The most common finding is cerebral atrophy with marked hypoplasia of the corpus callosum (Chou and Waisman, 1965). Circumscribed ulegyrias may be seen occasionally. Fresh thrombi may be found in the superior sagittal sinus, the great vein of Galen, and smaller veins (Cochran and Packmann, 1992). The subcortical white matter appears grayish and soft. Old and recent hemorrhagic infarcts are seen particularly in the occipital lobes and the thalamus. Ischemic lesions of various ages are scattered throughout the brain.

Light microscopy. Infarcts may be seen in various stages of evolution. Blood vessels in the neighborhood of fresh infarcts may be surrounded by a layer of fibrin and macrophages containing sudanophilic lipid (Chou and Waisman, 1965). Partially organized mi-

crothrombi are seen in arterioles, and, less commonly, in venules and capillaries. Endothelial proliferation and hyalinization of the vessel wall is found in arterioles remote from foci of softening that may be surrounded by loose fibrillar connective tissue. Perivascular demyelination and gliosis are seen throughout the cerebral and cerebellar white matter, particularly in the corpus ovale. The demyelination may exceed the extent attributable to vascular involvement. Vacuolar rarefaction of the white matter may be observed in the brain stem and the spinal cord.

Pathogenesis Methionine is demethylated through *S*-adenosylmethionine to homocysteine. This reacts with serine in a reaction dependent on pyridoxal phosphate and catalyzed by cystathionine β-synthase to form cystathionine. This is metabolized by a lyase to cysteine and homoserine or 2-oxobutyrate. In homozygotes of homocystinuria, the activity of cystathionine β-synthase is reduced in the liver and the brain. This enzyme defect leads to increased blood levels of methionine and homocysteine. The latter may be responsible for the thrombotic tendency, as it increases platelet adhesiveness and activates the Hageman Factor (Factor XII). Fryer *et al.* (1993) believed the high homocysteine concentration to be responsible for endothelial damage, which they considered to be the primary lesion, with thrombosis as a secondary phenomenon. Celermajer *et al.* (1993) could demonstrate a functional impairment in endothelial cells. High plasma concentrations of copper and ceruloplasmin were thought to act as contributory factors. The correlation of the metabolic disorder with clinical symptoms is unclear. The repeated subclinical cerebral thromboses probably contributed to the mental retardation.

Hypoglycemia is thought to be due to alterations in insulin release associated with high levels of circulating sulfur-containing amino acids such as methionine (Lowe *et al.*, 1994). The human gene for cystathionine β-synthase maps to chromosome 21q22.3 and encodes the subunit of 551 amino acid residues (663 kDa). Kraus (1994) identified 14 mutations in homocystinuria. The most common mutation in patients of predominantly Celtic origin is the G-to-A transition, at position 919, which substitutes for 307.

Cystinosis

Abderhalden (1903) described a child with cystine crystals in the liver and the spleen, and Beumer and Wepler (1937) pointed out the relationship between cystinosis and Fanconi's syndrome. The latter, however, may also be due to other causes.

Clinical Picture There is great variation of the clinical spectrum in different families, ranging from a severe nephrotic syndrome with rickets and dwarfism to a benign asymptomatic form. In the benign form psychomotor development is normal, although children with cystinosis have a significantly lower mean IQ than their siblings and their parents (Williams *et al.*, 1994). More than half of the patients with the severe chronic form of cystinosis suffer moderate to severe swallowing abnormalities. Cerebral calcifications on CT were detected in 25% of the patients (Theodoropoulos *et al.*, 1993). Death is usually due to uremia.

Pathology Cystine crystals are found in the cornea, conjunctiva, bone marrow, lymph nodes, spleen, and liver. These crystals can be seen in unfixed frozen sections or in alco-

hol-fixed material and may assume different shapes. They are easily recognizable in semithin sections of plastic-embedded material (Fig. 62A). Crystals are rarely found in skeletal muscles, but a distal vacuolar myopathy is a common late complication of untreated nephropathic cystinosis (Charnas *et al.*, 1994). Electron microscopy reveals rectangular or polygonal crystals (Fig. 62B) that may contain membranes or a loose floccular material (Cruz-Sanchez *et al.*, 1989a).

Neuropathology *Gross appearances.* Hydrocephalus has been observed occasionally. Moderate atrophy of the frontal lobes was found to result from an atrophic and shrunken white matter (Vogel *et al.*, 1990).

Light microscopy. Crystals are found in the interstitial cells of the choroid plexuses and in the leptomeninges (Levine and Paparo, 1982). Symmetrical calcifications in the internal capsule and the brachium pontis were described by Vogel *et al.* (1990). Peripheral nerves and muscles are spared, as a rule.

Electron microscopy. Electron microscopy of the brain documented cytoplasmic deposition of cystine crystals in membrane-bound vacuoles within the cytoplasm of pericytes and within parenchymal cells of the white matter (Vogel *et al.*, 1990).

Pathogenesis The disorder is autosomal recessive and consists of an increase in the amount of cystine in the tissues. The cystine remains intracellular and accumulates in the

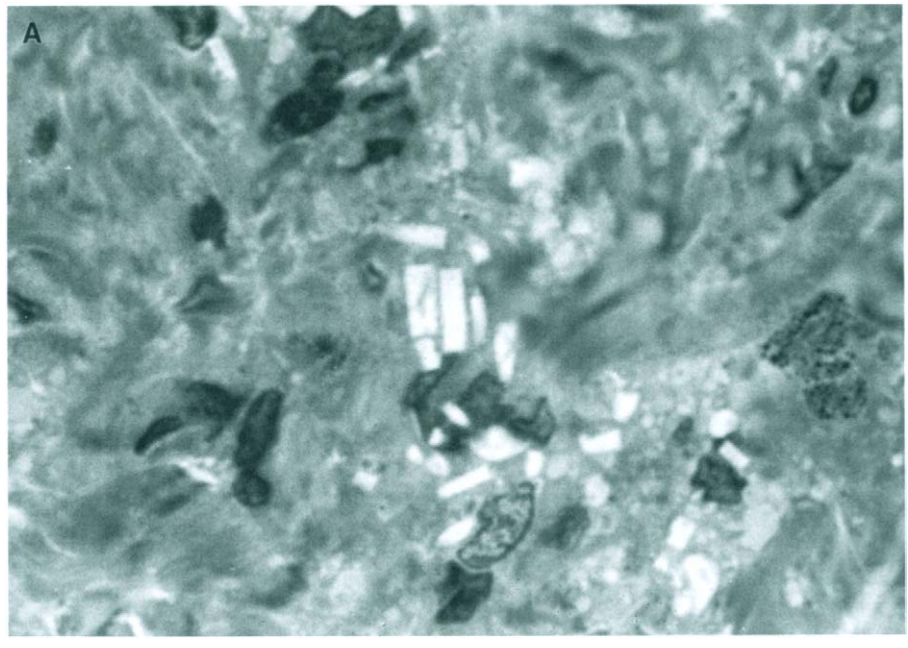


Fig. 62 A conjunctival biopsy of a patient with cystinosis. (A) Numerous rectangular crystals in the tunica propria, ×700. (B) Cystine crystals in conjunctival fibroblasts, ×9000.

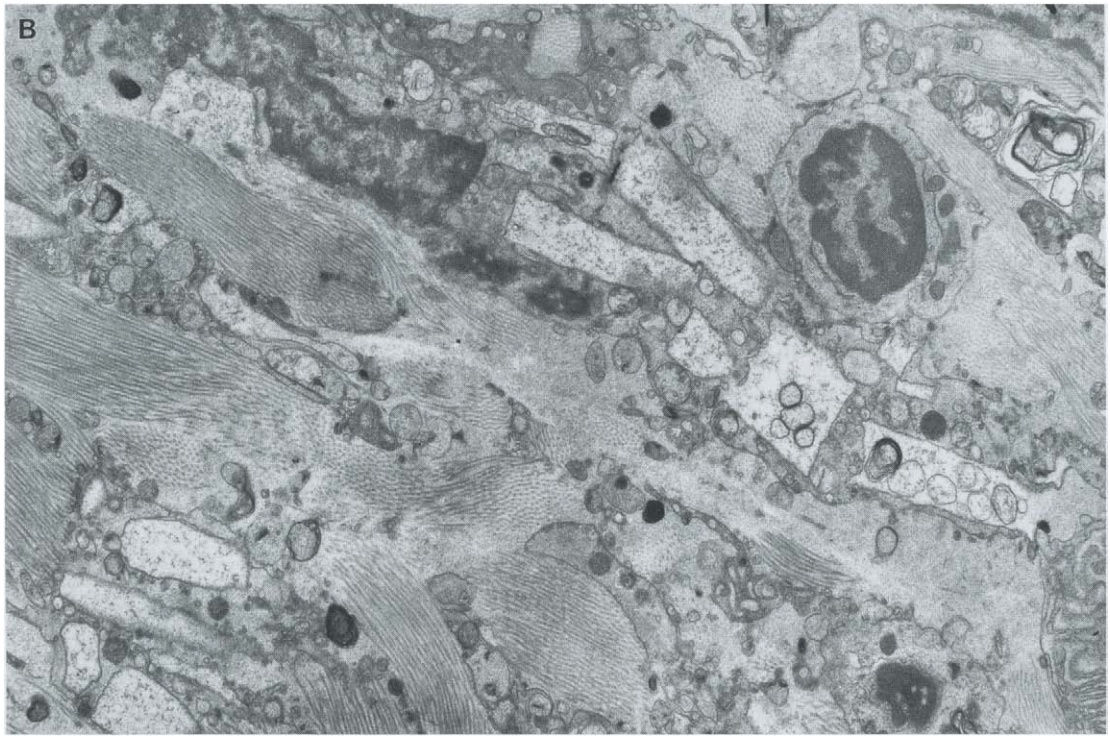


Fig. 62 Continued.

lysosomes. The formation of crystals has a particularly deleterious effect on the kidneys. A disturbance of the transport of cystine out of the lysosomes is thought to be the cause of the disease.

Swallowing disturbances are probably related to muscular dysfunction (Sonies *et al.*, 1990). The hydrocephalus has been ascribed to a disturbance of CSF dynamics caused by crystal deposition in the choroid plexuses, but this appears unlikely. Levine and Paparo (1982) explained the observed parenchymal necrosis by metabolic disturbances that manifest themselves only after a prolonged course of the disease.

Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)

Mudd *et al.* (1967) described the case of a 2½-year-old boy with severe mental retardation, blindness, and spastic quadriplegia. Additional cases have since been reported. The patient's urine contained *S*-sulfocysteine, thiosulfate, sulfite, and taurine. Intractable seizures in the neonatal period may be caused by molybdenum cofactor deficiency, an inborn error that combines the deficiencies of sulfite oxidase and xanthine dehydrogenase (Slot *et al.*, 1993). Molybdenum cofactor deficiency can mimic postanoxic encephalopathy (Bakker *et al.*, 1993). In molybdenum cofactor deficiency the most frequently noted clinical features are neonatal seizures, abnormal tone, and opisthotonos. Though common

later, lens dislocation may not be present in infancy. Craniofacial dysmorphic features, including narrow bifrontal diameter and enophthalmos, have been reported (Bamforth *et al.*, 1990). The liver showed fatty metamorphosis (predominantly microvesicular) in the second and third acinar zones, as well as diffuse centrilobular necrosis, hemorrhage, and acute inflammation.

Neuropathological examination showed multicystic encephalopathy involving both cerebral hemispheres, including the centrum semiovale, basal ganglia, thalamic nuclei, and inner layer of the cortex. The cavities were separated by thick glial scar tissue stained by hemosiderin. Organizing cavities were filled with fat-laden macrophages. The gray matter had areas of micronodular mineralization.

This disorder is inherited as an autosomal-recessive trait, and the presence of two complementation groups in patient fibroblasts suggests that mutations in at least two different peptides can cause the condition (Arnold *et al.*, 1993).

Pathogenesis The molecular structure of *S*-sulfocysteine resembles that of glutamate and other excitotoxic amino acids. The cytotoxicity of *S*-sulfocysteine was demonstrated by Olney (1993). A deficiency of xanthine oxidase is often present in addition to that of sulfite oxidase, due to a defect in the metabolism or transport of molybdenum, which is an essential component of both enzymes. Molybdenum supplementation significantly increases the activities of xanthine dehydrogenase/oxidase, sulfite oxidase, and superoxide dismutase in rat liver (Wang *et al.*, 1992).

The gene encoding sulfite oxidase in the rat contains a single open reading frame of 1464 nucleotides. The amino acid sequence shows significant similarity to those of sulfite oxidase from chicken and nitrate reductase from algal, fungal, and plant sources (Garrett and Rajagopalan, 1994).

Disorders of Folate Metabolism

Folic acid, a pteridine derivative, is a vitamin required for various steps in the synthesis of purines and pyrimidines, for the catabolism of glycine and histidine, and for the synthesis of methionine. About 16 enzymes are involved in the metabolism of folic acid (Erbe, 1979). The most active form of the vitamin is tetrahydrofolic acid (tetrahydrofolate, or FH_4). Folates appear in relatively high concentrations in the brain; their concentration in the CSF is several times higher than in the plasma. Methionine synthase is the only enzyme that simultaneously requires vitamin B_{12} and methyltetrahydrofolic acid. This enzyme converts L-homocysteine into L-methionine by methylation. There are several inborn errors of folate uptake and metabolism. These lead to mental retardation and neurological symptoms, while folate deficiency in adults causes only insomnia, forgetfulness, and irritability.

5,10-Methyltetrahydrofolate Reductase Deficiency

Mudd *et al.* (1972) were the first to describe a form of homocystinuria with normal cystathionine β-synthase activity, but with a deficiency of 5,10-methyltetrahydrofolate reductase.

Clinical Picture Three forms of the disorder are recognized. The first manifests itself soon after birth with apnea and generalized seizures. Death occurs in childhood. In the second form psychomotor retardation becomes apparent after the first year or later (Erbe, 1979). The patients develop hyperactivity and spasticity and often die suddenly early in the second decade. The CT scan shows mild cortical atrophy and MRI reveals increased intensity on T_2-weighted images in the cerebral white matter (Takenaka *et al.*, 1993). In the third form symptoms appear in adolescence (Mudd *et al.*, 1972). Occasionally, patients have developed a schizophrenia-like syndrome that dominated the clinical picture. Patients in this group survive to adult life and may develop a peripheral neuropathy (Ludolph *et al.*, 1993) as well as recurrent strokes (Visy *et al.*, 1991). No anatomopathological observations are available for the third form.

Pathology Patients with the neonatal and late infantile forms of this deficiency show similar abnormalities. Extensive thrombi are found in the pulmonary arteries, causing multiple pulmonary infarcts. Atherosclerosis and hyalinosis are seen in the blood vessels of the liver, spleen, and skeletal muscles. The aorta and other arteries show focal hyperplasia of the intima and splitting of the elastica. Electron microscopy reveals lipid droplets and peculiar multivesicular bodies in the hepatocytes.

Neuropathology *Gross appearances.* Thrombosis of the superior sagittal and lateral sinuses has been found in a few cases.

Light microscopy. Perivascular foci of demyelination are seen in the white matter of the cerebrum, cerebellum, pons, and medulla oblongata (Narisawa, 1979). A prominent hyalinosis and occasional thrombosis are found in the arterioles. Isolated neurons in the second and third cortical layers show ischemic changes.

Electron microscopy. In cortical neurons Hirano bodies and in Purkinje cells crystalline structures can be found. The demyelination of individual axons reported by some authors may well be due to artifact.

Pathogenesis The connection between folate deficiency and mental retardation is obscure. Lanzkowsky (1970) thought that folate deficiency inhibited the development of the brain. This may be supported by the observation that hydrocephalus in rats kept on a folate-free diet is aggravated by the addition of a 5-methyltetrahydrofolic acid antagonist. The importance of methyltetrahydrofolate and particularly of endogenous methionine for the biosynthesis of neurotransmitters may explain the high vulnerability of the CNS (Rowe, 1983).

5-Methyltetrahydrofolate–Homocysteine Methyltransferase and Methylmalonyl-CoA Mutase Deficiency

Two groups of patients (CblC and CblD) diverge so widely in their clinical pictures as to lead to the conclusion that they are due to different biochemical causes. The patients of type CblD are recognized only during the second decade, when they exhibit behavior disorders and minimal mental retardation. They show few neurological abnormalities and are not considered further here.

Clinical Picture Patients of type CblC present from birth with a megaloblastic anemia, renal failure, psychomotor retardation, RP, and petit mal seizures (Hall, 1990). Some patients die within a few weeks or months (Chenel *et al.*, 1993), whereas others survive to a later age. On MRI major leukodystrophic changes can be observed (Chenel *et al.*, 1993).

A distinctive phenotype of the disease that is intermediate between the fulminant and benign forms of methylmalonic aciduria has been reported (Crane *et al.*, 1992).

Pathology With the exception of megaloblastic changes in the bone marrow and focal intimal thickening in the blood vessels, the reported lesions in various organs differ from patient to patient, and no constant pattern is recognizable. Thromboembolism may be part of the disease (Brandstetter *et al.*, 1990).

Neuropathology *Gross appearances.* Mild to moderate cerebral atrophy affects mainly the frontal and parietal lobes. The white matter shows a diffuse grayish discoloration with small sunken areas around the blood vessels. The lateral ventricles may be slightly dilated.

Light microscopy. In the case reported by Dayan and Ramsey (1974), multiple perivascular foci of demyelination were scattered throughout the centrum ovale. They were particularly abundant in the subcortical U-fibers. In the smallest foci swollen axons were seen, with signs of active myelin breakdown and a few lipid-laden macrophages. In larger foci no oligodendrocytes could be seen; they contained only a few fibrillary astrocytes. In the globus pallidus the demyelination was particularly striking and the number of fat granule cells was more abundant than in the centrum ovale. The arterioles in the white matter showed focal fibrinoid necrosis, staining positively with PAS and deep purple with Mallory's phosphotungstic acid–hematoxylin. Other vessels showed intimal swelling and endothelial proliferation, some containing microthrombi. In a neonate there is selective cell death of immature neurons involving the germinal matrix, migrating neuroblasts, and both external and internal granular cell layers of the cerebellum and the dentate gyrus of the hippocampus. In a 7-day-old girl who died from a disorder in the metabolism of methylmalonic acid, Ostergaard *et al.* (1991) found severe reactive gliosis of the cerebral white matter and the deeper layers of the cortex, incomplete development of the fetal granular layer of the cerebellum and Bergmann's glial cells, and delayed myelination of the cerebellum, brain stem, and cervical spinal cord. Traboulsi *et al.* (1992) found ultrastructural evidence of possible lysosomal dysfunction and mucopolysaccharide storage in the ganglion cells of the retina. Mozzicato *et al.* (1990) demonstrated in a skin biopsy rectilinear profiles in lysosomes of sweat gland epithelial cells. The inclusions were composed of stacks of electron-dense lamellae that were generally straight in configuration. Sum *et al.* (1993) reported in their case optically empty spaces in their myelin sheaths due to adaxonal separation of their myelin lamellae.

Pathogenesis In patients excreting homocysteine and methylmalonic acid in their urine, there is a deficiency of two enzymes: the 5-methyltetrahydrofolate–homocysteine methyltransferase (methionine synthase) and methylmalonyl-CoA mutase. Both enzymes require vitamin B_{12} derivatives for their catalytic action. It can be demonstrated that the

inactivity of these enzymes in both forms of the disease (CblC and CblD) is not caused by lack of apoproteins, but by a deficiency of the active vitamin B_{12} derivatives methylcobalamin and adenosylcobalamin. In glial cells cobalamin coenzyme synthesis and function are exquisitely sensitive to short-term cobalamin deprivation (Pezacka *et al.*, 1992). CNS methyltransferases methylate is a wide range of substrates, including proteins, lipids, nucleic acids, and hormones. In every instance the methyl donor is *S*-adenosylmethionine and the demethylated product is *S*-adenosylhomocysteine. Disorders such as vitamin B_{12} deficiency or folate deficiency inhibit methylation by limiting the availability of *S*-adenosylmethionine or by elevating levels of the inhibitor *S*-adenosylhomocysteine (Scott *et al.*, 1994).

The pathogenesis of the vascular changes and perivascular demyelination is probably the same as in homocystinuria (see p. 176). The presence of fibrinoid necrosis implies increased permeability of the vessel wall to plasma components. L-Methylmalonyl-CoA mutase is controlled by a gene that has been mapped to chromosome 6 (Sertic *et al.*, 1990).

Distinct genotypic and phenotypic forms of methylmalonyl-CoA mutase apoenzyme deficiency can be delineated by biochemical analysis of the mutant fibroblasts. One form, designated *mut*−, expresses a phenotype in which residual enzyme methylmalonyl-CoA mutase apoenzyme deficiency and methylmalonic aciduria are characterized by undetectable enzyme activity (Qureshi *et al.*, 1994). Phenotypic pleomorphism without a consistent pattern of neurological injury suggests some broad correlation between mutase class and phenotype (Shevell *et al.*, 1993).

Congenital Malabsorption of Folates

Congenital folate malabsorption is a rare inborn error of metabolism characterized by the selective inability to absorb folates from the gastrointestinal tract and across the blood–brain barrier. The first case of this disorder was described by Luhby *et al.* (1961). Megaloblastic anemia was diagnosed a few months after birth, followed by mental retardation, ataxia, and seizures. Lanzkowsky *et al.* (1969) reported the case of a 20-year-old woman with a congenital folate malabsorption, megaloblastic anemia, and athetoid movements. Calcification of the basal ganglia was revealed radiologically. In contrast to the resolution of systemic symptoms, the neurological sequelae have been more recalcitrant to therapy (Steinschneider *et al.*, 1990). No morphological observations are available.

Celiac Disease, Epilepsy, Bilateral Occipital Calcifications, and Folate Deficiency

An increased prevalence of epilepsy in patients with celiac disease (CD) has been known since the observation of Laidlow *et al.* (1977). Later, the association of epilepsy, intracranial calcifications, and CD was reported (Ventura *et al.* 1991; Gobbi *et al.*, 1992). A possible correlation with folic acid deficiency has been postulated. Patients with bilateral intracranial calcifications and intractable epilepsy showed low folic acid levels and have been diagnosed as having CD (Bye *et al.*, 1993).

In most patients epilepsy started before the diagnosis of CD, at the age of 1–14 years, mostly as occipital seizures and other types of partial seizure. These patients showed fo-

cal abnormalities on the EEG and less frequently generalized abnormalities. As a rule, the seizures are drug resistant. Other neurological disorders in CD are peripheral neuropathy and cerebellar disease (Kristoferitsch and Pointner, 1987). Occipital seizures associated with CD but without cerebral calcifications may be an early manifestation of the disorder, with the calcifications developing later (Ambrosetto *et al.*, 1992). Hypodensity on CT and an abnormal MRI signal, usually also anterior to the calcifications, have been described (Gobbi *et al.*, 1992). Psychomotor development was normal in most patients at the beginning of the epilepsy, but progressively deteriorated in half of the patients. Dementia was described only in isolated cases (Collin *et al.*, 1991).

A calcified area in the centrum semiovale was also found. MRI showed a hyperintense area in the same region on T_2-weighted images. Multiple hyperintense areas on T_2-weighted images were present in the white matter of the occipital, temporal, and frontal regions. This finding was clearly more diffuse, and a possible progressive leukoencephalopathy was suggested.

The intracranial calcifications display a serpentine double-contoured pattern. Some of the cases previously described as "atypical Sturge–Weber syndrome" (epilepsy with calcifications but without angiomas and mental retardation) may have been caused by folic acid deficiency, possibly due to CD.

Glutamate Formiminotransferase Deficiency

Arakawa *et al.* (1972) described a series of Japanese patients with glutamate formimino transferase deficiency who suffered from severe mental retardation. In other patients with the same enzymopathy, neither mental nor neurological abnormalities were found (Perry *et al.*, 1975). A 7-year-old boy with this enzyme deficiency showed hyperkinetic behavior, delayed development of speech, and an abnormal EEG.

Other Inborn Errors of Amino Acid Metabolism

Hyperglycinemias

Hyperglycinemia, or glycinemia, must be distinguished from glycinuria, in which high concentrations of glycine are found in the urine, but not in the serum. The first case of hyperglycinemia was described by Childs *et al.* (1961). According to the symptomatology and the clinical course, the condition may be divided into two forms: an acidotic (ketotic) and a nonacidotic (nonketotic) form (Rampini *et al.*, 1967). In some cases the same biochemical abnormality may have very little, if any, clinical expression. The hyperglycinemia observed in some cases of methylmalonic acidosis is an epiphenomenon (Ugarte *et al.*, 1979).

Ketotic Hyperglycinemia

Clinical Picture Ketotic hyperglycinemia manifests itself soon after birth, as a rule, or occasionally appears later in infancy (Gerner and Hughes, 1984). Somnolence and

poor mobility proceed to lethargy and unresponsiveness. Muscle tone is often increased to begin with, followed by hypotonia. Myoclonic jerks are common; epileptic seizures, less so. Life-threatening crises occur with vomiting, metabolic acidosis, hyperpnea, ketonuria, thrombocytopenia, and neutropenia. In the ketotic form these crises are related to protein intake. Children may die during one of the crises, even in the neonatal period. Psychomotor retardation may be observed between the acute episodes.

Pathology *Light microscopy.* Diezel and Martin (1966) found vacuoles in the cells of the adrenal medulla, the epithelia of the liver, and the renal tubules. These contained water-soluble proteins and small quantities of a nonspecific esterase. Vacuolation of the hepatocytes was continued only in some cases.

Electron microscopy. The contents of the vacuoles appear partly amorphous and partly filamentous (Bachmann *et al.*, 1971).

Neuropathology *Gross appearances.* Occasional cerebral edema and grayish discoloration of the white matter (Fig. 63A) may be seen.

Light microscopy. A defect in the maturation of the myelin sheaths is seen in most cases. In the phylogenetically old tracts the amount of myelin is reduced (Diezel and Martin, 1966). In these areas the white matter is studded with small empty spaces with a diameter of up to 100 μm, producing a fine status spongiosus (Fig. 63B). In cryostat sections of unfixed material, the spaces are seen to be filled with a weakly PAS-positive fluid, rich in protein (Diezel and Martin, 1966). In tissue treated with absolute ethanol, the protein tends to precipitate and form birefringent crystals (Bachmann *et al.*, 1971). The status spongiosus is found exclusively in the myelinated parts of the CNS, including the brain stem (Scher *et al.*, 1986) and, with some variation from case to case, in the spinal cord. Both inside and outside the areas of status spongiosus, fat-laden astrocytes are more numerous than the myelinization glia of normal age-matched controls.

Abnormalities in the cellular structure also occur in the cerebral and cerebellar cortices, and in patients dying in infancy the external granular layer of the cerebellum is exceptionally broad.

Electron microscopy. Widening of the extracellular spaces is prominent in the cerebral cortex (Bachmann *et al.*, 1971). Aside from swelling of the dendrites, the oligodendroglia is also swollen and correlates with the status spongiosus (Fig. 64). The cytoplasm of the hyperplastic astrocytes contains numerous organelles and glial fibers (Fig. 65).

Nonketotic Hyperglycinemia

Brandt *et al.*, (1974) described a metabolic disorder similar to hyperglycinemia with high levels of D-glycolate in the serum. Grandgeorge *et al.* (1980) described a similar case without hyperglycinemia.

Clinical Picture Children with nonketotic hyperglycinemia (NKH) develop a generalized hypotonia with hypertonic crises and myoclonus during the first few months after birth. In the cases with less pronounced symptoms, but accompanied by slight mental retardation, the diagnosis can be confirmed by demonstration of a defect in the activity of

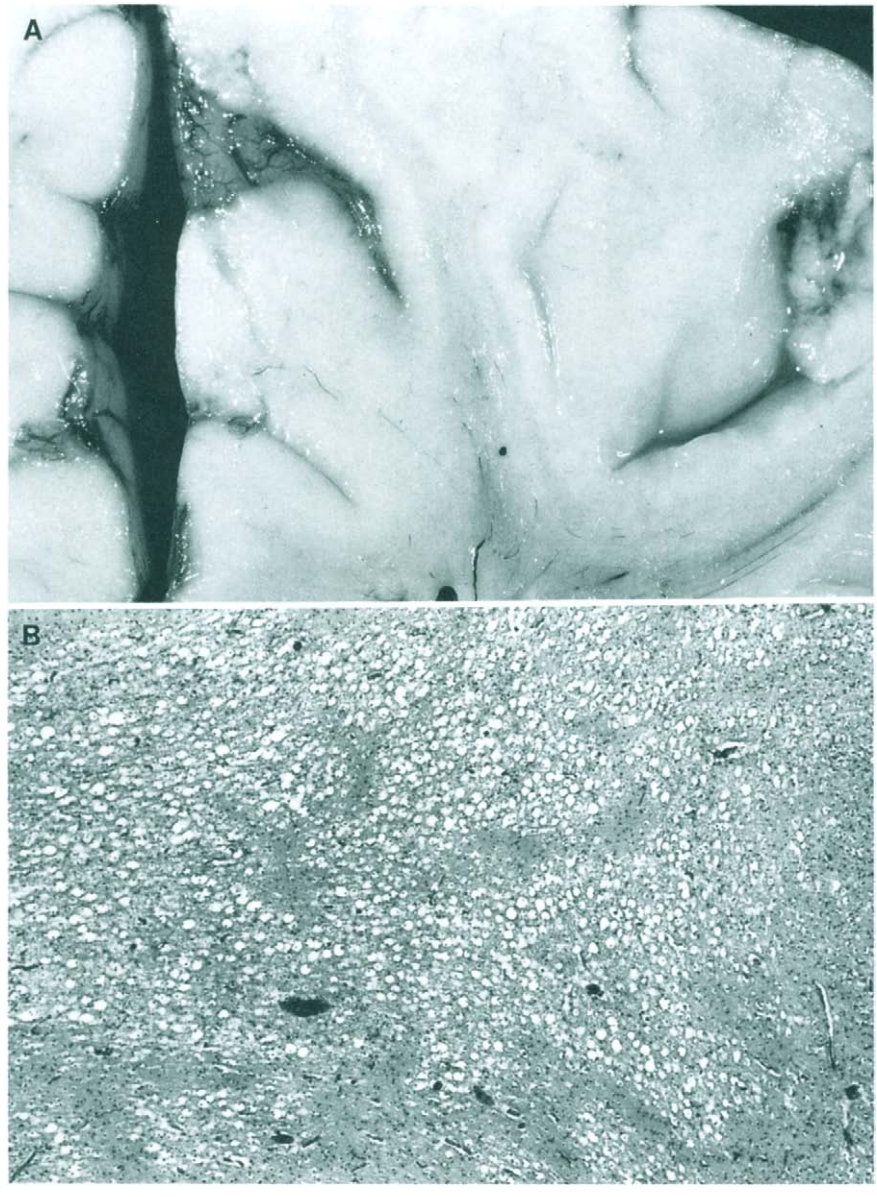


Fig. 63 Hyperglycinemia. (A) Gray discoloration of the white matter. (B) Status spongiosus in the frontal white matter, ×80.

the glycine cleavage system in cultured lymphoblasts (Ko *et al.*, 1993). The clinical course is variable. The plasma and CSF glycine concentrations are elevated, and the CSF–plasma glycine ratio can be mildly elevated. Some children die after a few months

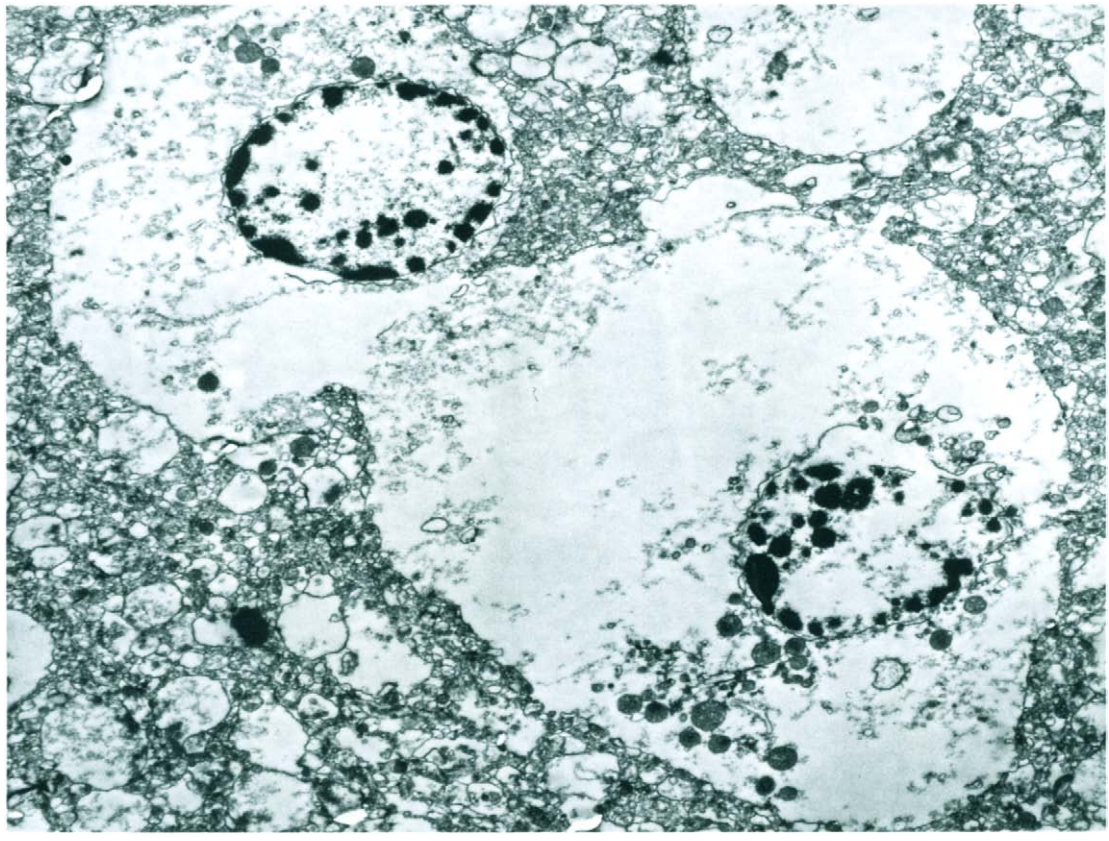


Fig. 64 Same case shown in Fig. 63. Swelling of the oligodendroglia, ×12,000.

with progressive severe hypotonia, coma, and dyspnea (Tokoro *et al.*, 1994), whereas others die after several years. Despite normalization of the biochemical values, severe neurological sequelae may be observed (Eyskens *et al.*, 1992). Retinal impairment and blindness have been reported in adult patients (Tanaka *et al.*, 1993).

Neuropathology Identical twins with NKH and dysplasia of the corpus callosum have been described (Rogers *et al.*, 1991). Light microscopy shows a delay in myelinization of the entire CNS.

On electron microscopy Grandgeorge *et al.* (1980) found edematous swelling of the axons and the postsynaptic dendrites. In the presynaptic terminals inclusions were seen, consisting of rolled-up membranes, with an occasional pseudocrystalline arrangement. Abnormal mitochondria showed scanty cristae and an accumulation of glycogen.

Pathogenesis The biochemical cause of this disorder is a lack of activity of D-glycerate dehydrogenase, leading to a disturbance of serine and glycine metabolism in presynaptic ter-

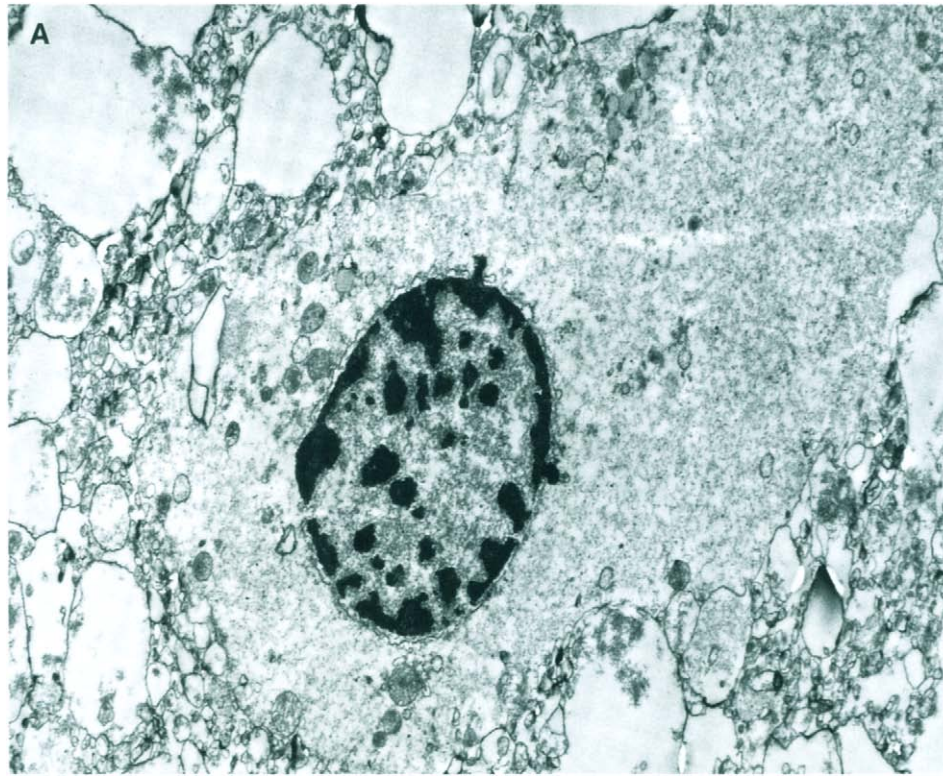


Fig. 65 Same case shown in Fig. 63. Hyperplastic astrocytes with (A) abundant glial fibrils and (B) an increased number of organelles, ×12,000.

minals. The loss of the inhibitory action of this neurotransmitter accounts for the hypertonic crises and the myoclonus, which are the presenting symptoms. A high concentration of glycine in the brain may contribute to the pathophysiology of NKH by overactivating *N*-methyl-D-aspartate receptors allosterically, which may result in intracellular calcium accumulation, DNA fragmentation, and neuronal death. The fundamental defect is in the glycine cleavage system, which consists of four protein components. The majority of the patients had a specific defect in P-protein (glycine decarboxylase). The majority of the NKH patients in Finland, where there is a high incidence of this condition, were found to be due to a common point mutation resulting in the amino acid 564 substitution of I for S Tada and Kure, 1993.

In patients with the typical neonatal form of the disease, defects were demonstrated in P-protein (pyridoxal phosphate-dependent decarboxylase) and, to a lesser degree, in T-protein (tetrahydrofolate-dependent enzyme) (Hayasaka *et al.*, 1987).

The hyperglycinemia is a secondary phenomenon due to blockage of the glycine breakdown, which can be attributed to an accumulation of glycolic acid. In the course of time, glycine synthesized by an alternative pathway accumulates in synaptic terminals with effects similar to those observed in ketotic hyperglycinemia.

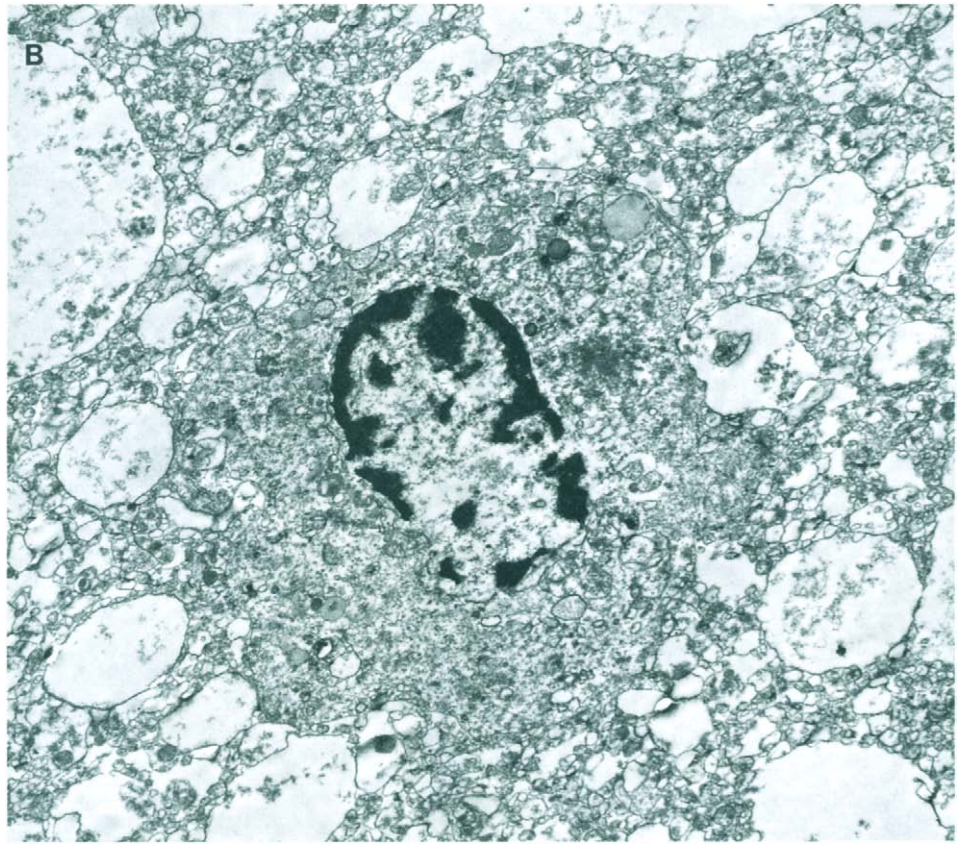


Fig. 65 Continued.

A patient with typical NKH was identified as being homozygous for a missense mutation in the T-protein gene, a G-to-A transition leading to a G-to-D substitution at amino acid 269. Patients with atypical NKH had different missense mutations in less conservative amino acid residues (Nanao *et al.*, 1994). Deletions of the 5.0-kb *Sac*I fragment in the genome of patients with NKH resulting from the lesion of glycine decarboxylase and common aberrations identified with the 5.2-kb *Eco*RI and 5.5-kb *Sac*I fragments were demonstrated by Koyata and Hiraga (1991), suggesting that rearrangements occur in multiple genomic loci of patients with NKH.

Disorders of the Glutamyl Cycle

The synthesis, degradation, and transport of glutamate occur in a series of reactions catalyzed by several enzymes. An important compound of glutamate is glutathione, a tripeptide (γ-glutamyl-cysteinyl-glycine) present in considerable amounts in all mammalian cells.

Glutathione Synthase Deficiency

The first patient with this deficiency was described by Jellum (1970). Further reports followed. Three of the 12 patients with a generalized absence of glutathione reviewed by Larsson (1979) presented with neurological symptoms.

Glutathione levels are reduced in the substantia nigra of Parkinson's disease patients. A reduction of oxidized glutathione levels in the caudate was found in those with progressive supranuclear palsy and Huntington's chorea. In multi-system atrophy an increase in reduced glutathione (196%) was coupled with a reduction in oxidized glutathione levels (60%) in the globus pallidus. The altered reduced glutathione and oxidized glutathione levels ratio in the substantia nigra in Parkinson's disease is consistent with the concept of oxidative stress as a major component in the pathogenesis of nigral cell death in Parkinson's disease.

Clinical Picture The remaining nine patients were children in whom neurological involvement might appear later. Aside from psychomotor retardation, spastic paralyses and cerebellar disorders have also been recorded. All patients suffered from severe acidosis (Pejaver and Watson, 1994).

Neuropathology Cerebellar atrophy and cystic changes in front of and behind the central sulcus were noted by Skullerud *et al.* (1980). The cerebellum showed a selective atrophy of the granular layer. The cystic changes in the cortex as well as in the left thalamus turned out to represent old infarcts. There was also a focal selective laminar necrosis with astrocytosis in the visual cortex.

Pathogenesis Glutathione, which is synthesized within the cells, is a component of a pathway that uses NADPH to provide cells with their reducing milieu. This is essential for maintenance of the thiols of proteins and of antioxidants, the reduction of ribonucleotides to form the deoxyribonucleotide precursors of DNA, and protection against oxidative or free radical damage.

The lack of activity of glutathione synthase leads to a reduction in the amount of glutathione. This enhances the activity of γ-glutamylcysteine synthetase, normally inhibited by glutathione. This leads to an accumulation of γ-glutamylcysteine, which is easily transformed into 5-oxyproline. As a consequence, 5-oxyproline is excreted in the urine and severe acidosis develops.

Glutathione has various functions, including that of a hydrogen donor for the detoxication of hydrogen peroxide. The correlation between the glutathione functions and the hitherto described cerebral lesions has not been established.

Glutathione deficiency induced in newborn rats by giving buthionine sulfoximine, a selective inhibitor of γ-glutamylcysteine synthetase, led to markedly decreased cerebral cortex glutathione levels and striking enlargement and degeneration of the mitochondria.

γ-Glutamyl Transpeptidase Deficiency (Glutathionuria)

The two patients reported with this condition (Schulmann *et al.*, 1975; Wright *et al.*, 1979) were mentally retarded. A patient of Wright *et al.* also displayed severe be-

havioral disorders. The latter authors considered the possibility that the behavioral disorders could be caused by a lack of inactivation of peptides by the glutamyltranspeptidase. No autopsy findings have been reported to date.

γ-Glutamylcysteine Cysteine Synthetase Deficiency

This syndrome was described by Richards *et al.* (1974) in two siblings. It consisted of hemolytic anemia, peripheral neuropathy, myopathy, spinocerebellar degeneration, and aminoaciduria. However, Beutler *et al.* (1990) found that the only manifestation of the enzyme deficiency was hemolytic anemia. They concluded either that the occurrence of neurological symptoms in the family reported on by Richards *et al.* (1974) was a chance association or that the clinical expression of this rare defect is pleomorphic. No morphological data are available.

Neuroexcitatory Amino Acids

Curtis and Watkins (1960) were the first to draw attention to the neuroexcitatory properties of aspartate, glutamate, and other amino acids. The pathogenetic significance of these amino acids has now been established in the production of anoxic–ischemic (Rothman and Olney, 1986; Ikonomidou *et al.*, 1988) and postepileptic lesions (Olney *et al.*, 1986). Because of the localization of the lesions, a role for the neuroexcitatory amino acids has also been postulated in Huntington's chorea and in hereditary bilateral striatal necrosis. It is therefore assumed that a neuroexcitatory mechanism may be responsible for the phenotypic expression of some enzymopathies. Glutamate dehydrogenase deficiency and the enzymopathies of glutamate metabolism (see p. 194) must be considered in this context.

The toxicity of neuroexcitatory amino acids is mediated through excitatory receptors and manifests itself in a continuous depolarization of postsynaptic dendritic membranes, enhanced permeability, and disturbance of ionic homeostasis. Glutamate-triggered neurotoxicity requires Ca^{2+} influx, and neurotoxicity is a function of the transmembrane CA^{2+} gradient (Tymianski *et al.*, 1993). In experimental models the systemic administration of these amino acids leads to lesions in the retina and in periventricular areas. Injection directly into the brain parenchyma produce dendritic lesions in any chosen area. The swellings are confined to the postsynaptic dendrites or the perikarya, while the axons remain intact. The pathogenesis of nerve cell death in neurodegenerative diseases is unknown. Glial cells of the CNS express receptors for the main inhibitory and excitatory neurotransmitters, GABA and glutamate. The functional role of these receptors is, as yet, speculative (Blankenfeld and Kettenmann, 1991). An attractive hypothesis is that an impairment of energy metabolism may underlie slow excitotoxic neuronal death. Several studies have demonstrated mitochondrial or oxidative defects in neurodegenerative diseases (Beal *et al.*, 1993).

Iminoglycinuria (Familial Iminoglycinuria; Joseph's Syndrome; Prolinuria)

Joseph *et al.* (1958) were the first to describe iminoglycinuria in connection with familial epilepsy. Paine (1966) called the condition "Joseph's syndrome," while Tada *et al.* (1965)

classified two patients under the term *prolinuria*. The term *Joseph's syndrome* is best avoided, as it may lead to confusion with *Joseph disease* (see p. 615). Iminoglycinuria can occur in conjunction with hyperprolinemia.

Clinical Picture While in some families this disorder does not express itself clinically, other patients exhibit mental retardation, epileptic seizures, amblyopia, and deafness. Gyrate atrophy of the choroid and the retina has been described. No neuropathological observations have been reported.

Pathogenesis As a result of disturbances of membrane transport, excessive quantities of free proline, hydroxyproline, and glycine are excreted in the urine. The fact that many individuals with iminoglycinuria are otherwise symptom free led to doubt as to whether the symptoms reported in some patients are related to the iminoglycinuria. Some authors postulated a disturbance of amino acid transport in the brain to explain the coexistence of iminoglycinuria with cerebral symptoms.

Hyperprolinemia

Efron (1966) distinguished two types of hyperprolinemia. Type I was caused by proline oxidase deficiency; type II, by a lack of proline dehydrogenase. Type II causes more severe neurological symptoms; neuropathological observations, however, are confined to type I.

Clinical Picture Symptoms in type I are inconstant and consist of epileptic seizures, mental retardation, and deafness. Occasionally, severe neurological abnormalities have been reported. Diffuse white matter involvement can be seen on MRI, and electroretinography has detected tapetoretinal degeneration (Steinlin *et al.*, 1989). An association with photogenic epilepsy was reported by Ishikawa *et al.* (1991).

In type II the retardation is more severe, and almost all patients suffer from seizures and have an abnormal EEG. Flynn *et al.* (1989) found a strong association between type II hyperprolinemia and seizures during childhood but no significant association with mental retardation. The proline level in the CSF is elevated in both types.

The association of Coffin–Lowry syndrome (mental retardation and dysmorphic features) and hyperprolinemia seems fortuitous (Lacombe *et al.*, 1994).

Neuropathology In some cases no lesions were found; in others a diffuse loss of neurons was observed in the cerebral cortex. Woody *et al.* (1969) also found hypomyelinization with status spongiosus of the white matter in the cerebrum and the cerebellum.

Pathogenesis The association between type II hyperprolinemia and seizures may be related to the neuromodulatory and reducing–oxidizing effects of proline and pyrroline-5-carboxylate, respectively, which have been shown *in vitro*. Alternatively, another genetic defect closely linked to the type II hyperprolinemia allele could provide an explanation.

Disorders of Lysine Metabolism

In the metabolism of lysine, pipecolic and glutaric acids are formed. Their increased excretion in the urine has been found in some patients with neurological symptoms. Hyperpipecolinemia is included among peroxisomal disorders (see p. 336).

Goodman *et al.* (1975) described the clinical and biochemical features of glutaric aciduria as an inborn error of lysine, hydroxylysine, and tryptophan metabolism. Przyrembel *et al.* (1976) found glutaric aciduria in a newborn in whom, however, the enzyme deficiency was not identified. This condition received the designation *glutaraciduria type II.*

Glutaric Aciduria Type I (Glutaryl-CoA Dehydrogenase Deficiency)

Clinical Picture Symptoms may appear soon after birth (Ozand *et al.*, 1991) or during the first, or even as late as the third, year. They consist of psychomotor retardation, recurrent metabolic acidosis, choreoathetosis, and progressive quadriparesis. Bilateral subdural hygromas and hypoglycemia have also been observed. Frontotemporal atrophy and the presence of hygromas can be seen on CT; destruction of the caudate and the deep white matter is visible on MRI (Amir *et al.*, 1991; Kimura *et al.*, 1994). The course of the disease is variable. Some patients die in childhood, while others are still alive at the end of the first decade. Campistol *et al.* (1992) described a patient in whom although the clinical presentation was typical of glutaric aciduria type I, the urine concentrations of glutaric, glutacoic, and 3-hydroxyglutaric acids remained normal, even during episodes of clinical decompensation. An increased free glutarate level was demonstrated only in the CSF.

Neuropathology *Gross appearances.* Gross lesions may range from slight shrinkage to frontotemporal hypoplasia as well as massive necrosis of the entire putamen and part of the caudate nucleus (Goodman *et al.*, 1977).

Light microscopy. Light microscopically marked vacuolation of the white matter (status spongiosus), most severe in the optic nerves and chiasm, centrum semiovale, corpus callosum, cerebellum, pons, and brain stem, and striatal degeneration with sparing of the tail of the caudate have been reported (Soffer *et al.*, 1992).

Electron microscopy. On electron microscopy empty vacuoles are seen in the cytoplasm of astrocytes, as well as swelling and degeneration of postsynaptic processes in the cerebral cortex (Amir *et al.*, 1991).

Pathogenesis Both the similarity of the neuropathological findings to those seen in glutamate decarboxylase deficiency and in the reduction of GABA in the basal ganglia and the substantia nigra, on the one hand, and the structural similarity of glutaric and glutamic acids, on the other, have led investigators to propose an excitotoxic pathogenesis. Inhibition of the breakdown of glutamate in the synaptic cleft by an excess of glutarate, and a neurotransmitter agonist function of glutarate enhancing the excitotoxic action of glutamate have been considered as possible mechanisms. Heyes (1987) suggested the possibility that a deficiency of glutaryl-CoA dehydrogenase might lead to an overproduction of cholinic acid, which is strongly neurotoxic.

Previously reported cases of symmetrical striatal degeneration (see p. 539) were tentatively ascribed to glutaric aciduria. Goutieres and Aicardi (1983), however, have pointed out the differences between cases of glutaric acidosis and other types of bilateral striatal necrosis.

Glutaric Aciduria Type II (Electron Transferring Flavoprotein Deficiency)

Clinical Picture Two forms of this disorder are distinguished: a severe form apparent at the time of birth or shortly after (Przyrembel *et al.*, 1976; Colevas *et al.*, 1988) and a mild one that manifests itself toward the end of the second decade and undergoes decompensation only under metabolic stress (Amendt and Rhead, 1986).

Children with this disorder exude a "sweaty" feet odor and exhibit acidosis, hypoglycemia, hyperammonemia, and aciduria. The concentrations of glutamic and other organic acids are raised. The children die in a coma hours or days after birth. The condition is inherited as an autosomal-recessive trait.

Pathology In the majority of cases examined at autopsy, the findings included polycystic kidneys, hypoplasia of the ductus choledochus, cholestasis, siderosis, and fatty degeneration of the liver. Hypoplasia of the lungs and a "Potter-type face" have also been observed (Böhm *et al.*, 1982).

Neuropathology *Gross appearances.* A warty dysplasia of the cerebral cortex with polymicrogyria and macrogyria is the most striking feature (Colevas *et al.*, 1988). Intraventricular hemorrhages, cysts of the septum pellucidum, and cerebral edema are also seen (Goodman *et al.*, 1983).

Light microscopy. Various authors found neuronal heterotopias (Böhm *et al.*, 1982), leukodystrophy with reactive gliosis, and periventricular gliosis with calcification.

Electron microscopy. Harkin *et al.* (1986) found inclusions of homogeneous moderate density in the cytoplasm of neurons and glial cells.

Pathogenesis This biochemical defect is due to a deficiency either in electron transferring flavoprotein or in electron transferring flavoprotein oxidoreductase (Colevas *et al.*, 1988). The distribution of lesions, particularly the localization of the renal dysplasia, suggests the accumulation of teratogenic toxic metabolites in the fetus, which remains uncorrected by the placenta.

3-Methylglutaconic Aciduria (MGA; Optic Atrophy, Behr Syndrome)

Costeff *et al.* (1989) reported a syndrome in Israeli patients with early onset of optic atrophy and movement disorder. During their second decade, most patients developed spastic paraparesis, mild ataxia, and a mild cognitive deficit. Excessive excretion of 3-methylglutaconic and 3-methylglutaric acids was found (Gibson *et al.*, 1993) in patients with a deficiency of methylglutaconyl-CoA hydratase, degradation enzyme (type I MGA), speech delay, macrocephaly, metabolic acidosis, and moderate elevation of creatine phosphokinase were the main findings. These symptoms are compatible with Behr's syndrome (Sheffer *et al.*, 1992). Axonal degeneration and regeneration were detected in some pa-

tients (Thomas *et al.*, 1984) and Marzan and Barron (1994) described diffuse, symmetric white matter abnormalities. This syndrome was found to be relatively common among Iraqi Jews that showed abnormally elevated excretion of 3-methylglutaconic acid in their urine (Costeff *et al.*, 1993).

A milder degree of MGA accompanied by 2-ethylhydracrylic aciduria has been reported in patients with cardiomyopathy, growth retardation, neutropenia, and normal cognitive functions (type II). The activity hydratase in patients' fibroblasts was normal, and the origin of the MGA is, at present, unknown.

A homogenous group of patients with type III MGA differs from patients with type I MGA because of the normal methylglutaconyl-CoA hydratase activity in their fibroblasts; they differ from patients with type II MGA because of the absence of cardiomyopathy, short stature, and neutropenia. In addition, the mode of transmission in type III seems to be autosomal recessive, whereas in type II it is likely to be X linked (Elpeleg *et al.*, 1994).

Histidinemia (Histidine Ammonia-lyase Deficiency)

The first patients with histidinemia were described by Ghadimi *et al.* (1961). The failure of degradation of histidine to urocanic acid (urocanate) is due to a deficiency of histidine ammonia-lyase (histidase) (La Du *et al.*, 1962). Over one half of the patients suffer from mental retardation and speech defects. Some patients suffer from seizures, and several experience ataxia. Whether these symptoms are due to focal lesions or to a generalized metabolic disturbance is debatable. Scriver and Levy (1983) do not consider histidinemia to be a disease entity and attribute to the enzyme deficiency only the status of a risk factor. Aiken *et al.* (1992) discussed the effects of histidinemia on the zinc transport system.

No neuropathological findings have come to our knowledge.

Homocarnosinosis (Homocarnosinase Deficiency)

Homocarnosine is a brain-specific dipeptide of GABA and L-histidine. The syndrome homocarnosinosis is characterized by a raised level of the dipeptide homocarnosine (γ-aminobutyrylhistidine) in the CSF, spastic paraplegia, mental retardation, and retinal pigmentation. It has been described in only a few families (Lunde *et al.*. 1986). In a biochemically examined brain biopsy (Perry *et al.*, 1979) a lack of homocarnosinase was found in the tissue. The gyri appeared narrow, but no abnormality was found under light microscopy. The presumptive mode of inheritance is autosomal recessive (Jakobs *et al.*, 1993).

Carnosinemia (Carnosinase Deficiency)

Carnosinemia was described by Perry *et al.* (1967). A lack of carnosinase prevents the splitting of carnosine into β-alanine and histidine.

Clinical Picture Most of the patients with this condition were male, with a few exceptions. The symptoms appear during the patient's first 6 months and consist of seizures; pyramidal, extrapyramidal, and suprabulbar symptoms; and a peripheral neuropathy. No

correlation could be established between the residual activity of the enzyme and the severity of the neurological symptoms (Cohen *et al.*, 1985).

Neuropathology Wisniewski *et al.* (1981) considered the described neuropathological findings to be nonspecific. Spongiosis and cyst formation in the putamen, as well as neuronal loss, have been reported in the cerebrum, cerebellum, and brain stem. Axonal spheroids and a loss of myelin were observed in the pyramidal and spinocerebellar tracts of the spinal cord. Axonal degeneration and a loss of myelin were seen in the peripheral nerves.

On electron microscopy of the peripheral nerves, an accumulation of glycogen was found in the axons, as well as an increase in the number of nonmyelinated axons.

Hypertyrosinemia

Tyrosinemia type I is a recessively inherited disorder caused by a deficiency of fumarylacetoacetase, the final enzyme in tyrosine degradation. The major clinical features are progressive liver damage and renal tubular defects with hypophosphatemic rickets. Severe peripheral neuropathy is common in hereditary tyrosinemia and resembles the crises of the neuropathic porphyrias (Mitchell *et al.*, 1990).

In addition to hereditary tyrosinemia type I, all patients with persistent hypertyrosinemia are mentally retarded (La Du and Gjessing, 1978). The metabolic disorder in hereditary tyrosinemia type II is occasionally due to hepatic cytosolic tyrosine aminotransferase deficiency and is associated with the oculocutaneous manifestations of Richner–Hanhart syndrome (Chitayat *et al.*, 1992).

The gene for fumarylacetoacetase has been mapped to chromosome 15q23–q25 (Kvittingen 1991).

Richner–Hanhart Syndrome (Palmoplantar Keratosis with Corneal Dystrophy and Mental Retardation; Tyrosinosis Type II)

The first case of this metabolic disorder was published by Richner (1938) and confirmed by Hanhart (1947).

Clinical Picture The principal symptoms are hyperkeratosis of the skin and keratitis. All patients are mentally retarded and inclined to self-mutilation. Neurological dysfunction is particularly variable. These patients have asymmetrical knee jerks, extensor plantar responses, and tics. The plasma, CSF, and urinary tyrosine levels are raised. The cutaneous and ocular manifestations respond promptly to treatment with a low-protein diet (Barr *et al.*, 1991). The response of neurological symptoms is less clear (Paige *et al.*, 1992).

Pathology Conjunctival biopsies show a thickened vacuolized epithelium with plasma cell infiltration. In the skin the thickened parakeratotic stratum corneum contains homogeneous refractile inclusions. Enzyme studies reveal a deficiency of tyrosine aminotransferase in the cytosol of hepatocytes.

Electron microscopy shows intracytoplasmic vacuoles and lipid droplets in the epidermis and the conjunctiva. Some inclusions are needle shaped and considered to be "crystal ghosts," presumably of tyrosine (Shimizu *et al.*, 1990).

No neuropathological findings have yet been published, even in the case of Thiel and Weidle (1982) in which a hepatolenticular degeneration was apparently present. The similarity of the clinical picture to that of PKU hints at the possibility of similar lesions.

Pathogenesis The observation of raised CSF homovanillic acid suggests that the accumulation of tyrosine may lead to increased catecholamine synthesis in the CNS, and this may contribute to the dysfunction (Paige *et al.*, 1992).

This condition is due to a deficiency of the hepatic cytosomal enzyme tyrosine aminotransferase. The gene coding for this enzyme has been located on chromosome 16q22.1–q22.3 (Natt *et al.*, 1987).

Hartnup Disease

This clinically and biochemically defined disease was described by Baron *et al.* (1956) in an English family named Hartnup.

Clinical Picture The symptoms are highly variable both in their severity and in their age incidence. They often appear during the second year, sometimes later. They commonly consist of gastrointestinal disturbances. Added to these are pellagra-like skin lesions with photosensitivity, on the one hand, and mental and neurological symptoms with ataxia and nystagmus, on the other.

A distinct intention tremor with poor coordination and dysdiadochokinesia has frequently been reported. Intermittent dystonia is rare (Darras and Gilmore, 1985).

Neuropathology *Gross appearances.* Severe cerebral atrophy with dilatation of the ventricles is seen. In some cases the cerebellum is more severely affected (Schmidtke, 1990).

Light microscopy. A diffuse loss of neurons is found in the cerebral cortex with preserved cytoarchitecture and without gliosis. The white matter shows diffuse pallor, most marked in the optic radiation (the geniculocalcarine tract), in which there is a severe loss of axons and dense gliosis. Schmidtke *et al.* (1992) found conspicuous demyelination. A loss of laminar architecture, loss of neurons, and gliosis are conspicuous in the lateral geniculate bodies. The majority of surviving nerve cells show a dark pyknotic nucleus, basophilic cytoplasm, and a loss of Nissl bodies. In the cerebellum a loss of Purkinje cells is accompanied by Bergmann's gliosis. The surviving Purkinje cells show axonal and dendritic swellings. The granular layer shows diffuse atrophy commensurate with that of other parts of the brain (Tahmoush *et al.*, 1976).

Pathogenesis The defect is one of transport of neutral amino acids in the gut and the kidneys, leading to their increased excretion. Acid and alkaline amino acids are not affected. Substances produced by bacterial decomposition of unabsorbed tryptophan (indole compounds) may be neurotoxic.

Disorders of Protein Metabolism

Amyloidoses (β-Fibrilloses)

In 1854, Virchow demonstrated that the tissue deposits in waxy degeneration of the liver and spleen, as defined by Rokitansky (1842), reacted with iodine-like starch (amylum). He therefore called the substance *amyloid*. Already in 1859, Friedreich and Kekule proved by chemical analysis that this substance was neither starch nor cellulose, but a protein. Nevertheless, the name *amyloid* remained.

Amyloidosis is a generic term for a group of clinically and biochemically diverse diseases characterized by the deposition of an insoluble fibrillary protein in the extracellular space. Over 16 biochemically distinct amyloids are known. Despite this diversity, all amyloids have a particular ultrastructural and tinctorial appearance. A large number of different proteins have amyloidogenic properties. Peculiarities of the amyloid proteins are their sheet configuration, poor solubility, and resistance to protease digestion. Because of their sheet configuration (β-structure), the amyloidoses are also known as β-fibrilloses (Glenner, 1980) and are codeposited with a group of amyloid-associated proteins. The most common amyloidosis is found in Alzheimer's disease, in which Aβ is the main component of the amyloid. This condition is discussed in the chapter on degenerative diseases of the cerebral cortex and the white matter. Recently, it has been found that Aβ exists as a normal soluble protein (sAβ) in biological fluids. This links Alzheimer's disease more closely to some of the systemic amyloidoses, in which the amyloid precursor is normally found in the circulation. Many mutations are also found in some of the hereditary amyloidoses. However, amyloid deposition can occur with no mutation (Ghiso *et al.*, 1994).

Classification The systemic amyloidoses may be divided into primary and secondary (reactive) forms, which may appear spontaneously or as a consequence of other diseases. The hereditary systemic forms include familial Mediterranean fever, the familial amyloid polyneuropathies, and systemic senile amyloidosis. Glenner *et al.* (1978) divided the hereditary amyloidoses into generalized and localized types. In both of these forms, there

are various disease entities that may involve the nervous system. The traditional classification was being supplemented or modified based on chemical and immunological criteria. Amyloids are now categorized on the basis of their chemical structure, but the clinical classification of localized and systemic amyloids is still useful. Cerebral amyloid deposits can be divided into several groups based on their chemical constitution: first, β/A4 amyloid occurs in Alzheimer's disease, Down syndrome, sporadic cerebral amyloid angiopathy (CAA), normal aging, and hereditary cerebral hemorrhage with amyloidosis of the Dutch type. Second, cystatin C amyloid occurs in hereditary cerebral hemorrhage with amyloidosis of the Icelandic type. Third, proteinase-resistant protein amyloid occurs in Creutzfeldt–Jakob disease (CJD) and Gerstmann–Sträussler–Scheinker syndrome (GSS). Finally, in a small group of familial diseases, the nature of the amyloid deposits has not yet been clarified. The primary systemic amyloidoses are also called "immunocytic." This group also includes the amyloidoses associated with myeloma and other monoclonal gammopathies (Schenone *et al.*, 1989).

It can be demonstrated immunologically that the protein in immunocytic amyloidoses consists of the light chains (λ-chains) of immunoglobulins. These proteins are designated by the abbreviation *AL*. In more than half of the AL amyloidoses, no immunocytic dyscrasia can be demonstrated in the serum (Browning *et al.*, 1985).

In the reactive or secondary amyloidoses, the amyloid is derived from the serum amyloid A protein and is designated by the abbreviation *AA*. This protein forms generalized deposits in the whole body, predominantly in the organs of the reticuloendothelial system, such as the liver and the spleen. In the AL amyloidoses, which can also be generalized, the gastrointestinal and cardiovascular systems are predominantly affected. Because of this differential distribution, the latter have been called *paramyloidoses*. This designation is misleading, as both forms have the characteristic sheet configuration of their proteins.

The question of whether the amyloid deposits that occur in both physiological old age and senile and presenile cerebral atrophies are primary or secondary is still unresolved. The same applies to the amyloid deposits found in younger patients with Down syndrome (Belza and Urich, 1986), as well as those seen in transmissible encephalopathies, particularly in CJD (Kitamoto *et al.* 1986) and GSS. In the various diseases in which amyloid deposits are found predominantly in the vessel walls (see p. 207), it may be presumed that different etiological factors operate via the same pathogenetic mechanisms. In some of the diseases with known etiology and pathogenesis, a hereditary predisposition has been suspected. These diseases, however, must be distinguished from those conditions, both hereditary and sporadic, in which amyloid deposition is the primary event.

Morphology of Amyloid Macroscopically, amyloid can be demonstrated by its strong reaction with iodine and sulfuric acid. Under light microscopy amyloid stains homogeneously red with H&E (Fig. 66A), yellow with van Gieson's solution of trinitrophenol and acid fuchsin, and weakly positive with PAS. In Masson's trichrome and Mallory's aniline blue, amyloid stains like collagen.

A number of specific stains have been devised for the demonstration of amyloid. Crystal violet and methyl violet often stain it metachromatically. Phosphotungstic acid–hematoxylin stains it reddish orange. A pale red color is obtained with Congo red

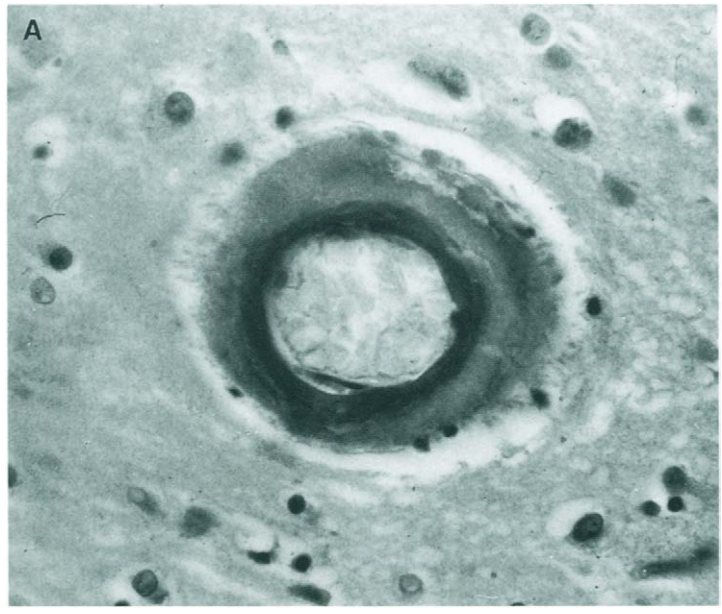


Fig. 66 Amyloid angiopathy in an aged brain. (A) Hematoxylin–eosin stain, ×400. (B) Congo red stain. (C) Under polarized light, ×270.

(Fig. 66B), and an almost pathognomonic green dichroism is obtained under polarized light (Fig.66C). Staining with Congo red is considered by most authors to be a fast and reliable method. With thioflavine T amyloid is fluorescent under ultraviolet light. Differences in the substructure of amyloid can be demonstrated in paraffin sections by the trypsin method or by the less damaging potassium permanganate method of Wright *et al.* (1977). Immunohistochemically, various monoclonal and polyclonal antibodies have been used (Castano and Frangione, 1988) as well as antibodies against synthetic polypeptides with various amino acid sequences (Vinters *et al.*, 1988), to distinguish between different forms of amyloid, sometimes with contradictory results. They do, however, demonstrate clearly the localization of those amyloid deposits with which they react. An additional component, which is not an integral part of the amyloid structure but is found in almost all types of amyloid, is the P component (Gorevic *et al.*, 1985). It has a pentagonal structure and consists of an outer shell 3.5 nm thick and a central core 2.5 nm long. It is coded by a gene localized on chromosome 1 (Ohnishi *et al.*, 1986).

Using electron microscopy, Cohen and Calkins (1959) were the first to demonstrate the fibrillary nature of amyloid. Subsequent reports distinguished between the perireticulin and pericollagen deposition of amyloid fibrils.

The specific protein conformation of amyloid fibrils is always the same, irrespective of the chemical nature of the protein. It is the structure of the fibrils that is responsible for the staining properties and the polarization peculiarities of amyloid (Glenner, 1981).

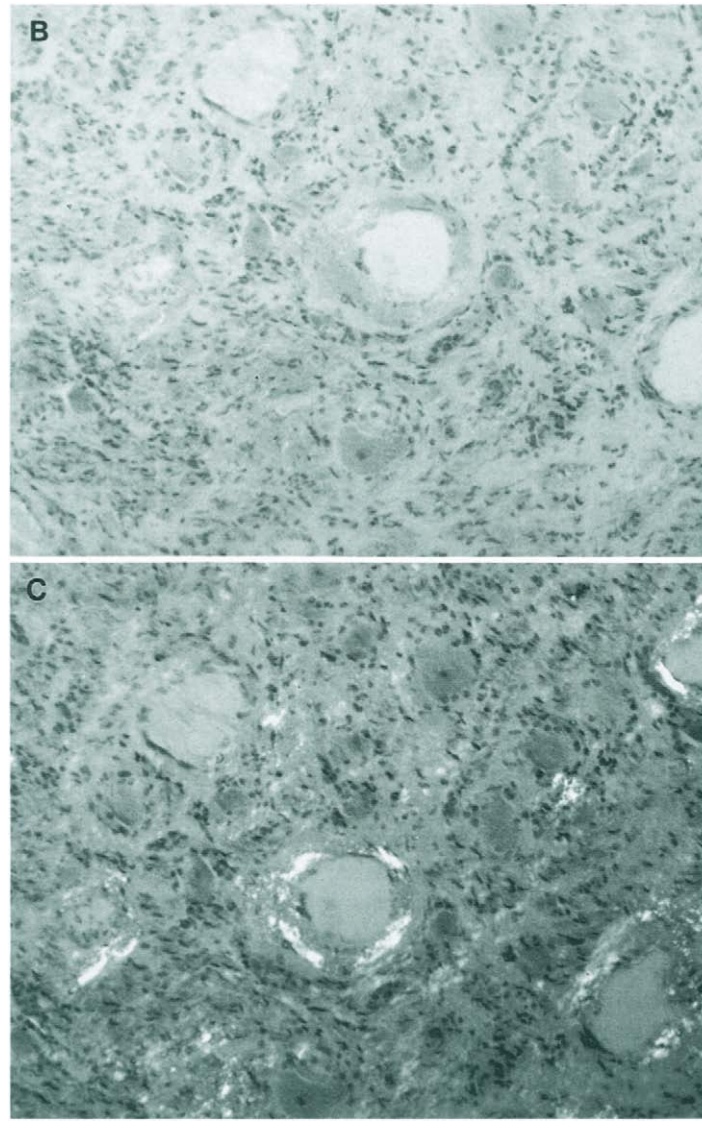


Fig. 66 Continued.

Primary Systemic Amyloidosis (Immunocytic Amyloidosis, Paramyloidosis; Amyloidosis of Monoclonal Gammopathies)

The involvement of the CNS in systemic amyloidoses is minimal and is limited to certain specific structures. On the other hand, the peripheral nervous system is affected in most cases. In about one half of the cases, amyloid is deposited in the vasa nervorum or

the endoneurium. In the remaining patients amyloid deposition is confined to the perineurial and epineurial blood vessels (Yamada *et al.*, 1984).

Familial Amyloid Polyneuropathies

In a number of patients, amyloidosis occurs in families and has a predilection for peripheral nerves. Although the chemical picture and the morphological findings center on the peripheral nervous system, other organs are also involved. These conditions are therefore hereditary systemic forms of amyloidosis with local preferential involvement.

The familial amyloid polyneuropathies have been classified into several types, in accordance with the pattern of distribution of the neurological deficit and the localization of the amyloid deposits. McKusick and Neufeld (1983) were the first to identify five types of amyloidosis that, with the exception of the cardiac form, involved the peripheral nerves. Meanwhile, the conditions have been reclassified based on biochemical and genetic data.

Familial Amyloid Polyneuropathy Type I (Andrade Type; Portuguese Form of Amyloid Polyneuropathy)

Andrade (1952) reported on 74 Portuguese patients with peripheral neuropathy caused by amyloid deposition. This form has also been described outside Portugal: in Japan, Sweden, the United States, England, and Germany.

Clinical Picture Symptoms usually begin in the third or fourth decade but may appear as early as the second decade or as late as the seventh. Longitudinal studies of affected families have revealed anticipation by a decade in successive generations.

The principal features are dissociated sensory loss, starting in the lower extremities and progressing proximally; trophic changes; and disturbances of bladder, rectal, and sexual functions. Opacities of the vitreous body have been observed in elderly patients. The disease progresses with a severe loss of weight; orthostatic hypotension may also develop. Death usually occurs 5–8 years after the onset of symptoms; some patients survive longer, however. The common causes of death are cachexia, urinary and pulmonary infections, and cardiac failure. Slight deviations from the described symptomatology occur in individual families in different countries.

Pathology Amyloid deposits of pericollagen distribution are found in the kidneys and, to a lesser extent, in the gastrointestinal tract. In the testes and the ovaries and in the heart, amyloid deposits have been found in both intra- and extramyofiber locations (Fiori *et al.*, 1994). In the liver, spleen, and adrenals the changes are confined to the vessel walls.

Neuropathology *Gross appearances.* Thickening of the leptomeninges is particularly pronounced in the spinal cord.

Light microscopy. Amyloid is found in the meninges, choroid plexuses, and subependymal zones. Da Silva Horta *et al.* (1964) found structures resembling senile plaques (SPs), but devoid of amyloid, in the gray and white matter of the brain and the spinal cord. The meningeal and intracerebral vessels are considerably thickened by amyloid deposits, with

appreciable narrowing of the lumen (Ushiyama *et al.*, 1991). As a result, small infarcts may be found in the brain and the spinal cord. Exceptionally, cerebral hemorrhage was reported (Arpa-Gutierrez *et al.*, 1993). The endoneurium of the spinal ganglia, spinal roots, and peripheral and autonomic nerves is studded with round or spherical amyloid deposits. The axons are displaced by the deposits. Demyelination and axonal degeneration can be seen in places. The U-fibers are particularly affected (Said *et al.*, 1984).

The amyloid fibril protein in patients with this disease has been shown to be composed of a variant of transthyretin (TTR; previously called prealbumin) with a single V-to-M substitution at position 30 (Tawara *et al.*, 1983).

All amyloid deposits are invariably immunoreactive to anti-human TTR antibody, and the formic acid pretreatment results in a strong intensification of the immunoreaction. Immunohistochemical reactions for anti-human cystatin C antiserum or anti-β-protein antibody are negative, even after formic acid pretreatment of the sections.

Electron microscopy. Electron microscopy reveals amyloid fibrils in apposition to both endoneurial collagen fibers and the basement membranes of Schwann cells (Giangaspero *et al.*, 1985).

Familial Amyloid Polyneuropathy Type II (Rukavina Type, Indiana Type)

The first patient with this form of familial amyloid polyneuropathy was observed by Falls *et al.*, (1955). Subsequently, families affected by this type were reported from Indiana (Rukavina *et al.*, 1956) and Maryland. The Indiana families were of Swiss descent, and the Maryland families were of German ancestry.

Delank and Kutzner (1982) observed a shift in clinical symptomatology from the Portuguese to the Indiana type over several generations. The disease begins between the third and fifth decades and characteristically presents with carpal tunnel syndrome. After a prolonged insidious progression, the symptoms may extend to the lower limbs. The eye symptoms comprise clouding of the vitreous body and periarteritis of the retinal vessels. Amyloid deposits are found in the myocardium, blood vessels, and extracellular spaces of the tongue, lungs, liver, spleen, pancreas, adrenals, kidneys, and prostate. In a familial case with late onset (Izumoto *et al.*, 1991), autopsy revealed prominent amyloid infiltration of the dorsal root ganglia, peripheral nerves, perineurium, epineurium, and vitreous body, and perivascular amyloid deposition in the kidneys, heart, lungs, liver, spleen, choroid plexuses, and leptomeninges.

Familial Amyloid Polyneuropathy Type III (van Allan Type, Iowa Type)

Van Allan *et al.* (1969) described this syndrome in eight families in Iowa, descendants of Scottish, English, and Irish immigrants. An additional case was reported by Gimeno *et al.* (1974). The patient descended from an Irishman who had married a Basque woman in the 19th century.

Clinical Picture The disease appears in the third or fourth decade and lasts for 15 years, on average. The main feature is the simultaneous development of a polyneuropathy, nephropathy, and gastric ulcers. Renal disease is the principal cause of death. Neu-

ropathy first affects the lower limbs and later spreads to the upper limbs. The symptoms consist of pareses, paresthesias, and impairment of pain sensation. Impotence may occur. Overactivity of the adrenal cortex has been noted in some cases. CSF protein levels may be raised above 200 mg/dl. Amyloid deposits are found mainly in the liver, spleen, adrenals, kidneys, and testes.

Neuropathology In the brain amyloid is present only in the choroid plexuses. Deposits are found in the spinal leptomeninges, posterior roots, and particularly in the posterior root ganglia, which may be enlarged to several times their normal size. Massive but circumscribed deposits are present in the peripheral and autonomic nerves.

Familial Amyloid Polyneuropathy Type IV (Meretoja Type, Finnish Type)

The condition described by Klaus *et al.* (1959) in three sisters with bulbar palsy, suppurative corneal dystrophy, and hyperplastic skin probably belongs to this type, although amyloid staining was not carried out. This entity was defined by Meretoja (1969), who described Finnish patients. Similar cases have been reported in patients of Dutch and American origin as well.

Clinical Picture The disease begins with lattice dystrophy of the cornea in the third decade. In the fifth decade the first cranial nerve palsies appear, particularly involving the upper branch of the facial nerve. The skin is thickened over the forehead and the scalp and dry over the extremities. The patients suffer from pruritus.

Pathology Corneal dystrophy is characterized by amorphous yellow deposits between the epithelia (Kaunisto, 1973). It spreads radially from the limbus toward the center of the cornea. The presence of amyloid can be demonstrated with Congo red. Within the amyloid deposits nerve fibers can be visualized by silver impregnation (Meretoja, 1972). Skin deposits of amyloid are found in the dermis, particularly around the sweat glands. Amyloid is also deposited in the intima and media of blood vessels throughout the body.

Neuropathology The dura mater and the leptomeninges and their vessels are involved in the disease process. No deposits are found in the CNS parenchyma. The peripheral nerves, particularly the cranial ones, show heavy amyloid deposits. Some branches of the facial nerve consist almost exclusively of pure amyloid.

Pathogenesis Transthyretin (TTR) is the most common constituent amyloid fibril protein deposited in familial amyloid polyneuropathy, and there are, to date, 28 point mutations in the *TIR* gene described in the TTR-related form of this disorder (Chance and Reilly, 1994; Jacobson and Buxbaum, 1994). The gene coding for TTR is located on chromosome 18q11.2–q12.1 (Sparkes *et al.*, 1987). Several substitutions of amino acids at different positions in the TTR polypeptide chain have been identified. In type I amyloid neuropathy there is a V-to-M substitution at position 30 (Furuya *et al.*, 1987). In type II there is an I-to-S substitution at position 84 (Dwulet and Benson, 1986). Other substitutions, recorded in single families, include Y/T for S at position 77, H for L at position 58, V for L at position 33, A for

I at position 60, and M for L at position 111 (Kyle and Dyck, 1992). Not all familial cases have been fully characterized, however. In particular, the TTR in type IV has not yet been sequenced (Maury *et al.*, 1988). Derivation of amyloid from immunoglobulin has been demonstrated in some sporadic cases (Feule *et al.*, 1984).

The absence of a blood–nerve barrier in the spinal and sympathetic ganglia is thought to make them the primary site of peripheral amyloid neuropathies. The extensive involvement of the vasa nervorum would point to an ischemic element in the pathogenesis of the neuropathy. This, however, does not explain the selective involvement of the thin myelinated fibers and U-fibers, since, in other vascular neuropathies, all fibers, particularly the large myelinated ones, are affected. This selective involvement of the small sensory fibers accounts for the dissociated sensory neuropathy. Similarly, the involvement of the sympathetic ganglia and fibers explains the visceral manifestations and the orthostatic hypotension.

Sporadic Amyloid Neuropathies

Peripheral neuropathies occur in about 15% of the primary systemic amyloidoses, which, in contrast to the hereditary forms, occur sporadically. Clinical neuropathies may occur in patients with myeloma or in benign gammopathies without lymphoplasmacytic tumors. In these patients amyloid deposits can be demonstrated immunohistochemically in the peripheral nerves.

Clinical Picture Neuropathy manifests itself between the sixth and ninth decades and affects predominantly males. The symptomatology resembles that of type I hereditary neuropathy with involvement of the lower limbs. Disturbances of bladder and rectal function appear later than in the Andrade type. Only in rare cases involvement of the cranial nerves (Little *et al.*, 1986) or a picture resembling amyotrophic lateral sclerosis (Abarbanel *et al.*, 1986) has been observed.

A Japanese woman with nonfamilial amyloidosis with polyneuropathy, profound autonomic neuropathy, and lattice dystrophy of the cornea showed AA and AP proteins involving the vestibulocochlear nerve, similar to FAP type IV (Tsunoda *et al.*, 1994).

The distribution of amyloid in the viscera corresponds to that seen in generalized amyloidosis.

Neuropathology In peripheral nerves amyloid is deposited primarily around the capillaries of the endoneurium and the arterioles of the perineurium and the opineurium. Less commonly, nodules of amyloid are seen distributed loosely in the tissue. The number of nerve fibers is considerably reduced. The thinly myelinated fibers and U-fibers are primarily affected and show axonal degeneration. Segmental demyelination is rare. Binding of immunoglobulin M (IgM) can be demonstrated immunohistochemically in patients with plasma cell dyscrasias and peripheral neuropathy.

Systemic Amyloidosis with Central Nervous System Participation

Clinical Picture The reported onset of symptoms ranges between 36 and 58 years. As a rule, the patients present with depressive symptoms, disturbed sexual function, car-

diac disorders, nocturnal diarrhea, and macroglossia. The first symptoms are often those associated with sensorimotor disturbances in the lower limbs. Death occurs within several month to a few years.

Pathology Marinesco (1931) was the first to point out the connection between systemic amyloidosis and plaque formation in the brain. Amyloid deposits are found in the heart, tongue, skin, intestinal tract, kidneys, testes, vagina, skeletal muscles, tendons, and adipose tissue and in the entire vascular system. The liver and the spleen are unaltered or only minimally affected. The distribution of lesions in different organs and their intensity vary from case to case.

Neuropathology *Gross appearances.* The leptomeninges have a glassy appearance. At the boundaries of arterial territories, and sometimes beyond, the cerebral cortex shows granular atrophy. Upon slicing of the brain, a soft consistency of the white matter becomes apparent. The ependyma is covered with extensive deposits, up to 1 mm in thickness, from which nodules extend into the neighboring parenchyma. These lesions are particularly striking in the corpus callosum and the septum pellucidum. The choroid plexuses appear atrophic in some cases.

Light microscopy. The homogeneous substance filling the arachnoid meshwork stains with Congo red and is birefringent. Nodular deposits of amyloid extend into the superficial layers of the cerebral parenchyma. Inside layer I small deposits resembling amyloid plaques are seen. Massive amyloidosis associated with calcification is present in the choroid plexuses, both in the vessels and in the interstitial tissue. Amyloid deposits are also seen in the leptomeningeal and intracerebral arteries and veins.

The most striking feature is amyloid deposition in the entire ventricular system, which was reported by Krücke (1950). The deposits cover both the intact ependyma and raised areas denuded of ependyma. Plaquelike amyloid deposits extend into the surrounding white matter. In the medulla oblongata and the spinal cord amyloid deposits are seen in the entry zones of the cranial and spinal nerves, particularly of the dorsal roots.

In granular atrophy of the cortex, small glial scars and softening are seen. Krücke (1950) pointed out a vacuolation of the neuronal cytoplasm. In the cerebral and cerebellar white matter a diffuse pallor was observed, which was caused by confluent small foci of demyelination. In some cases myelin loss is seen in the posterior columns of the spinal cord. Amyloid deposits are also found in the neurohypophysis.

Cerebral Amyloid Angiopathy (Primary Cerebrovascular Amyloidosis; Plaquelike Degeneration of the Cerebral Vessels—Scholz; Dysoric Angiopathy—Morel and Wildi; Congophilic Angiopathy—Pantelakis)

Amyloid deposits in the cerebral vessels occur in senile dementia of the Alzheimer type, in cerebrovascular encephalopathies, in elderly patients with or without dementia, in normal old age in transmissible spongiform encephalopathies and degenerative disorders, and in dementia pugilistica (punch-drunk encephalopathy). These deposits are also found in the foci of radionecrosis, in the neighborhood of the foci of demyelination, and in vascular malformations. They are a frequent finding in spontaneous nonhypertensive cerebral

hemorrhages, both familial and sporadic, and occur in young and old patients without dementia. Nadeau *et al.* (1987) regarded the condition as a nonspecific accompaniment of various degenerative processes and did not attribute any pathogenetic significance to it unless associated with hemorrhages.

Classification of Cerebral Amyloid Angiopathy

The debate as to whether vascular amyloidosis is an epiphenomenon produced by various pathogenetic mechanisms or a primary lesion has been largely resolved by our increasing understanding of the gammopathies. Hence, the distinction between primary and concomitant forms is not particularly useful. Most published cases, especially those reported before 1970, cannot be related to a definite gammopathy and thus to a pathogenetically definable group. Because of the wide range of clinical and pathological manifestations and the small number of cases that fall into individual subgroups a definitive genetic classification is not yet possible. We have therefore divided the entity into three broad groups based partly on clinical, partly on morphological, and partly on genetic criteria.

Asymptomatic and Concomitant Forms

The asymptomatic forms of cerebrovascular amyloidosis include that found in normal old people (Cervós-Navarro, 1980; Esiri and Wilcock, 1986) as well as those found in younger patients who died of unrelated causes. In the latter cases, however, it cannot be ruled out that the condition might have become symptomatic if the patients had survived. We understand concomitant forms to comprise those cases in which the amyloid angiopathy occurs within the context of Alzheimer's disease (see p. 460) and is associated with senile plaques (SPs) and neurofibrillary tangles (NFTs). This group cannot be clearly separated from the vasculo-parenchymatous form. Aging tissues are favorable ground for amyloid formation; therefore, the association of amyloid angiopathy with Alzheimer's disease has been interpreted as a coincidence to be expected. Many authors, however, described a much higher incidence of combined lesions than could be expected from mere coincidence (Esiri and Wilcock, 1986). In our present state of knowledge, a common pathogenetic mechanism of amyloid angiopathy and Alzheimer's disease appears likely, but clinical, morphological, and genetic considerations still make it desirable to separate Alzheimer's disease from other amyloid angiopathies.

Vasculo-parenchymatous Form (Juvenile Alzheimer's Disease; Atypical Alzheimer's Disease)

This group includes patients who develop dementia at a younger age, which is characterized by the presence of an amyloid angiopathy and SPs, whereas NFTs are rare. Familial cases are also assigned to this group, even if they occur at a later age (Oelenberg *et al.*, 1987).

Clinical Picture Age of onset, clinical course, and symptomatology are highly variable and the number of patients is small. The group therefore appears to be clinically heterogeneous. The first symptoms may appear in childhood, but most familial cases manifest themselves between the ages of 50 and 60 years. In contrast to the case in typical

Alzheimer's disease, focal neurological symptoms may be more prominent than psychiatric ones. The neurological symptoms are manifold. Pareses of central origin, even spastic paralyses as well as disturbances of gait and coordination, frequently occur. Unilateral or bilateral loss of the abdominal reflexes may follow. Disturbances of speech are predominantly dysarthric. Love and Duchen (1982) reported on a case of familial ataxia without dementia in a patient with CAA. In about half of the patients, oculomotor or facial weakness is apparent. CT typically demonstrates a diffuse atrophy (Cosgrove *et al.*, 1985). Global loss of mental functions is the prominent psychiatric symptom.

Neuropathology *Light microscopy.* Amyloid deposition in the leptomeningeal arteries and arterioles is present in all cases, while involvement of the intracerebral vessels is more variable. Most authors have reported an accentuation of lesions in the occipital and temporal lobes (Cervós-Navarro, 1980). Cosgrove *et al.* (1985), on the other hand, found a frontal predilection, and in Love and Duchen's (1982) case, the lesions were most pronounced in the hippocampus and the cerebellum. Vinters and Gilbert (1983) found sparing of the hippocampal subcortical white matter. Amyloid may also be found in veins and venules, but to a lesser degree than in arteries. Amyloid infiltrates the media and the adventitia. Obliteration of the layers of the vessel wall makes the distinction of arterioles and venules particularly difficult. The affected vessels, especially in the leptomeninges, frequently have a double contour. Some segments of the vessel may undergo necrosis or aneurysmal dilatation (Vonsattel *et al.*, 1984). The coexistence of arteriosclerotic lesions with amyloid may be the result of coincidental arterial hypertension.

SPs are almost constantly present, but may be scanty (Mandybur, 1986). In contrast to the situation in Alzheimer's disease, the plaques are homogeneous, contain only little argyrophilic material, and reach a size of 100–150 μm. They have a predilection for the hippocampus and the cerebellum. The presence of angiopathy and SPs in the white matter also differentiates this condition from Alzheimer's disease. In the majority of cases, Alzheimer's NFTs are scanty or absent.

In some brains ischemic damage may be seen in the form of focal selective neuronal necrosis with gliosis. Microinfarcts and petechial hemorrhages may also be found. The relationship of these lesions to the affected meningeal or cortical arteries is always recognized. Primary degeneration of the parenchyma in the form of neuronal alterations or loss, as in Alzheimer's disease, is rarely seen. Love and Duchen (1982) found a slight loss of Purkinje cells as well as axonal torpedoes in the cerebellum of their case.

In addition to amyloid infiltration, other lesions in the blood vessels are found in individual cases (Mandybur, 1986). Glomerular proliferation with variable amyloid infiltration, microaneurysms with constant amyloid deposits, vascular occlusions, double-barreled vessels, hyalinosis, and fibrinoid necrosis have also been observed (Vonsattel *et al.*, 1984). Schlote (1965) confirmed the amyloid structure of the deposits by electron microscopy.

Vascular Amyloid and Senile Plaques

The relationship between amyloid angiopathy and NFTs, on the one hand, and amyloid angiopathy and SPs, on the other, has often been discussed. Some authors have found histochemical differences between the amyloid in vessels and in SPs.

Rowe *et al.* (1984) detected the amyloid P component in the vessels, but not in the plaques. They explain this divergence with the fact that serum amyloid protein with a molecular mass of 35 kDa cannot pass through the blood–brain barrier to reach the plaques. These authors did not obtain a positive reaction with antibodies against TTR either in the vessels or in the plaques.

Forms with Intracerebral Hemorrhages

The separation of cases with massive intracerebral hemorrhages from other types of amyloid angiopathy is justified on clinical, medicolegal, diagnostic, and therapeutic grounds, even though the demarcation from vasculo-parenchymatous forms with microinfarcts and small hemorrhages may be difficult. Aside from the fact that the boundary is fluid, additional difficulties arise from the evaluation of publications in which all cases of amyloid angiopathy, with or without hemorrhages, are treated together.

In the group of amyloid angiopathies with hemorrhages, one can distinguish familial and sporadic cases. The distinction becomes problematic, however, when one considers Swedish and Japanese patients in whom no familial incidence could be demonstrated, but who all came from a small circumscribed geographic area.

Sporadic Cerebral Hemorrhages in Amyloid Angiopathy

Clinical Picture In the majority of cases, this condition affects patients over 60 years of age (Blömer *et al.*, 1993), but cases occurring in younger age groups have also been reported (Erkwoh *et al.*, 1986). The clinical picture resembles that of an apoplectic stroke. CT will demonstrate the atypical localization of the bleeding in the cerebral lobes rather than in the basal ganglia or the pons. Recurrent hemorrhages are common. As a rule, these patients are normotensive (Michel *et al.*, 1988). Transient ischemic attacks are occasionally recorded in a patient's history.

In some cases bleeding occurs after trivial trauma or after surgical intervention. This is an important aspect, since, in some patients, the hemorrhages may be preceded by a long history of dementia or the clinical picture of chronic encephalitis (Erkwoh *et al.*, 1986). In such cases a diagnostic brain biopsy may precipitate a massive hemorrhage.

Neuropathology Macroscopically, recent and old hemorrhages are seen, usually located in or near the cerebral cortex and frequently ruptured into the subarachnoid space. Cerebellar and pontine hemorrhages are rare (Kyriakides *et al.*, 1994). In many cases old and recent cerebral infarcts are present at similar sites of predilection.

Light microscopy. Light microscopy demonstrates amyloid infiltration of blood vessels in the neighborhood of bleeding sites. Similarly affected vessels can be found in other areas with a distribution similar to that seen in amyloid angiopathy without hemorrhages. However, microinfarcts preferentially occur in the subcortical white matter. SPs are also present in practically all cases. Powers *et al.* (1990) described the distribution and histological characteristics of the multinucleated giant cell reaction in a case of sporadic CAA. They implied that it represents a foreign body reaction rather than giant cell arteritis.

Electron microscopy. Electron microscopy confirmed the amyloid nature of the deposits in vessels. Destruction of the smooth muscle cells and collagen deposition in the vessel walls have been assumed to be the cellular correlates of arteriolar weakening that can lead to CAA-related brain hemorrhage (Vinters *et al.*, 1994).

Colocalization of β/A4 and cystatin C in patients with sporadic CAA has been reported (Maruyama *et al.*, 1992).

Hereditary Cerebral Hemorrhage with Amyloidosis

Arnason (1935) reported the hereditary occurrence of cerebral hemorrhages in several families in Iceland. Gudmundsson *et al.* (1972) demonstrated the deposition of amyloid in the cerebral blood vessels. A hereditary amyloid angiopathy with hemorrhages was also recorded in a Dutch family (Wattendorf *et al.*, 1982).

Although the clinical manifestations show similarities, biochemical characterization revealed that amyloid in the Icelandic patients consists of cystatin C and in the Dutch patients, of β-protein. Therefore, it seems advisable to treat both forms separately.

Hereditary Cystatin C Amyloid Angiopathy (Icelandic Form of Hereditary Cerebral Hemorrhage with Amyloidosis)

Clinical Picture The average age at onset of hemorrhages in patients with the hereditary cystatin C amyloid angiopathy form was 44 years in the first and second generations, 29.6 years in the third generation, and 22 years in the fourth generation (Gudmundsson *et al.*, 1972).

Migraine was the initial symptom in some patients. In most patients the episodes of stroke recurred at intervals ranging from days to years. Occasionally, a progressive dementia developed, usually starting after one of the stroke episodes (Abrahamson *et al.*, 1992).

Neuropathology *Gross appearances.* Fresh, occasionally also old, subdural, subarachnoid, and intracerebral hemorrhages are present. The hemorrhages are multiple in most cases and frequently occur in the internal capsule.

Light microscopy. Thickening of the meningeal arteries and of meningeal and intracerebral arterioles can be seen to be caused by amyloid deposition. Amyloid is located in the intima or the adventitia, occasionally in both layers. The intimal deposits can lead to stenosis of the lumen and occasionally to thrombosis. SPs have not been seen in any of the Icelandic patients.

Hereditary Aβ Protein Amyloid Angiopathy (Dutch Form of Hereditary Cerebral Hemorrhage with Amyloidosis)

Hereditary Aβ protein amyloid angiopathy (HAβAA) is an autosomal-dominant disease, manifesting itself in the fifth or sixth decade with hemorrhagic stroke. Even in the absence of clinical or radiological evidence of strokes, dementia may develop. In the affected families there is also an acceleration of the appearance of symptoms from one generation to the next.

A severe deposition of amyloid in the cerebral and meningeal blood vessels is a common feature. Wattendorf *et al.* (1982) found small cortical infarcts immediately beneath thrombosed leptomeningeal vessels. Kawai *et al.* (1993) found β-amyloid precursor protein (β-APP) bound to the tunica media of vessels, but not other brain elements. They postulated that Aβ in blood vessels derives from degenerating β-APP–containing smooth muscle cells.

Besides the amyloid angiopathy, cortical silver-stained, noncongophilic, plaquelike structures have been described in HAβAA (Maat-Schieman *et al.*, 1992). Electron microscopy typically shows amyloid fibrils in the affected vessels (Wattendorf *et al.*, 1982).

Pathogenesis Hereditary cystatin C amyloid angiopathy is an autosomal-dominant disorder characterized by the deposition of amyloid in most investigated tissues. Chiso *et al.* (1986) were able to show that the protein unit was similar to cystatin, an inhibitor of lysosomal cysteine proteinases.

The disorder is caused by a T-to-A point mutation in the codon for the L at position 68 in exon 2 of the cystatin C gene, which results in an L-to-Q amino acid substitution in the cystatin C molecule (Jonsdottir and Palsdottir, 1993).

HAβAA is caused by a point mutation in the amyloid gene on chromosome 21, substituting Q for E at position 22 of Aβ protein (position 693 of β-APP770) (Levy *et al.*, 1990; Van Broeckhoven *et al.*, 1990).

Both diseases are caused by a single base mutation leading to the similar amino acid. Furthermore, both cystatin C and the β-protein precursor are protease inhibitors, and the mechanism of amyloidogenesis may be similar in both diseases (Haan and Roos, 1992).

Cerebral Amyloid Angiopathy with Leukoencephalopathy

This is a clinically and morphologically heterogeneous group consisting of a few patients in whom the common feature was the coexistence of extensive demyelination with an amyloid angiopathy. Several patients have presented with symptoms reminiscent of multiple sclerosis, in some cases punctuated by remissions and relapses. These patients typically died in the fifth decade after a prolonged illness of several years' duration. Amyloid angiopathy was prominent in all cases, and similar clinical and neuropathological features were observed in a young patient who, at the age of 22 years, developed symptoms of an atypical multiple sclerosis with psychotic manifestations and died 6 years later.

Gray *et al.* (1985) found diffuse demyelination of the cerebral hemispheres in eight of 12 patients with cortical amyloid angiopathy aged between 55 and 83 years. Neuropathological studies have revealed areas of demyelination in patients of various ages, some periventricular, but mostly subcortical. The presence of Rosenthal fibers and corpora amylacea in the demyelinated areas was a conspicuous feature. All patients reported by Gray *et al.* (1985) had microinfarcts and petechiae, and nine also had massive hemorrhages. The U-fibers, corpus callosum, and internal capsule were spared. SPs and Alzheimer's NFTs have been reported in half of the cases. Swelling of the oligodendroglia, dilated perivascular spaces, and hyalinosis of the blood vessels were seen in the white matter, but there was no evidence of amyloid. The authors drew attention to the similarity of the subcortical lesions here to those of Binswanger's dementia and suggested that failure of perfusion of the white matter may be the common pathogenetic

mechanism in both disorders. Diffuse changes in the white matter resembling Grinker's myelinopathy have also been recorded (Salama *et al.*, 1986).

Cases of CAA without hemorrhages have also been described (Vonsattel *et al.*, 1991). Morphologically, most cases of CAA consist of the deposition of a type of amyloid (β/A4 protein) in the wall of cerebral blood vessels, which can be recognized using Congo red staining. Other changes such as SPs with a prominent amyloid core and few NFTs have also been described (Vinters *et al.*, 1988). The finding of SPs and NFTs may point to a close relationship of this condition with Alzheimer's disease. Results obtained with a number of antibodies against these structures support this contention (Vinters *et al.*, 1988; Maruyama *et al.*, 1990). However, Cruz-Sánchez *et al.* (1992a) found differences between the amyloid in the SPs and in the vessels.

Pathogenesis of Cerebral Amyloid Angiopathy and Amyloid Plaques The development of amyloid deposits differs in blood vessels and SPs. All β/A4 amyloid is derived from the β-APP by splitting off a polypeptide chain that consists of 39 or 40 amino acids in vascular amyloid (Prelli *et al.*, 1988) and 42 to 43 amino acids in plaque amyloid (Masters *et al.*, 1985). These deposits also differ in their amino terminals and in their solubility in guanidine hydrochloride, with only vascular amyloid being soluble.

Vascular amyloid is formed by smooth muscle cells and is first deposited in their basal lamina (Wisniewski and Wegiel, 1994). It then surrounds individual myocytes, which degenerate and die, leading to the formation of a collar of amyloid in the outer and middle zones of the vascular media. Plaque amyloid is produced by perivascular cells enclosed within the basal lamina of capillaries and by microglial cells (Wisniewski *et al.*, 1992; Wisniewski and Wegiel, 1993).

The conversion of the secreted β/A4 polypeptide into amyloid fibrils requires additional "chaperone" factors, mainly amyloid-associated proteins that alter its state of aggregation (Busciglio *et al.*, 1993). These include proteases and protease inhibitors, serum amyloid P component, α_1-antichymotrypsin, complement components, and apolipoprotein E subtypes (Wisniewski and Frangione, 1992; Wisniewski *et al.*, 1993a).

The amyloid of prion diseases is produced in a similar fashion, with the difference that prion protein (PrP) takes the place of β/A4. Again microglial cells are the principal cells involved in the process, but ependymal cells are also capable of producing amyloid (Wisniewski *et al.*, 1994). The conversion of PrP into amyloid fibrils requires chaperone proteins (Guiroy and Gajdusek, 1989; Guiroy *et al.*, 1991). These include glycosaminoglycans, amyloid P component, apolipoprotein E, and α_1,chymotrypsin.

Amyloid Plaques in Spongiform Encephalopathies (Prion Diseases)

The transmissible spongiform encephalopathies are a group of dementing disorders affecting both humans and animals. The human diseases include CJD, GSS, fatal familial insomnia, and kuru. Eighty to 90% of cases of CJD are sporadic, 10% are familial with autosomal-dominant inheritance, and occasional cases of iatrogenic CJD resulting from the use of contaminated corneal and dural grafts, growth hormone preparations, or EEG electrodes have also been reported. This disease is distributed worldwide. Several regional clusters are known, the largest focus of which is among Libyan Jews, in whom the incidence is 100 times greater than that worldwide. The lat-

ter familial form of CJD is caused by a point mutation of PrP at codon 200. Mental deterioration including memory loss and behavioral abnormalities, signs of cerebellar, oculomotor, and vestibular dysfunction, are usually presenting features of CJD. The disease follows a subacute clinical course: most patients die within 1 year, half of them within 5 months after disease onset. GSS is a rare familial disorder with a more chronic course. A predominantly dementing form of GSS, the telencephalic variant, is caused by a mutation at codon 117; in a predominantly atactic form, including the original GSS family, there is a mutation at codon 102 of PrP. Kuru is an endemic disease, caused by infection through ritual cannibalism of the brains of deceased relatives; this form is confined to the Fore tribe in New Guinea. In fatal familial insomnia, which has been described in only a few families so far, there is severe disruption of sleep activity. Pathology is almost confined to the thalamus. The disease is caused by a PrP mutation at codon 178.

The genetics of human spongiform encephalopathies have recently been reviewed by Prusiner and Hsiao (1994). Animal diseases include scrapie of sheep, bovine spongiform encephalopathy ("mad cow disease"), and mink encephalopathy. These disorders share the morphological features of a fine spongiform rarefaction of the gray matter of the cerebral cortex, basal ganglia, thalamus and cerebellum. Most cases of prion disease, with the exception of fatal familial insomnia, were transmitted to experimental animals by intracerebral inoculation. The transmissible agent (prion) differs from conventional viruses by being resistant to most methods of sterilization and appears to be devoid of nucleic acids, although the latter view has not been proven. The transmitted material consists of an abnormal isoform of a ubiquitous cellular membrane protein, the PrP. Studies using human pathogenic PrP mutants in transgenic animals have shown that these develop the disease sporadically (Hsiao *et al.*, 1990); knockout mice in which PrP was ablated cannot be infected with the disease (Bueler *et al.*, 1992). These experiments have proven the central role of PrP in the familial diseases, and demonstrated that in transmitted CJD, host PrP is necessary for the development of the disease. In sporadic CJD the cause of accumulation of the pathological isoform of PrP is enigmatic. DeArmond (1993) discussed the overlap of pathogenic mechanisms between CJD and Alzheimer's disease, in which there is also a plaque amyloid protein (Aβ) with pathogenic mutations in familial variants. One explanation for the occurrence of sporadic CJD is that spontaneous conversion of the normal isoform to the abnormal one may occur sporadically and that the abnormal form catalyzes the transformation of further normal molecules into abnormal ones. The molecular difference between normal and abnormal isoforms lies in their three-dimensional structure: normal PrP is devoid of β-sheets, whereas in the abnormal pathogenic amyloid form β-sheets predominate. Interestingly, most known pathogenic mutations of PrP are located in the hydrophobic core of the molecule, where they may alter the configuration of PrP.

Histoblotting provides a useful method for screening large areas of tissue for the presence of pathological PrP and may be helpful in the differential diagnosis of difficult cases (Jendroska *et al.*, 1994).

Amyloid plaques composed of PrP occur in most cases of prion diseases, albeit with different frequencies. The so-called kuru plaques are found, by definition, in all cases of GSS and in 50–70% of kuru. In CJD they are rarely seen, but their incidence increases with the duration of the disease (Kitamoto and Tateishi, 1988). More frequently, multi-

centric PrP-reactive plaques can be found. Plaques occur in all animal models, both natural and experimental (Gajdusek, 1993).

The plaques consists of amyloid fibrils arranged radially and surrounded by a narrow halo of astrocytic processes. Dystrophic neurites are absent or scanty. In GSS plaques may be surrounded by NFTs. The main component of the fibrils is PrP, although mixed plaques containing both PrP and β/A4 occur in elderly subjects. Their localization is mainly perivascular, but subpial or subependymal plaques also occur, the latter particularly in experimental animals inoculated with prion material (Wisniewski *et al.*, 1994). In addition to the spongiform state, neuronal depletion, and PrP-reactive amyloid plaques, there is severe gliosis, sometimes prominent in areas of otherwise mild pathology. Pathology and regional infectivity correlate well with the regional concentration of PrP (Jendroska *et al.*, 1991, Hecker *et al.*, 1992).

Amyloid Tumor of the Brain (Amyloidoma)

The first case of a tumor of the CNS found to consist of a mass of amyloid was published by Saltykow (1935). Tumor-forming masses of amyloid were found in intraventricular as well as in extracerebral, intracranial, and extramedullary spinal locations. In the posterior cranial fossa, amyloidomas were reported to arise from the temporal bone (Ferreiro *et al.*, 1990), the gasserian ganglion (Bornemann *et al.*, 1993) and from the fifth or seventh cranial nerves (Matsumoto *et al.*, 1985).

Clinical Picture Most patients develop the disease in the fifth decade. A later onset in the seventh decade—and by vertebral amyloidomas in the eighth—has been reported. The symptomatology depends on the localization of the tumor. A large amyloidoma at the skull base may cause neural tissue compression (Unal *et al.*, 1992). Single vertebral amyloidoma is an unusual cause of spinal cord compression (Vila *et al.*, 1994; Villarejo *et al.*, 1994). The course of the disease is slowly progressive. The prognosis after removal of the tumor is as good as it is with amyloidomas in other organs.

Neuropathology *Gross appearances.* Upon sectioning the brain, one finds one or more circumscribed foci of yellowish color and a firm consistency in various parts of the white matter, but rarely in the cortex (Saltykow, 1935). The walls of the ventricles may be coated with a yellowish or whitish substance, which spreads subependymally. The extracerebral and extramedullary amyloidomas may contain calcifications.

Light microscopy. A homogeneous substance is arranged around the blood vessels or lies loose in brain tissue in the affected areas (Fig. 67A,B). It stains with all amyloid stains and shows the characteristic dichroism in polarized light. Perivascular lymphocytic and plasmacytic infiltrates may be seen around several blood vessels. Plasma cells, monocytes, and foreign body giant cells have also been observed occasionally (Erikson *et al.*, 1993).

Electron microscopy. The presence of typical amyloid fibrils with a diameter of 7.5 nm has been confirmed (Fig. 67C).

Pathogenesis Because amyloidoma displayed a positive immunohistochemical reaction with anti-IgM antibodies, it has been considered a variant of primary amyloidosis. Hori *et al.* (1988) found focal intracerebral accumulation of a novel type of amyloid

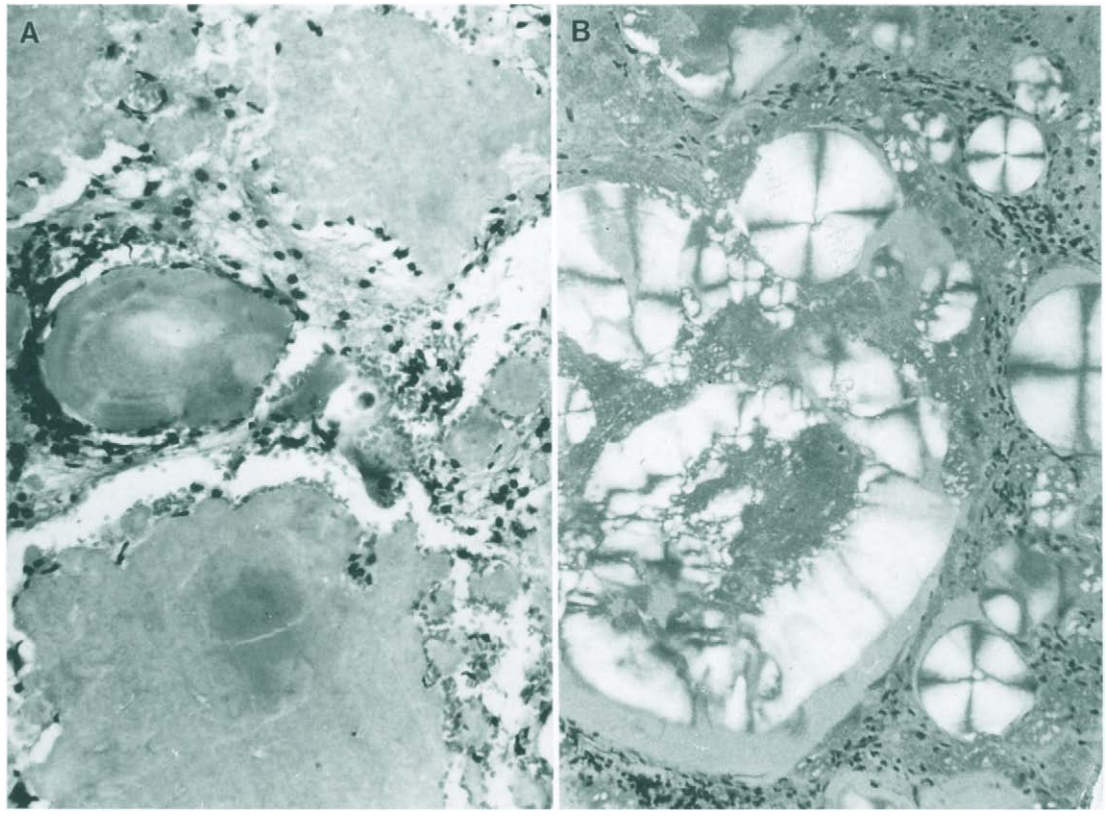


Fig. 67 An amyloid tumor of the brain. (A) Plasma cells and foreign body giant cells lying around the amyloid substance. (B) Under polarized light. Congo red stain, ×120. (C) Amyloid fibrils with a diameter of 7.5 nm, ×6500 (inset ×26,400). (Reproduced from Spaar *et al.*, 1981.)

which they considered to be the precursor of amyloidoma. Erikson *et al.* (1993) found, by amino acid sequence analysis of a major fibril subunit, protein homology with the variable region of a monoclonal λ immunoglobulin light chain, subgroup III or IV. This shows that the amyloid in the "tumor" was of the AL type and presumably derived from local synthesis by plasma cells.

Other Disorders of Protein Metabolism

Lipid Proteinosis (Urbach–Wiethe Disease; Hyalinosis Cutis et Mucosae)

Lipid proteinosis is a rare hereditary disorder, described by Urbach and Wiethe (1929) as a disease of the skin and mucous membranes. It has since turned out to be a generalized disease that can affect all organs (Rosenthal and Duke, 1967).

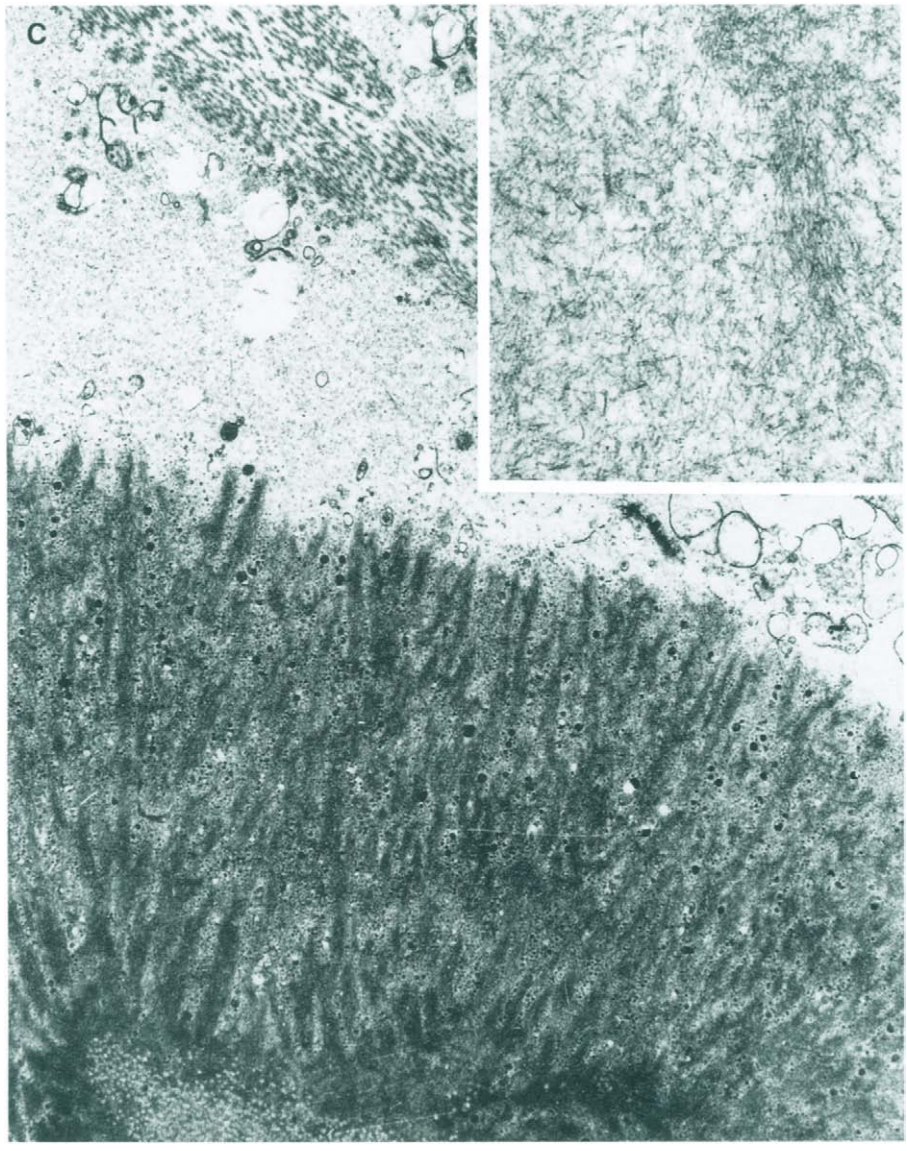


Fig. 67 Continued.

Clinical Picture The symptoms appear already in childhood with hoarseness and a papular ulcerating rash affecting primarily the perioral region, but also the elbows and the knees. Papular lesions are also present in the mucous membranes. Neurological manifestations include psychomotor attacks with selective amnesia but intact intelligence or with

mental retardation. A longstanding psychotic syndrome with ataxia and paraparesis has also been described (Kleinert *et al.*, 1987). Intracerebral calcifications can be present (Kchouk *et al.*, 1992).

Pathology PAS-positive hyalinlike deposits with lipid accumulation are seen in the dermis (Disdier *et al.*, 1994). The epidermis is frequently hyperplastic and hyperkeratotic.

Electron microscopy. Electron microscopy of the skin shows an accumulation of fine fibrillary material among the collagen fibers (McDonagh and Bleehen, 1990).

Neuropathology *Gross appearances.* One can detect calcifications in the falx, tentorium, and hippocampus of some patients, and sometimes also in the temporal lobe. Angiofibrosis of the arteries at the base of the brain and the small infarcts may be present (Kleinert *et al.*, 1987).

Light microscopy. Striking changes are present in the intracerebral vessels, affecting primarily the arterioles (Fig. 68A and B). Aside from fibrosis and hyalinosis, a deposition of a homogeneous substance is found in the media. This does not take up amyloid stains, but stains strongly with fibrin stains (Kleinert *et al.*, 1987). Lymphoplasmacytic infiltrates and a pronounced gliosis surround the affected vessels.

Pathogenesis Histochemical investigation of the changes in skin vessels reveal an association of a glycoprotein with a lipid in the hyaline material. Newton *et al.* (1971) rejected the concept of lipid proteinosis, as neither lipids nor proteins are present in significant quantities in the deposited material. They prefer the eponymous designation *Urbach–Wiethe disease*, at least until the composition of the stored substance is clarified.

Studies of gene expression by fibroblast cultures from a patient with lipid proteinosis have shown a 4.5-fold increase in the levels of mRNA that codes for type IV collagen, without an increase in fibronectin, procollagen type I, or the laminin *B2* gene mRNA (Paller, 1994).

Monoclonal Gammopathies (Paraproteinemias)

The term *monoclonal gammopathies* includes benign and malignant conditions characterized by increased levels of monoclonal immunoglobulins. Gammopathies of known or unknown etiology may lead to neurological symptoms affecting the peripheral nervous system and, less commonly, the CNS (Yeung *et al.*, 1991). There may be signs of CNS involvement even in the apparently pure peripheral neuropathies (Vital *et al.*, 1985). Julien *et al.* (1984) described a sensorimotor neuropathy developing over a few months in a patient with biclonal gammopathy. Isolated cerebral macroangiopathy in IgA paraproteinemia of the κ light-chain type has been reported (Eckert *et al.*, 1994). The role that monoclonal gammopathies may play in the pathogenesis of motor neuron diseases has been discussed (Sadiq and Latov, 1991).

Light microscopy. Deposition of M components and κ light chains has repeatedly been observed in the myelin sheaths and the endoneurium (Vital *et al.*, 1985). Direct immunofluorescence revealed IgM and κ light chains deposited around Schwann cells. Amyloid, when present, showed IgG and λ light chains. Some of the results have been contradic-

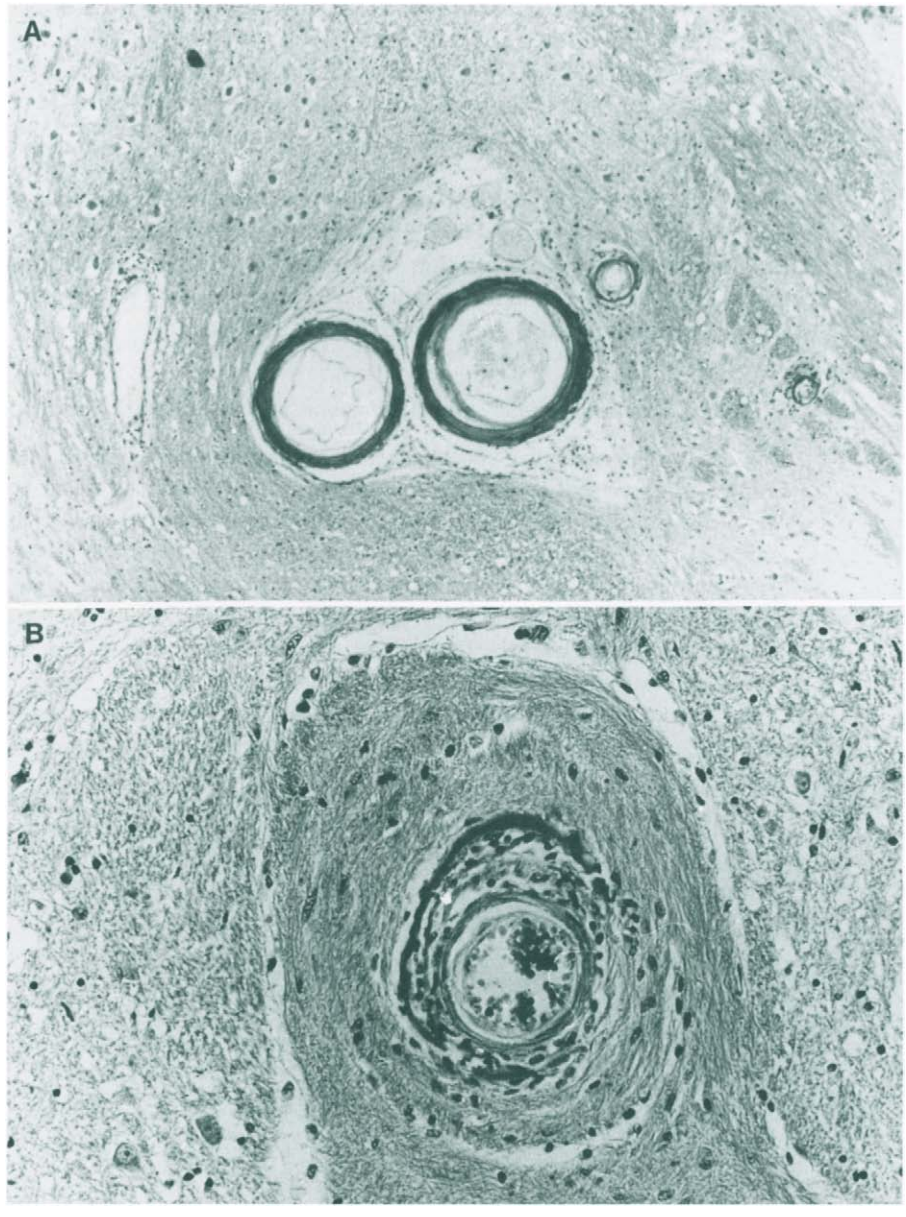


Fig. 68 (A) A paraventricular area, showing extreme hyalinosis and fibrosis of the arteries, amyloid-like deposits in the whole vessel wall, perivascular lymphoplasmocytic infiltrations, and edema. (B) The pons, showing a perivascular conspicuous glial cell and fiber proliferations, chronic inflammatory changes, and amyloid-like deposits in the adventitia of the artery. Masson's trichrome stain, (A) ×252 and (B) ×324.

tory and, while an immunological mechanism of the peripheral nerve involvement in gammopathies is certain, the exact pathogenesis has not been fully elucidated. Approximately half of the patients with peripheral neuropathy and IgM monoclonal gammopathy have antibodies binding to myelin-associated glucoprotein (Latov *et al.*, 1988). Similar changes have not been seen in the CNS. This may be due to the use of autopsy, rather than biopsy, material.

Electron microscopy. Nerve biopsies from patients with monoclonal IgM κ gammopathy and sensorimotor demyelinative neuropathy have revealed marked loss demyelination and remyelination with "onion skin" formation. Myelinated fibers displayed characteristic widening of the myelin lamellae along the interperiod lines and deposition of amyloid in the endoneurium (Vital *et al.*, 1985; Lach *et al.*, 1993).

X-Linked Agammaglobulinemia (Gonosomal Agammaglobulinemia)

Aside from degenerative encephalopathies of probable viral etiology in the course of congenital agammaglobulinemia (Neipp Lindenau *et al.*, 1990), chronic encephalopathies without identifiable infectious agents have also been described (Lyon *et al.*, 1980). A systematic review of the clinical findings of patients reported in the literature allows the distinction of two subgroups of patients according to their form of presentation: acute or insidious. In each subgroup there are significant clinical differences (Macaya-Ruiz *et al.*, 1993).

In most cases, the white matter is most severely affected. The distribution of lesions, however, differs from that of subacute sclerosing panencephalitis.

The gene for X-linked agammaglobulinemia (*XLA*) has been mapped to Xq22. (Lovering *et al.*, 1993).

Disorders of Lipid Metabolism

Introduction

The lipid component of biological membranes consists, in essence, of glycerophosphatides, cholesterol, and sphingolipids. In disturbances of lipid metabolism, particularly lipid catabolism, an increase in storage of the affected lipids occurs in various organs. The resulting diseases are covered by the term *lipidoses*. Lipid accumulation may also occur as a secondary manifestation of various systemic diseases, such as diabetes mellitus, hypothyroidism, and nephrosis. These abnormalities of lipid metabolism and the not uncommon "essential" hypercholesterolemias and hyperlipidemias outnumber the primary errors of lipid metabolism with intracellular storage. The latter, however, form the most important group of lipidoses affecting the nervous system.

Terminology

The increasing understanding of lipid metabolism has made it possible for investigators to define disease entities and to separate unrelated ones from each other. The systematization of these conditions, however, is complicated by the fact that the concept of *lipids* includes many chemically unrelated or remotely related substances. The principal characteristic of lipids—insolubility in water and solubility in organic solvents—does not offer any clues to their chemical structure, quite apart from the fact that some amphophilic lipids may be water soluble to a certain extent.

Classification

We have classified the lipid storage diseases according to the nature of the stored substances in ascending order of complexity, from simple fatty acids (peroxisomal enzyme

deficiencies) through sphingolipids to gangliosides. Wherever possible, the responsible enzyme defect was accepted as the principal criterion. For this reason we have abandoned the traditional division into *leukodystrophies* and *neurolipidoses.*

Primary Abnormalities of Blood Lipids

Primary quantitative changes in blood lipids appear as either hyper- or hypolipoproteinemias. The hyperlipoproteinemias are accompanied by a variety of abnormalities in cholesterol metabolism, without necessarily raising the blood level of the latter. A general increase in blood lipids is referred to as hyperlipidemia, while an increase in neutral fats is covered by the term *hypertriglyceridemia.* The hypolipoproteinemias are more clearly defined, although their pathogenesis is obscure.

Hyperlipoproteinemias

The familiar hyperlipoproteinemias is a common and important risk factor in the occurrence of cerebral infarcts, which may be ascribed to the tendency of the affected individuals to develop atheromatous changes in arteries (Cervós-Navarro, 1980). Otherwise, primary disorders in the nervous system are rarely found in the various subtypes into which hyperlipoproteinemias have been divided. In type IV, and less commonly in type V, dementia and sensorimotor neuropathy have been recorded. Both regress with treatment of the lipid disorder.

In the hypercholesterolemic xanthomatosis (types II and III) involvement of the CNS, apart from vascular lesions, is extremely rare. In the few cases in which the brain is affected, xanthomatous lesions appear in areas devoid of the blood–brain barrier. If they appear at other sites, a breakdown of the barrier has been postulated (Wolman, 1976).

Cerebrotendinous Xanthomatosis (Cholestanolosis; van Bogaert–Scherer–Epstein Disease)

The first case of cerebrotendinous xanthomatosis was reported by Schneider (1936) as "vascular lipoidosis," but it was van Bogaert *et al.* (1937) who gave a detailed description of the disease and differentiated it from other rare forms of cholesterosis affecting the CNS. Jervis (1957) published a report of an unusual case of cholesterosis of the basal ganglia and cortical degeneration. This relatively rare disease appears to be more common in Japanese patients (Kim *et al.*, 1994; Nakashima *et al.*, 1994) and in Jews of North African origin (Leitersdorf *et al.*, 1993; Reshef *et al.*, 1994).

Clinical Picture Apart from nodular swellings of the tendons, a neuropsychiatric syndrome may appear in childhood or later (Shapiro, 1983). A great variety of neurological symptoms have been described in various combinations. Common manifestations are spastic paresis, cerebellar ataxia, and progressive dementia (Cali *et al.*, 1991; Arlazoroff *et al.*, 1991). A parkinsonian syndrome is uncommon (Fiorelli *et al.*, 1990; Fujiyama *et al.*, 1991; Rogelet *et al.*, 1992), as are seizures (Matsumuro *et al.*, 1990; Arlazoroff *et al.*,

1991; Fujiyama *et al.*, 1991). Cerebral involvement without xanthomas has also been recorded (Hubar *et al.*, 1992). Peripheral neuropathy has been observed, particularly in older patients (Ben Hamida *et al.*, 1991; Donaghy *et al.*, 1990).

Hypodense areas may be seen on CT and MRI, due partly to the presence of xanthomas and partly to secondary demyelination (Hokezu *et al.*, 1992; Rogelet *et al.*, 1992; Berginer *et al.*, 1994). Xanthomas of the choroid plexus can also be visualized by CT.

Xanthelasmas of the cyclids may be present, but not consistently. Juvenile cataracts are the rule. Osteoporosis is common and is the cause of frequent fractures (Berginer *et al.*, 1993). Raised levels of cholestanol and apolipoproteins are found in the CSF (Salen *et al.*, 1987). Hyperbetalipoproteinemia was recorded by Schreiner *et al.* (1975).

Pathology In addition to the tendons, the lungs may also contain xanthogranulomas. Under light microscopy the nodules in the tendons consist predominantly of pure extracellular cholesterol crystals with a moderate granulomatous and foreign body giant cell reaction. The crystals are birefringent and stain weakly with Sudan III and Nile blue sulfate. The needlelike crystals lie parallel to the collagen fibers and sometimes are arranged irregularly, but they are always extracellular. The xanthomatous cells and giant cells are filled with lipid. On electron microscopy hypertrophic mitochondria and peroxisomes are seen in the liver cells. The matrix of the peroxisomes contains crystalline inclusions.

Neuropathology *Gross appearances.* Yellowish crunchy focal infiltrations are found in the brain. The lesions are particularly prominent in the cerebellar white matter and the cerebral peduncles (Philippart and van Bogaert, 1969).

Light microscopy. The granulomatous foci consist of free lipid crystals, intermingled with xanthomatous cells. The lipid in the latter stains lightly with Sudan dyes and forms small granules that stain reddish with Nile blue sulfate. The crystals are mostly needle shaped, are birefringent, and form Maltese crosses under polarized light. Both in the cerebellum and in the cerebral peduncles one can see extensive demyelination, which is also present in the medulla oblongata and the spinal cord. The blood vessels in the demyelinated areas are surrounded by fat granule cells. A strong reactive gliosis extends beyond the areas of demyelination, involves the corpus callosum, and spreads subependymally to the anterior horns of the lateral ventricles. The neurons in all cranial nerve nuclei and in the gray matter are generally preserved. Only the Purkinje cells show some loss (Giampalmo, 1969; Philippart and van Bogaert, 1969). Morphometric studies of the peripheral nerves have revealed some loss of large fibers, as well as frequent "onion bulb" structures.

Electron microscopy. Membranocystic lesions, resembling those seen in Nasu–Hakola disease, have been seen in the perivascular foam cells (Elleder *et al.*, 1989, 1990). Both segmental demyelination and axonal degeneration have been seen on peripheral nerve biopsies.

Pathogenesis This disease is inherited as an autosomal-recessive trait and is caused by a deficiency of the hepatic mitochondrial enzyme sterol 27-hydroxylase. The gene coding for this enzyme (*CYP27*) is located on the long arm of chromosome 2 in the region 2q33–qter (Cali *et al.*, 1991). The gene contains nine exons and eight introns and

encompasses at least 18.6 kb of DNA (Leitersdorf *et al.*, 1993). The sterol 27-hydroxylase catalyzes steps in the oxidation of sterol intermediates and in the biosynthesis of bile acids, particularly chenodeoxycholic acid, an important link in the feedback mechanism of sterol metabolism (Salen *et al.*, 1991).

Numerous point mutations that inactivate the enzyme have been found in cerebrotendinous xanthomatosis (Cali *et al.*, 1991; Leitersdorf *et al.*, 1993; Reshef *et al.*, 1994; Kim *et al.*, 1994). As a result, chenodeoxycholic acid is almost absent from the bile, and intermediate products of sterol metabolism, particularly cholestanol (5β-cholestane-3α-7α-12α-25tetrol), accumulate in the serum and are deposited in the tissues. Feeding with chenodeoxycholic acid can arrest, or even partially reverse, the process (Donaghy, *et al.*, 1990; Baumgartner *et al.*, 1991).

The crystalline deposits in the tissues, including the brain, consist of a mixture of cholesterol and cholestanol. They produce a granulomatous reaction of foreign body type and are surrounded by a wide zone of demyelination. While atheromatous changes in the arteries are undoubtedly present in cerebrotendinous granulomatosis, it is impossible to support the view that the cerebral lesions are due to vascular occlusion. Cholesterol deposits and xanthomatous granulomas are extremely rare in the common ischemic softenings (Cervós-Navarro, 1980).

Hypertriglyceridemia with Myelopathy (Spinal Cholesterosis—van Bogaert)

Van Bogaert (1965) described a case of hyperlipidemia associated with myelopathy. Other cases of this rare disease were reported by Grundt (1970). Brain infarction associated with hypertriglyceridemia has been reported by Yamanouchi *et al.* (1990).

Clinical Picture The first symptoms appear in the fourth or fifth decade and consist of slowly progressive disturbances of gait and balance, as well as disorders of sphincter control. Spastic parapareses and sensorimotor disturbances follow. The serum triglycerides are considerably raised. In van Bogaert's patient hepatosplenomegaly and multiple xanthomas were present.

Neuropathology *Gross appearances.* The affected segments of the spinal cord in van Bogaert's patient were yellowish and soft. The cervical cord disintegrated upon dissection.

Light microscopy. The blood vessels in the medulla oblongata are surrounded by foam cells. Their contents stain strongly with neutral fat stains. Needle-shaped crystals—in places, arranged in bundles—are seen between the myelinated fibers. The lesions increase in severity in the cervical cord and decrease further caudally. Dense gliosis was present in all affected areas.

Xanthogranulomas of the Choroid Plexuses (Xanthomas of the Choroid Plexuses: Cholesterol Granulomas of the Choroid Plexuses)

These xanthogranulomas were already known to Luschka (1855). They are a common incidental finding at the time of autopsy, mostly in adults. Their incidence varies in differ-

ent autopsy series, between 1.6% and 7%, depending on age. They have occasionally been observed in children (Gaskill *et al.*, 1992).

Clinical Picture The plexus granulomas are rarely of clinical interest. Generalized seizures, mental symptoms, pareses, headaches, obesity, personality changes, psychomotor retardation, jacksonian epilepsy, and autonomic disturbances have all been recorded. Several symptomatic cases have recently been reported (Bruck *et al.*, 1991; Marks *et al.*, 1991; Hicks *et al.*, 1993). These are the result of hydrocephalus and raised intracranial pressure developing in childhood or adulthood.

Pathology *Gross appearances.* The granulomas may appear in a polycystic mulberry form or as larger single or multiple nodules. Their preferential site is the choroid plexus of the lateral ventricle. A xanthogranuloma of the third ventricle has been described by Tatter *et al.* (1994). The granulomas are yellowish white to orange in color and are of variable consistency. Cystic changes within the granulomas have been described.

Light microscopy. Lipid-laden foam cells and granulomas contain cholesterol crystals, connective tissue, lymphocytes, and foreign body giant cells (Fig. 69A and B) in a typical foreign body reaction. Blood pigments are often found in the foam cells. In their case of granuloma of the third ventricle, Tatter *et al.* (1994) described microscopic foci of colloid cyst-like structure. In reviewing the literature, Bruck *et al.* (1991) concluded that granulomas of the third ventricle differed in structure from those of the lateral ventricles, and were instead more closely related to colloid cysts.

Fig. 69 Xanthogranuloma of the choroid plexus. An accumulation of cholesterol crystals in proliferated connective tissue, with lymphocytic infiltrates and foreign body giant cells. Hematoxylin–eosin stain, (A) ×30 and (B) ×120.

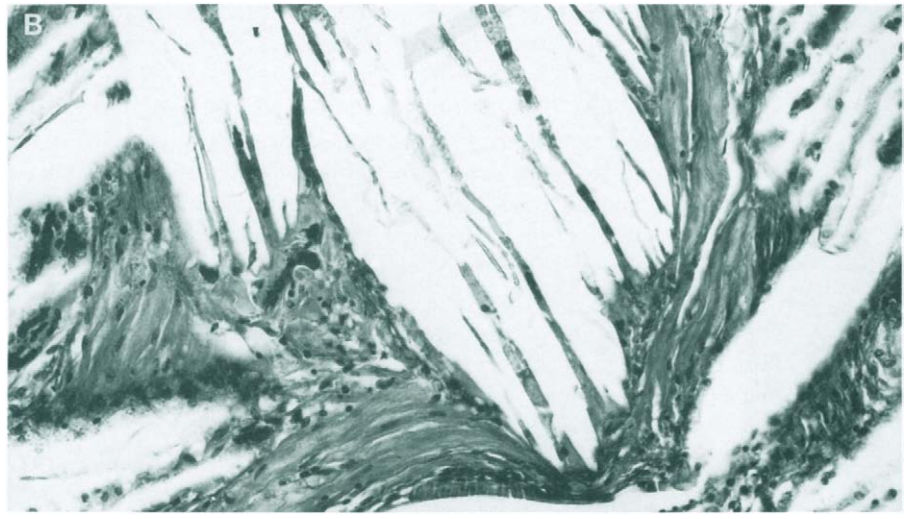


Fig. 69 Continued.

Electron microscopy. The cells have the characteristic features of meningeal cells with dense cytofilaments and desmosomes. The xanthoma cells show similar features (Razavi-Encha *et al.*, 1987). Sparse apical microvilli have been seen (Gherardi *et al.*, 1984).

Pathogenesis Xanthogranulomas are occasionally associated with a raised level of cholesterol and other lipids in the CSF. Intracellular lipids in the choroid plexus increase with age, in parallel with the incidence of granulomas. By longstanding hypercholesterolemia a patient with cholesterol granulomas displaying chronic progredient neurological symptomatology (Leel-Össy *et al.*, 1991) as well as bilateral asymptomatic xanthogranulomas (Rabl and Sigrist, 1992) has been documented.

The foam cells are derived from the arachnoidal cells of the plexus stroma. The leptomeningeal origin of some of these cells was confirmed by the ultrastructural investigations of Razavi-Encha *et al.* (1987). The disintegration of these cells liberates cholesterol crystals, which induce a granulomatous reaction.

In phytosterolemia, a familial lipid metabolic disorder with tuberous and tendinous xanthomatosis (Bhattacharyya and Conner, 1974), multiple intradural xanthomatous tumors restricted to the spinal denticulate ligaments were reported (Okabe *et al.*, 1992). Histological and immunohistochemical findings were fundamentally similar to those of tendinous xanthomas.

Wolman Disease (Acid Lipase Deficiency)

This disease was first described by Abramow *et al.* (1956) as a hereditary generalized xanthomatosis with adrenal calcification. The detailed nosological definition of the entity by Wolman *et al.* (1961) led to the eponym *Wolman disease*. Recently reported typical cases include those by Storm *et al.* (1990), Mahdi *et al.* (1991), Röyttä *et al.* (1992), and Mnif *et al.* (1994).

Clinical Picture During the first few weeks of life, infants with this disorder develop an ileus with vomiting, abdominal distention, diarrhea, and massive hepatosplenomegaly, sometimes with jaundice. After the sixth week severe anemia becomes apparent. Adrenal calcification is a constant feature. These children die within a few, usually 4, months.

Pathology *Gross appearances.* Hepatosplenomegaly, hypertrophy of the adrenals, and yellow lymph nodes are conspicuous features.

Light microscopy. The reticuloendothelial cells are transformed into foam cells in all organs. The vacuoles contain sudanophilic neutral fat and cholesterol esters. The plasma lipids are normal. The fat content of the liver and the spleen may be increased 100-fold. In the cytoplasm of the adrenal cortical cells, which are swollen with sudanophilic lipid, one may observe crystalline inclusions, consisting of calcium granules. The zonae fasciculata and reticularis are diffusely infiltrated with foam cells.

Neuropathology Guazzi *et al.* (1968) saw storage of a basophilic and sudanophilic material in the leptomeninges. Sudanophilic lipid may also be present in the astrocytes, oligodendrocytes, and endothelial and adventitial cells of the blood vessels (Fig. 70). The composition of the brain lipids is altered. The neurons of the CNS apparently are not involved. Neuronal storage, however, has been seen in the retina and in the autonomic nervous system (Guazzi *et al.*, 1968; Wolman, 1968).

Electron microscopy. Using electron microscopy, Byrd and Powers (1979) found lipid droplets in astrocytes, oligodendrocytes, and endothelial and adventitial cells of the blood vessels. Schwann cells and endoneurial cells in the peripheral nerves are similarly affected.

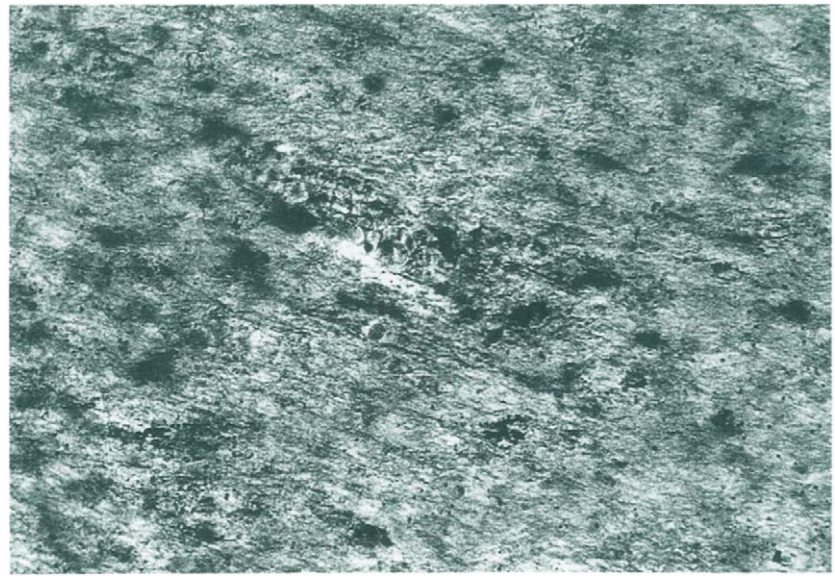


Fig. 70 Wolman disease in the white matter of the centrum ovale. Storage of sudanophilic material in the astrocytes and the vessel walls. Sudan IV stain, ×250. (Courtesy of M. Wolman, Tel Aviv, Israel.)

Pathogenesis This disease is inherited as an autosomal-recessive trait and is due to a defective lysosomal enzyme, the acid lipase/cholesteryl esterase (Lake and Patrick, 1970). The enzyme is coded by a gene located on chromosome 10q23.2–q23.3 (Anderson *et al.*, 1993). The gene consists of 10 exons spread over 36 kb (Anderson *et al.*, 1994). Two point mutations have been identified, each capable of completely disrupting the catalytic function of the enzyme (Anderson *et al.*, 1994). Abnormalities of this enzyme are also responsible for a milder form of the disease, affecting predominantly adults: the cholesterol ester storage disease (Ozmen *et al.*, 1992; Aslanidis *et al.*, 1994). Exon skipping (i.e., deletion) has been found to be the cause of this syndrome (Aslanidis *et al.*, 1994).

The lipid storage in epithelial, glial, and Schwann cells appears to be primary, while the reticuloendothelial cells may be involved secondarily.

Biochemical enzyme assays allow the identification of heterozygotes.

Experimental Hypercholesterolemia In subdiabetic rabbits hypercholesterolemia leads to the formation of Alzheimer's type II astrocytes in the basal ganglia. These astrocytes contain cholesterol crystals and in later stages may be converted into foam cells (Adachi *et al.*, 1971).

Multisystem Triglyceride Storage Disease

Contreras and Espinoza (1960) drew attention to the coexistence of tapetoretinal degeneration and a chronic tubulointerstitial nephropathy, reminiscent of Alström syndrome. In subsequent cases involvement of other organs was also observed. Schimke (1969) drew attention to an underlying disturbance of lipid metabolism, and Philippart *et al.* (1974) pointed out the pathogenetic similarity of this condition to Wolman disease. Another condition, in which neurological symptoms appear only in adult life, was described by Dorfman *et al.* (1974) under the name *ichthyosiform dermatosis with systemic lipidosis.*

The underlying enzyme defect is unknown at present and it is not certain that all of the reported cases belong to the same entity. On the basis of the clinical course, one can distinguish infantile and adult forms.

Infantile Form: Previously reported patients who could be included in this group have not been investigated either histologically or biochemically.

Clinical Picture In some of the patients, ichthyosis and hepatosplenomegaly are present at the time of birth or soon afterward. In others ichthyosis is absent. All develop subsequently progressive psychomotor retardation, tapetoretinal degeneration, deafness, and chronic tubulointerstitial nephropathy. Diabetes mellitus and bony displasia may occur. As a rule, these patients die within the first decade or at the beginning of the second.

Pathology *Gross appearances.* All organs, particularly the liver, gut, and heart, show a peculiar orange discoloration. The liver and the heart are hypertrophic; the kidneys, atrophic. The lungs are firm.

Light microscopy. The cytoplasm of foam cells is filled with lipid droplets. The parenchymal cells of all organs, particularly the liver, lungs, heart, gut, and kidneys, show lipid storage. The lipid droplets stain with oil red O, Sudan III, and Schultze's stain for cholesterol (Philippart *et al.*, 1974). The renal glomeruli show hyalinization and thickening of the basement membranes.

Neuropathology Philippart *et al.* (1974) have mentioned only degeneration of the optic pathways, neuronal loss in the cerebral cortex, and lipid storage in the surviving neurons.

Adult Form: The cases of Dorfman *et al.* (1974), Chanarin *et al.* (1975), Hays *et al.* (1976), and probably also Angelini *et al.* (1980) are of the adult form.

Clinical Picture The patients suffer from ichthyosis from birth. Muscular weakness and peripheral vascular atrophy appear later. The course of the disease is chronic, and neurological symptoms appear only in the fourth decade. These consist of loss of hearing, nystagmus, and ataxia. These are accompanied by a raised protein level in the CSF. The lipid content of individual organs has been measured by MRI spectroscopy, and confirmed the distribution and severity of lesions in the skeletal muscles (Leroy-Willig *et al.*, 1990).

Pathology There have been no autopsy reports. Aside from the lesions of ichthyosis, the findings are confined to various biopsies. The granulocytes in the peripheral blood and the bone marrow are vacuolated and store lipid. Liver, muscle, and intestinal biopsies also show multiple vacuoles, the contents of which strongly take up neutral fat stains, but are PAS negative.

Electron microscopy. On electron microscopy fibroblasts, monocytes, endothelia, and muscle contain lipid droplets. They are not membrane bound.

Neuropathology Lipid droplets are also found in the cytoplasm of Schwann cells (Slavin *et al.*, 1975).

Pathogenesis The difficulties in defining this syndrome, which is probably heterogeneous, are reflected in the different interpretations of the pathogenetic mechanisms in each reported case. In a series of tapetoretinal degenerations with or without ichthyosis, there was no evidence of a disorder of lipid metabolism (Cohan *et al.*, 1979). In earlier cases metabolic abnormalities were not mentioned, and probably were not investigated. In other patients diabetes mellitus, hyperuricemia, or hypertriglyceridemia were found without attribution of the pathogenesis to any of these abnormalities. In the infantile form Philippart *et al.* (1974) established a low activity of triglyceride lipase and acid lipase. On the other hand, Angelini *et al.* (1980) found a normal level of acid lipase and increased activity of thiokinase and carnitine palmitoyltransferase. Their patient was a child of $5\frac{1}{2}$ years with ichthyosis since birth, but without neurological symptoms, therefore probably belonging to the adult group. They attributed the triglyceride storage to an excessive synthesis or uptake of fatty acids and the formation of acylglycerol.

Cholesterol Granulomatosis (Hand–Schüller–Christian Disease; Histiocytosis X; Lipid Granulomatosis; Eosinophil Xanthomatous Granuloma; Essential Normocholesterolemic Xanthomatosis)

Hand (1893) was the first to describe the syndrome of cholesterol granulomatosis without, however, recognizing the nature of the disease. Schüller (1915) followed this with a report of two cases, and Christian's publication appeared in 1919. Hand (1921) evaluated an additional case of his own and one of Kay's and differentiated the disease from tuberculosis. Weidmann and Freeman (1924) were the first to interpret the proliferated tissue as xanthomatous. The term *histiocytosis X* (Kepes, 1979) also includes the eosinophilic granuloma of bone and the generalized Letterer–Siwe disease with Hand–Schüller–Christian disease.

Clinical Picture The characteristic triad consists of bony defects, exophthalmos, and diabetes insipidus. In some cases with primary involvement of the hypothalamus, diabetes insipidus remained the only symptom for many years (Beard *et al.*, 1970). Occasionally, granulomas at the apex of the petrous temporal bone may cause symptoms of either brain stem compression or impairment of CSF flow (Benecke, 1988).

Pathology Granulomas rich in cholesterol are found in the skin, orbit (Fig. 71), lymph nodes, and other organs without a consistent pattern of lesions. Interstitial fibrosis

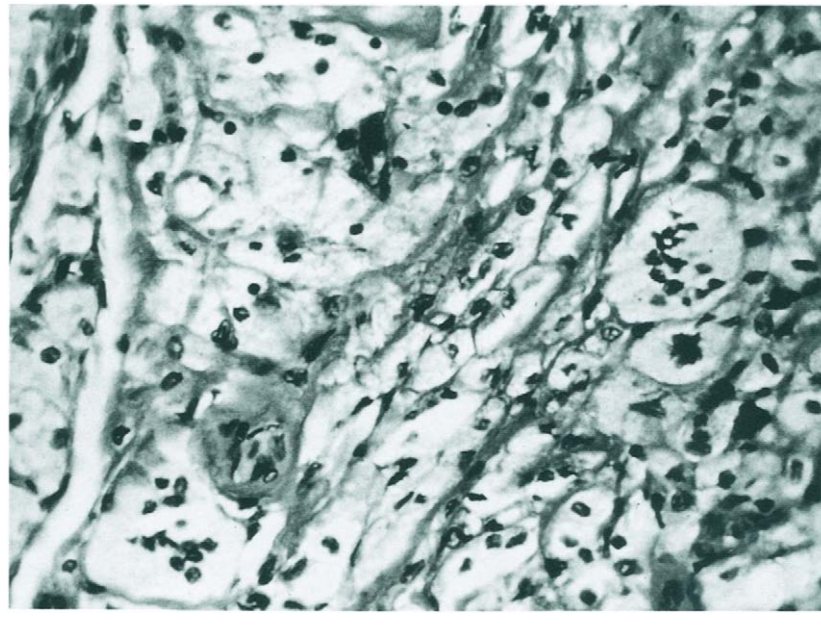


Fig. 71 Cholesterol granuloma of the orbit. Hematoxylin–eosin stain, ×200. (Courtesy of H. Witschel, Freiburg, Germany.)

with foam cells may be found in the lungs, and lipid granulomas may be seen in the perinephric fat.

Neuropathology *Gross appearances.* Earlier, cerebral involvement in Hand–Schüller–Christian disease was unknown, but cases with cerebral localization soon began to appear. Single or multiple subdural nodules may be seen in some cases (Rubens-Duval *et al.*, 1966). In the majority of the cases with CNS involvement, focal lesions may be present in the cerebrum and the cerebellum, and particularly in the hypothalamus. Spinal involvement is rare (Salcman *et al.*, 1974). A large granuloma of the dura, involving the falx and the tentorium and causing obstructive hydrocephalus, was reported by Jamjoom *et al.* (1993).

Light microscopy. There is a proliferation of histiocytes containing coarse and fine lipid droplets in the cytoplasm (Fig. 72A and B). An admixture of lymphocytes and plasma cells, frequently engulfed by macrophages, is commonly seen. Both in the periphery and inside the granulomas hypertrophic astrocytes may be included, sometimes with Rosenthal fibers.

A cerebral form of the condition with a disseminated demyelinating encephalomyelitis has occasionally been described (Beard *et al.*, 1970). In this form multiple foci of demyelination are found in the cerebellum, pons, medulla oblongata, basal ganglia, and cerebral white matter. In these foci a granulomatous inflammation is seen, of gliomesenchymal character, but devoid of cholesterol-storing foam cells. Small numbers of fat granule cells may be present. Occasionally, the macrophages assume the appearance of globoid cells (see p. 275), but without storage of cerebroside (Beard *et al.*, 1970).

The cerebral xanthomatous granulomatosis with participation of glial and mesenchymal elements is a specific reaction pattern of the CNS. Elsewhere, purely mesenchymal elements are involved.

The pathogenesis is unknown. Neoplastic, inflammatory, and metabolic hypotheses have been advanced.

Hypolipoproteinemias

Abetalipoproteinemia (Acanthocytosis with Pigmentary Degeneration of the Retina and Ataxia; Bassen–Kornzweig Syndrome; Familial Low-Density Protein Deficiency)

This disease was first described by Bassen and Kornzweig (1950) and is characterized by an absence of β-lipoproteins in the serum. *Acanthocytosis* refers to the spiky deformity of erythrocytes. Patients with acanthocytosis but without hypolipoproteinemia may suffer from a hitherto unexplained neuromuscular disorder (Levine *et al.*, 1968). A case of hypoprebetalipoproteinemia, acanthocytosis, RP, and pallidal degeneration (HARP syndrome) was described by Higgins *et al.*, (1992a). However, this seems to be closer to Hallervorden–Spatz syndrome (see p. 275).

Clinical Picture The disease appears in the first year of life with uncontrollable diarrhea and steatorrhea, which may subside spontaneously after a few years. Tapetoretinal degeneration in the form of a typical or atypical RP may be present (Kayden, 1972). Neurological symptoms usually appear after the first year of age and consist of an absence of

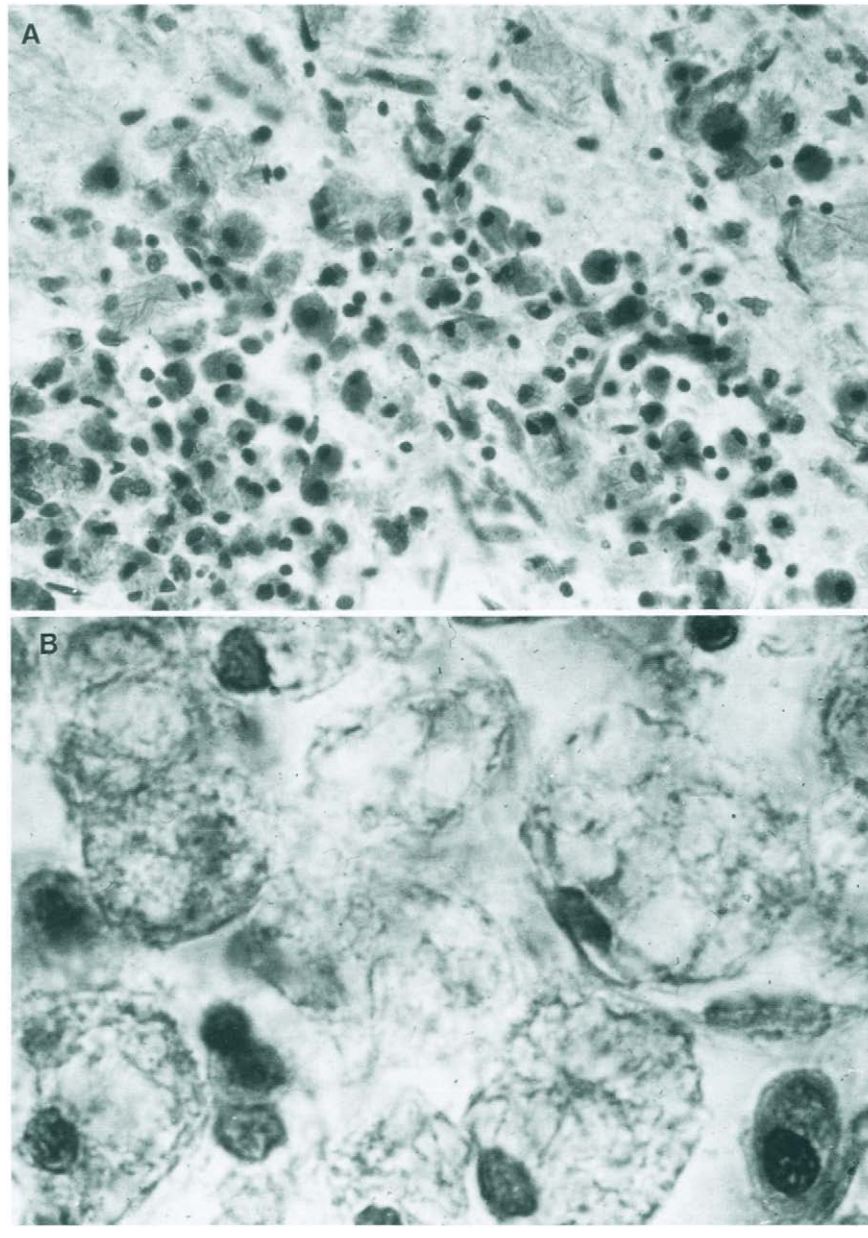


Fig. 72 Cholesterol granulomatosis. (A) A hypothalamic focus with a proliferation of lymphocytes, plasma cells, and histiocytes. (B) Lipid-laden macrophages. Hematoxylin–eosin stain, (A) ×200 and (B) ×800.

deep reflexes, atrophy of the muscles, ataxia, and nystagmus. The syndrome is that of a spinocerebellar degeneration, reminiscent of Friedreich's ataxia. Involvement of the peripheral nervous system is less pronounced, but occasionally mild hypoesthesia to pain, temperature, and light touch is noted in a glove-and-stocking distribution (Yao and Herbert, 1992). The prognosis is generally good, even though the disease is slowly progressive.

Pathology *Light microscopy.* Under light microscopy swelling of the jejunal mucosa with an accumulation of neutral fats may be seen.

Electron microscopy. Electron microscopy reveals the appearance of fat droplets in hepatocytes and in capillary endothelia a few hours after meals. An accumulation of ceroid pigments can be seen in the gut, heart (Kayden, 1972), and skeletal muscle. Micronodular cirrhosis of the liver has been observed.

Neuropathology *Gross appearances.* The brain appears normal, as a rule. A brownish discoloration of the anterior horns may be seen in the spinal cord.

Light microscopy. Degeneration of the posterior columns and the pyramidal and spinocerebellar tracts is present in the spinal cord. A loss of myelin is also apparent in the cerebellum (Sobrevilla *et al.*, 1964) and in the peripheral nerves (Lantos and Aminoff, 1972). The cerebellar nuclei and the anterior horns of the spinal cord show a reduction in the number of neurons (Sobrevilla *et al.*, 1964). In the eyes there was a severe loss of photoreceptors and external granular cells with some macular sparing, defective pigment epithelium with pigment deposition in the inner retinal layers, and a reduction in the diameter of the optic nerve, which contained peculiar round birefringent bodies.

Electron microscopy. Splitting of the myelin sheaths along the interperiod lines is seen in the peripheral nerves (Lantos and Aminoff, 1972). An increase in the number of lysosomes appears in the Schwann cells.

Pathogenesis This biochemical disorder consists of an absence of very low-density lipoproteins (VLDLs; density, 0.950–1.006 g/ml), intermediate-density lipoproteins (IDLs; density, 1.006–1.019 g/ml), and low-density lipoproteins (LDLs; density, 1.019–1.063 g/ml), while high-density lipoproteins (HDLs; density, 1.063–1.210 g/ml) are preserved. The underlying defect is an absence of apolipoprotein (apo) B, which is a component of lower-density lipoproteins. Absence of apo B also inhibits the formation of chylomicrons. As cholesterol is bound to lipoproteins, its level in the plasma is low, as is that of cholesterol esters, caused by a low activity of phosphatidylcholine–sterol acyltransferase, which catalyzes the esterification of cholesterol by transferring fatty acids from phosphatidylcholine (Scanu *et al.*, 1974). The level of triglycerides is also low, but a rare normotriglyceridemic variant of abetalipoproteinemia has been reported by Malloy *et al.* (1981).

Absorption of fat from the gut is only slightly impaired, leading to a mild steatorrhea. The ocular and neurological manifestations are the result of a deficiency of fat-soluble vitamins A, K, and particularly E, normally transported by chylomicrons (Yao and Herbert, 1992).

The disease is inherited as an autosomal-recessive trait and only homozygotes are affected, the heterozygotes being clinically and biochemically normal. No mutations in apo B have been observed. While this protein is always absent in the plasma, it may be present, even in normal quantities, at the cellular level (Bouma *et al.*, 1990). It has therefore

been suggested that abetalipoproteinemia may be due to defective cellular secretion of apo B.

Familial Hypobetalipoproteinemia: This syndrome, which closely resembles abetalipoproteinemia, but differs from it in some important aspects, was described by Cottrill *et al.* (1974); other reported cases include those of Aggerbeck *et al.* (1974) and Ross *et al.* (1988).

The clinical picture in homozygotes is identical to that in Bassen–Kornzweig syndrome, but is more variable, even in the same sibship (Aggerbeck *et al.*, 1974). On the other hand, heterozygotes are also affected and show LDL and apo B levels approximately 50% of normal amounts. They may show mild clinical manifestations in the form of acanthocytosis and fat malabsorption, and occasionally also a loss of tendon jerks and ataxia (Yao and Herbert, 1992).

In contrast with abetalipoproteinemia, mutations in the apo B gene are constant, leading to truncation of the apo B polypeptide chain (Young *et al.*, 1990). Eight different mutations have been recorded to date.

Hypo-α-lipoproteinemia (Tangier Disease)

Tangier disease is a rare autosomal-recessive metabolic disorder first described by Frederickson *et al.* (1961) in a patient who inhabited Tangier Island in Chesapeake Bay, Virginia. Subsequently, additional patients have been described in the United States, Germany, Switzerland, England, and New Zealand.

Clinical Picture The patient's age at onset varies considerably, ranging from 2 years to the sixth decade. The most conspicuous clinical feature is a hereditary enlargement and orange–yellow or grayish yellow discoloration of the tonsils. In contrast with the case in abetalipoproteinemia, CNS symptoms are rare in hypo-α-lipoproteinemia. An affection of the lower motor neuron and a syringomyelia-like syndrome with atrophy, paresis, and dissociated sensory loss was described in a few patients (Gibbels *et al.*, 1984; Schmalbruch *et al.*, 1987).

The physical and mental development of the patients appears normal. An intermittent asymmetrical polyneuropathy was reported in about one third of the cases. In homozygotes the plasma cholesterol levels are low (less than 120 mg/100 ml), the triglycerides are normal or increased, and the HDLs are totally absent or severely reduced. In spite of the low cholesterol levels, severe atheroma, including coronary atheroma, may occur (Mautner *et al.*, 1992; Genest *et al.*, 1993).

Pathology Cholesterol esters accumulate predominantly in reticuloendothelial cells in the tonsils, lymph nodes, thymus, bone marrow, liver, spleen, and rectal mucosa.

Neuropathology *Light microscopy.* Bale *et al.* (1971) found no evidence of storage in the brain, either in neurons or in macrophages. Schmalbruch *et al.* (1987) found an accumulation of lipids in the anterior horn cells of the sacral cord (Fig. 73A) and in the neurons of dorsal root ganglion L5 (Fig. 74A). The stored substance was not autofluorescent.

Motor neuron loss was severe in the cervical spinal cord and the facial nerve nucleus and slight at the lumbar level (Antoine *et al.*, 1991).

Under electron microscopy some neurons of the lower spinal cord showed atypical inclusions, composed of a granular, mildly osmiophilic substance mingled with rounded bodies from low to high electron density.

Endoneurial fibrosis was found in a peripheral nerve, as well as lipid storage in the cytoplasm of Schwann cells. The loss of small myelinated fibers and U-fibers correlated well with the dissociated sensory loss (Gibbels *et al.*, 1984; Schmalbruch *et al.*, 1987). Extreme lipid storage was described in the Schwann cells of small cutaneous nerves and of the myenteric plexus (Ferrans and Fredrickson, 1975). In a peripheral neuropathy of acute onset, Fazio *et al.* (1993) found both demyelination and axonal degeneration involving only some fascicles. They attributed the lesion to ischemia.

Electron microscopy. The neuronal inclusions in the sacral cord and the spinal ganglion consisted of granules resembling lipofuscin (Fig. 73b). In the cytoplasm of Schwann cells, one finds sharply defined vacuoles that appear empty, apart from a homogeneous substance arranged around the margin of the vacuole. In the U-fibers these structures exceed the diameter of axons, which show swellings along their course. Nonspecific osmiophilic, pleomorphic, and, less commonly, filamentous inclusions may also be seen.

Pathogenesis A deficient apo A-I forms the fundamental change of this disorder. The concentration of apo A-II is normal or reduced, while apo A-IV and apo C-III are normal (Genest *et al.*, 1993; Lackner *et al.*, 1993). The HDLs are considerably reduced. HDLs are required for the removal and breakdown of excess cholesterol in the cells. The deficiency of HDLs leads to an accumulation of cholesterol and cholesterol esters, which is a hallmark of the disease (Herbert *et al.*, 1983).

The absence or sparseness of lesions in the CNS may be attributed to the blood–brain barrier. In peripheral nerves the intensity of the disturbance of lipid metabolism depends on the local connection between the vascular and nervous tissues.

Other Types of Familial High-Density Lipoprotein Deficiency: Apart from the case in Tangier disease, HDLs are deficient in a variety of metabolic disorders including apo A-I deficiency type I, apo C-II deficiency, lipoprotein lipase deficiency, phosphatidylcholine–sterol acyltransferase deficiency, and fish eye disease. These disorders differ in their concentrations of apolipoproteins, cholesterol, and triglycerides (Breslow, 1989).

Multisystem Neuronal Degeneration with Fatty Acid Deficiency

Dyck *et al.* (1981) described a syndrome in two brothers, consisting of multisystem neuronal degeneration, hepatosplenomegaly, and adrenal insufficiency, associated with abnormally low concentrations of unsaturated fatty acids, including arachidonic acid.

Hypotonia and a progressive adrenocortical insufficiency had been present since birth. Other features were RP, nerve deafness, and mental retardation.

Electron microscopy of a nerve biopsy showed an increase in the numbers of mitochondria and concentric lamellar inclusions in the axons. Here and there aggregations of glycogen could be seen, particularly in the neighborhood of the Schmidt–Lanterman incisures.

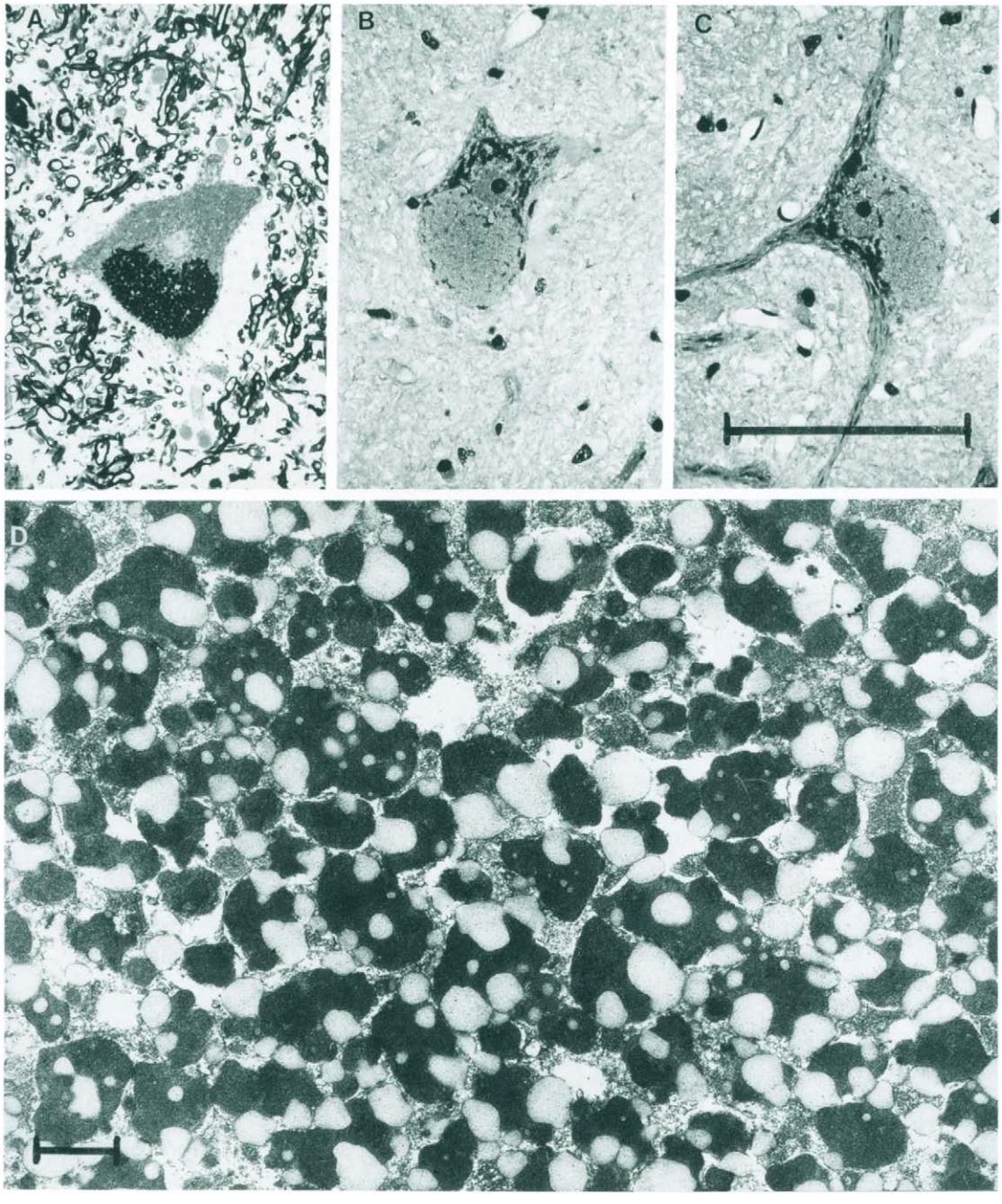


Fig. 73 Hypo-α-lipoproteinemia in the anterior horn cells of the spinal cord. (A) An expanded area of perikaryon with granular strongly osmiophilic material. Phenylene diamine stain. (B and C) Unstained deposits. Cresyl violet stain. (D) Ultrastructure of the neuronal inclusions. Bars: (A–C) 100 μm and (D) 1 μm. (Reproduced from Schmalbruch *et al.*, 1987.)

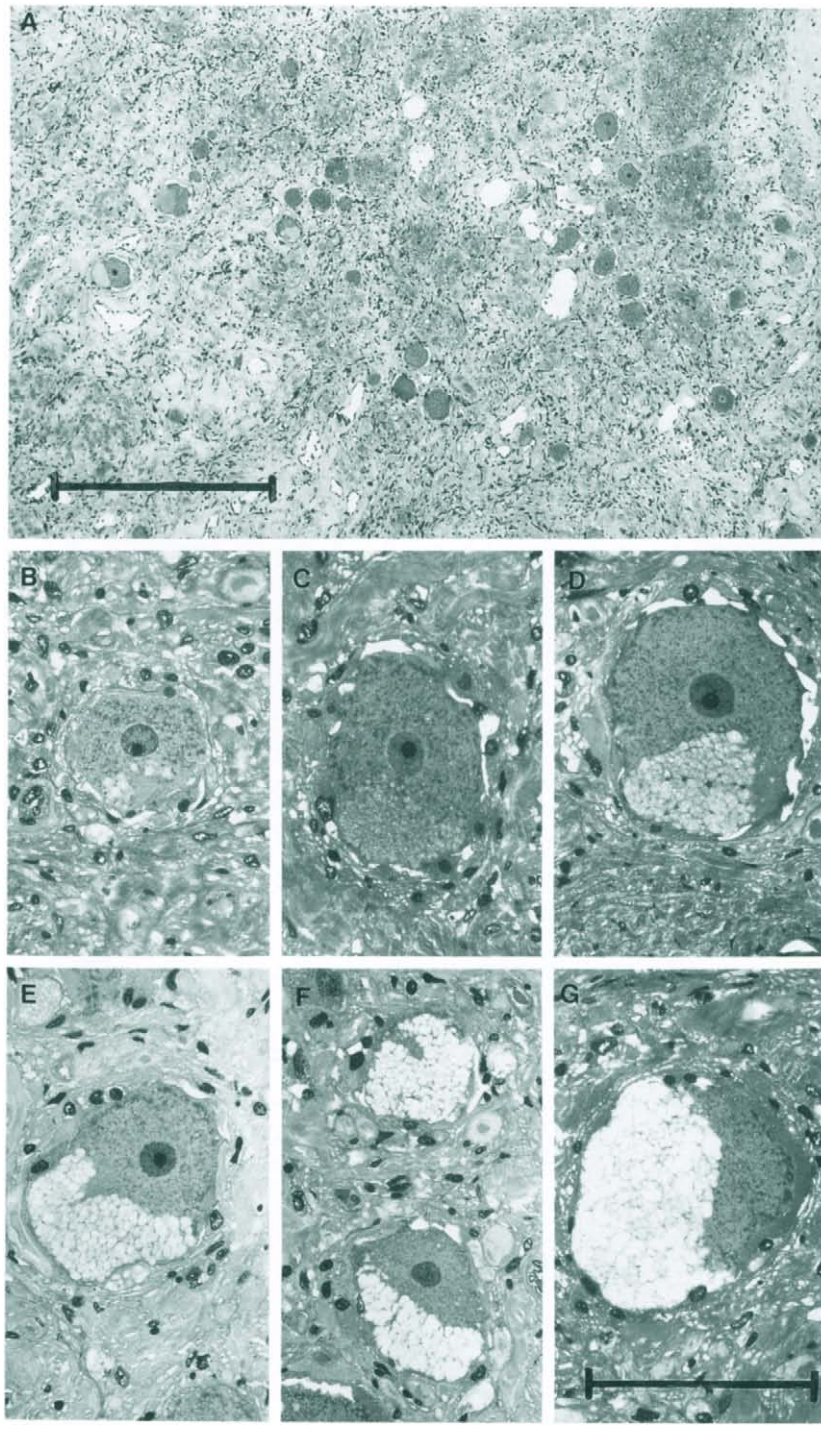


Fig. 74 Same case shown in Fig. 73. (A) A dorsal root ganglion with sparse, mainly large, neurons. (B–G) Neurons with vacuolar inclusions. Bars: (A) 0.5 mm and (B–G) 100 μm.

Systemic Carnitine Deficiency (Lipid Storage Myopathy Type I)

After Bradley *et al.* (1969) had described a lipid storage myopathy, Engel and Angelini (1973) demonstrated carnitine deficiency as the biochemical correlate of the disorder. In some of the fatal cases, changes in other organs were ascribed to a systemic carnitine deficiency (Gilbert, 1985). Human carnitine deficiency can be either hereditary or acquired. Hereditary carnitine deficiency can be grouped into three clinical entities: myopathic carnitine deficiency, systemic carnitine deficiency, and organic acidurias (Tanphaichitr and Leelahagul, 1993).

Clinical Picture Systemic carnithine deficiency can manifest itself soon after birth and lead to death from respiratory failure within a few weeks. In some cases the clinical symptoms appear only after some years. The common symptom is a slowly progressive proximal myopathy, aggravated after exercise, when it may lead to rhabdomyolysis and myoglobinuria (Mousson *et al.*, 1992; Mantz *et al.*, 1992). In some patients episodes of acute encephalopathy, resembling Reye's syndrome, occur in association with disturbances of liver function and muscular weakness (Kimura and Amemiya, 1990; Vianney-Saban *et al.*, 1993). Cardiomyopathy (Garavaglia *et al.*, 1991; Kadar *et al.*, 1994), metabolic acidosis, reversible coma, and epileptic seizures have also been reported. The encephalopathic crisis can precede the muscular weakness. Vomiting and confusion occur, associated with hypoglycemia, hypoprothrombinemia, and hyperammonemia (Künnert, 1988). Carnitine deficiency has also been implicated in some cases of sudden infant death syndrome (Coates, 1994) and malignant hyperthermia (Vladutiu *et al.*, 1993).

Patients generally die between the ages of 8 and 28 years. An autosomal-recessive inheritance has been demonstrated in several families (Cruse *et al.*, 1984). Heterogeneous expression of the diseases frequently occurs within an affected family (Shahar *et al.*, 1988).

Pathology *Light microscopy.* Under light microscopy storage of fat is found in skeletal and cardiac muscle tissue, as well as in the liver. The activity of mitochondrial enzymes is enhanced. A slight increase in glycogen may be present. In skeletal muscles a type I fiber preponderance has been observed. The characteristic histological finding is neutral fat (triglyceride) accumulation in four organs: the liver, kidneys, heart, and skeletal muscle.

Electron microscopy. Using electron microscopy, one finds, in addition to numerous lipid droplets in muscles, mitochondrial hypertrophy with paracrystalline inclusions (Cornelio *et al.*, 1981). The hepatocytes are filled with macrovesicular fat droplets without expanded mitochondria (Kimura and Amemiya, 1990).

Neuropathology *Gross appearances.* Severe cerebral edema has been seen macroscopically (Ware *et al.*, 1978).

Light microscopy. Occasionally, perivascular fat and pigment granule cells are seen, as well as acute changes in neurons and isolated lipid droplets, particularly in the hippocampus. Lipid storage is present in the Schwann cells of the peripheral nerves (Engel *et al.*, 1977).

Ultrastructurally, swelling of the astrocyte cytoplasm was found in the brain. Expanded mitochondria in the nerve cells and myelin sheath splitting in the white matter, which

have been reported to be specific to Reye's syndrome, were not observed (Kimura and Amemiya, 1990).

Pathogenesis Carnitine (β-hydroxy-γ-trimethyl-ammonium butyrate) has two main functions: the transport of long-chain fatty acids from the cytosol into the mitochondria and modulation of the mitochondrial ratio of acyl-CoA to free CoA (Gilbert, 1985; De Vivo and Tein, 1990; Shapira *et al.*, 1993). The former is essential for the β-oxidation of fatty acids, while abnormalities of the latter interfere with a number of mitochondrial functions. Aside from carnitine, three enzymes are involved in the transport of fatty acids: carnitine palmitoyltransferase types I and II and carnitine acyl-carnitine translocase (Angelini, 1990).

The sources of carnitine are nutritional, in that they are mainly present in foods of animal origin, and endogenous, as they are produced by synthesis from lysine and methionine in the liver and the kidneys. Carnitine deficiency may be primary (Scholte *et al.*, 1990) or secondary (Duran *et al.*, 1990). Primary deficiency may be caused by inhibition of synthesis or defects at the level of carnitine transport. The most severe form of carnitine deficiency is caused by a defect of the carnitine transport protein in the renal tubules (Scholte *et al.*, 1990). The effects of carnitine deficiency are as follows:

1. The accumulation of fatty acids may cause heart or liver failure, the latter leading to hepatic encephalopathy.
2. Increased acyl-CoA esters inhibit mitochondrial enzymes.
3. Accumulation of triacylglycerols in the tissues increases their stress susceptibility.
4. Decreased mitochondrial acetyl export lowers acetylcholine synthesis in the nervous system (Scholte *et al.*, 1990).

Secondary carnitine deficiency may be caused by inadequate nutrition, particularly in premature infants, vegetarians, and patients receiving parenteral nutrition (Duran *et al.*, 1990). It may be secondary to various enzyme deficiencies, such as carnitine palmitoyltransferase, acyl-CoA dehydrogenases, electron transferring flavoprotein, and 3-ketoacyl-CoA thiolase (Angelini *et al.*, 1992). A deficiency of carnitine palmitoyltransferase may cause a typical carnitine deficiency syndrome (Mantz *et al.*, 1992; Joutel *et al.*, 1993) as well as unusual neurological symptoms (Ohtani *et al.*, 1994). Carnitine deficiency may be induced by drugs, particularly valproate and other anticonvulsants (Coulter, 1991; Hug *et al.*, 1991; Matsumoto *et al.*, 1994; Melegh *et al.*, 1994) and zivuidine (Dalakas *et al.*, 1994). This deficiency has been reported in association with apparently unrelated mitochondrial diseases (Campos *et al.*, 1993), with Ruvalcaba–Myhre–Smith syndrome, consisting of macroencephaly, hypotonia, proximal weakness, and speech and motor delay (Powell *et al.*, 1993), and with Barth's syndrome, an X-linked recessive condition (located on Xq28) characterized by myopathy, cardiomyopathy, short stature, recurrent neutropenia, and normal cognitive function (Christodoulou *et al.*, 1994).

Sphingolipidoses

By far the largest group of metabolic disorders associated with lipid storage is formed by the sphingolipidoses. They are the result of failure of the breakdown of higher sphin-

golipids into sphingosine and fatty acids. The lack of activity of the enzyme controlling the successive catabolic steps leads to a variety of different diseases.

Sphingomyelinoses (Niemann–Pick Disease; Phospholipidosis Type I)

The first case of sphingomyelinosis was described by Niemann in 1914 as "an unknown clinical picture." In 1922 Pick differentiated the condition from Gaucher's disease and other related disorders based on histological criteria and called it "lipid-cell splenohepatomegaly, type Niemann." Today the term *Niemann–Pick disease* comprises a heterogeneous group of genetic metabolic disorders. The common factor is the storage of sphingomyelin in various organs, including, in some cases, the brain (Klenk, 1934).

Crocker (1961) distinguished the following types according to their clinical course.

Type A: Infantile acute–subacute with cerebral involvement
Type B: Chronic infantile with exclusively visceral manifestations without involvement of the CNS
Type C: Late infantile–juvenile with CNS involvement
Type D: Nova Scotia variant resembling type C
Type E: Adult, barely distinguishable from type B, without CNS involvement, although a mild cortical atrophy may be present (Terry *et al.*, 1954)

An intermediate form consists of type B without CNS involvement but with storage in the peripheral nerves, described by Takada *et al.* (1987). In this section we deal only with types A and C, and with cases resembling type C, including type D.

Schneider and Kennedy (1967) divided all of the cases into two groups: one characterized by sphingomyelinase deficiency (types A and B), the other with normal sphingomyelinase activity (types C and D).

Niemann–Pick Disease Type A

Type A constitutes 75–85% of all cases of Niemann–Pick disease and corresponds to the classical form of the disease. Harzer and Benz (1976) suggested that the term *Niemann–Pick disease* be confined to this type. About one half of the patients are of Jewish origin.

Clinical Picture In most cases the clinical picture is that of a floppy, poorly mobile infant with a protuberant abdomen, hepatosplenomegaly, and generalized lymphadenopathy. Between 1 and 2 years of age, the striking contrast between the distended abdomen and the emaciated body (Brady, 1978) is fully developed and goes hand in hand with the loss of acquired abilities. A somewhat later onset of the disease was observed in some members of an affected family. A cherry-red spot at the macula develops in about 50% of the cases. Xanthomas and xanthogranulomas have been repeatedly observed (Wood *et al.*, 1987). The head circumference is somewhat reduced. The patients are physically and mentally retarded and may suffer from occasional epileptic seizures. They are also subject to respiratory and intestinal infections. Death occurs usually before the age of 4 years. Hyperlipidemia occurs only in types A and B of the disease.

Pathology *Gross appearances.* The liver, spleen, and lymph nodes are enlarged and are of a firm consistency. The cut surfaces of the spleen are salmon pink; those of the liver and the lymph nodes are yellowish.

Light microscopy. Numerous foam cells are found in the enlarged viscera, lungs, lymph nodes, bone marrow, and tonsils. They were already described in detail by Bloom (1928). Similar storage cells have been observed in leukocytes of the peripheral blood (Volk *et al.*, 1972). These foam cells, commonly known as Neimann–Pick cells, are 20–90 μm in diameter and contain one or more nuclei displaced to the periphery (Crocker and Farber, 1958). The cytoplasm contains numerous fine droplets of various sizes, imparting a mulberry-like appearance to the cell. With the Giemsa method they stain poorly or not at all and appear as vacuoles. Under polarized light many of the "vacuoles" are birefringent, and under ultraviolet light they show a yellowish green fluorescence. Phase contrast microscopy helps in differentiating Niemann–Pick cells from Gaucher cells. The latter contain fibrillary structures in their cytoplasm (see p. 286). The stored substances stain a pale orange with scarlet R or Sudan III, grayish with Sudan black, and dark blue or bluish black with Baker's acid hematin and with the Smith–Dietrich reaction, both of which are specific for phospholipids. They also stain pale blue with Nile blue sulfate and black with osmium tetroxide (Crocker and Farber, 1958). A brilliant orange fluorescence of phospholipids can be obtained by staining with Nile red (Brown *et al.*, 1992). Cholesterol can be demonstrated by Schultze's test. The PAS reaction is generally positive, but may occasionally be negative.

Electron microscopy. The hepatocytes, Kupffer's cells, reticuloendothelial cells, and renal glomeruli contain intracytoplasmic membrane-bound cytosomes with a loosely arranged or parallel membranous structure. Electron-dense granules and vacuolar inclusions may also be present (Libert and Danis, 1975).

Neuropathology *Gross appearances.* A considerable degree of cerebral atrophy is apparent, with gaping sulci and reduced brain weight. The consistency of the atrophic white matter is firm, while the cortex is soft and has a waxy appearance. The ventricles are moderately enlarged. The cortex, basal ganglia, brain stem, cerebellar cortex, and dentate nucleus are shrunken and pale (Crocker and Farber, 1958). The globus pallidus and the substantia nigra may assume a deep yellow color.

Light microscopy. A considerable loss of neurons becomes immediately apparent. The surviving neurons show ballooning of their cytoplasm with fine vacuolation. Nissl bodies are reduced to a thin rim at the periphery of the perikaryon. The nuclei are displaced and often pyknotic. The degree of storage may vary from one part of the brain to another (Crocker and Farber, 1958). The loss of myelin is accentuated in the occipital lobes. The central white matter is generally preserved.

Changes in the cerebellum may be absent or minimal in some cases. In others the cerebellum, brain stem, and spinal cord are more severely affected than the cerebral cortex. The Purkinje perikarya are ballooned; their dendrites, expanded. The granular layer is rarefied, but the cells do not appear to contain an appreciable amount of storage material. A dense fibrillary gliosis, with proliferation of both astrocytes and microglia, is seen in the cerebral and cerebellar cortices and in the white matter. In some cases pseudosystemic changes have been observed, resembling pallidonigral degeneration (Elleder and Jirasek, 1981).

Foam cells are also present in the choroid plexuses and the leptomeninges. The ependymal cells and the vascular endothelia are also vacuolated (Elleder and Jirasek, 1981). The ganglion cells of the retina are ballooned and contain intracytoplasmic vacuoles. The cornea and the lens may also be involved in the storage process. A segmental demyelination may be present in peripheral nerves where the Schwann cells contain granular storage material (Landrieu and Said, 1984). Aside from sphingomyelin storage, an excess of glycolipid can also be demonstrated histochemically (Jorgensen *et al.*, 1974). Biochemical analysis confirms the excess of sphingomyelin in the brain.

Electron microscopy. Intracytoplasmic bodies are present in the neurons of the cerebrum and the cerebellum, 1–2 μm in diameter, of low electron density, and containing loosely stacked lamellae or concentrically arranged membranes (Kamoshita *et al.*, 1969), resembling the membranous cytoplasmic bodies of GM_2 gangliosidosis (see p. 316). The distance between membranes is smaller, however, and does not exceed 4.5 μm. The cytoplasmic bodies are usually adjacent to the cisternae of the endoplasmic reticulum. The mitochondria appear pale with broken cristae, and may contain myelin figures. Apart from the specific inclusions, an excess of lipofuscin granules may also be present. In microglial cells the lamellae are arranged horizontally.

In the myenteric plexus of the rectum, the neurons and the foam cells of the laminae propria and submucosa contain numerous lamellar bodies. The Schwann cells of peripheral nerves show similar appearances (Landrieu and Said, 1984).

In the eye lamellar bodies are seen in the ganglion cells of the retina. In one case similar changes were found in the cornea and the epithelium of the lens.

Pathogenesis The classical form of Niemann–Pick disease (type A) was, besides Gaucher's disease, the first biochemically characterized sphingolipidosis. Klenk (1934) demonstrated that the stored material in this disorder was sphingomyelin. Brady *et al.* (1966) showed the reduced activity of sphingomyelinase in the tissues of a patient. This enzyme is a lysosomal acid hydrolase (optimal activity at pH 5.0), ubiquitous in the body. It splits off the hydrophilic part, phosphorylcholine, from ceramide phosphorylcholine (Weinreb *et al.*, 1968), liberating the hydrophobic ceramide. A neutral sphingomyelinase is present in the cell membranes in the brain (Levade *et al.*, 1986). Several mutations of the acid sphingomyelinase (*ASM*) gene have been recorded. In a patient with type A disease a homoallelic T-to-A mutation in exon 2 predicted a premature stop at position 261 of the *ASM* polypeptide. In an unrelated type A patient a heteroallelic two-base deletion in exon 2 caused a frameshift mutation at *ASM* point 178, leading to a premature stop at point 190. In the same patient a G-to-A transition in exon 3 caused an M-to-I substitution at point 382. A type B patient exhibited two heteroallelic mutations: a G-to-A transition in exon 2 that predicted a G-to-R substitution at point 242 and an A-to-G transition in exon 3 that resulted in an N-to-S substitution at point 383. This patient has an approximately 15% residual activity in the lymphocytes, while in the two type A patients the enzyme was totally inactive. The mutations noted above were not found in other patients with Niemann–Pick disease type A or B who presumably had other defects (Takahashi *et al.*, 1992).

In types A and B the lysosomal nature of the inclusions is the result of the deficiency of the lysosomal enzyme. The narrower spacing of the lamellae of the cytoplasmic bodies

than is seen in gangliosidosis is due to a shorter hydrophilic component of sphingomyelin compared with ganglioside (Terry, 1971).

The neutral sphingomyelin involved in the structure of myelin contains C_{24} fatty acid in its ceramide, while all others contain C_{18} fatty acids (Jatzkewitz and Pilz, 1964). In a demyelinating process the C_{24} component would be reduced. However, as it cannot be catabolized in sphingomyelinase deficiency, it is actually slightly increased. C_{18} sphingomyelin is not a component of myelin and is found only in the gray matter and the components of the white matter other than myelin. It is therefore considerably increased whenever sphingomyelinase is deficient. The sphingomyelin storage in the brain offers a satisfactory explanation of the neurological findings. The loss of neurons entails a secondary loss of myelin. While the myelin galactolipids (cerebroside and sulfatide) are correspondingly reduced (Kamoshita *et al.*, 1969), the sphingomyelin in the white matter easily reaches double the normal values (Jatzkewitz and Pilz, 1964) and there is a 3.5-fold increase in the gray matter. Whether the demyelination is exclusively secondary or is a direct effect of the metabolic disorder on the myelin sheath is not clear. The cherry-red spot that appears in 50% of the cases of type A is caused by edema of the inner plexiform layer of the retina surrounding the macula. Its presence or absence depends on the lipid storage in the neighboring neurons or on their disappearance.

Niemann–Pick Disease Type C

Clinical Picture The clinical picture of type C is variable and differs in children and adults. In childhood the disease often begins with neonatal hepatitis, presenting with jaundice and splenomegaly (Kristiansson *et al.*, 1994). Apart from a few fatal cases, the condition unusually subsides but cholestasis remains, leading to fibrosis and, in a few cases, cirrhosis. By that time the clinical picture is overshadowed by neurological symptoms (Kelly *et al.*, 1993). In some cases, however, hepatosplenomegaly may develop late in the course of the disease or not at all (Norman *et al.*, 1967).

Neurological symptoms usually appear at about the age of 5 years. Higgins *et al.* (1992) divided all cases into two groups: one with disease onset in preschool, the other with onset at school age. In the first group movement disorders—and in the second, cognitive difficulties—were the presenting feature. Vertical supranuclear gaze palsy (Breen *et al.*, 1981) followed in both groups with increasing dysarthria, movement disorders, and cognitive failure. Pyramidal signs developed later and the condition ended in a vegetative state. Death occurs usually between the ages of 5 and 15 years.

Adult patients include childhood cases with long-term survival as well as cases with late onset (Turpin *et al.*, 1991). The disease progression is generally slow. Psychomotor retardation is almost constant, followed by cerebellar ataxia and extrapyramidal features. Supranuclear vertical gaze palsy is almost always present. Hepatosplenomegaly may be absent (Hulette *et al.*, 1992). Early diagnosis in all cases may be made based on bone marrow biopsies, in which foam cells can already be found at the age of 1–2 years. Typical lipid inclusions can also be seen on skin biopsies (Boustany, 1990).

MRI may show symmetrical cerebral and cerebellar atrophy and hypoplasia of the corpus callosum (Palmeri *et al.*, 1994).

Pathology *Gross appearances.* Aside from hepatosplenomegaly, one finds hypertrophy of the adrenal cortex and the lymph nodes.

Light microscopy. Foam cells, resembling those of type A, are present in the liver, spleen, lymph nodes, bone marrow, tonsils, kidneys, lungs, adrenals, and smooth muscle. These cells are confined to histiocytic elements. They are PAS positive, while the fat stains, as well as the reactions for cholesterol and phospholipid, may be negative. Lipid inclusions in the liver and the spleen have been found in a 20-week fetus (Dumontel *et al.*, 1993).

Electron microscopy. The histiocytes of the spleen, liver, and bone marrow contain lamellar vacuolar inclusions (Fig. 75), 0.5–3 μm in diameter, with an irregular arrangement of lamellae in groups of up to 10 with a periodicity of 5.5 nm. The groups of lamellae are separated by a granular or amorphous matrix. Sometimes the inclusions coalesce and form lobulated structures. Inclusions have also been seen in the conjunctival epithelia and endothelia (Arsenio-Nuñez and Goutieres, 1981).

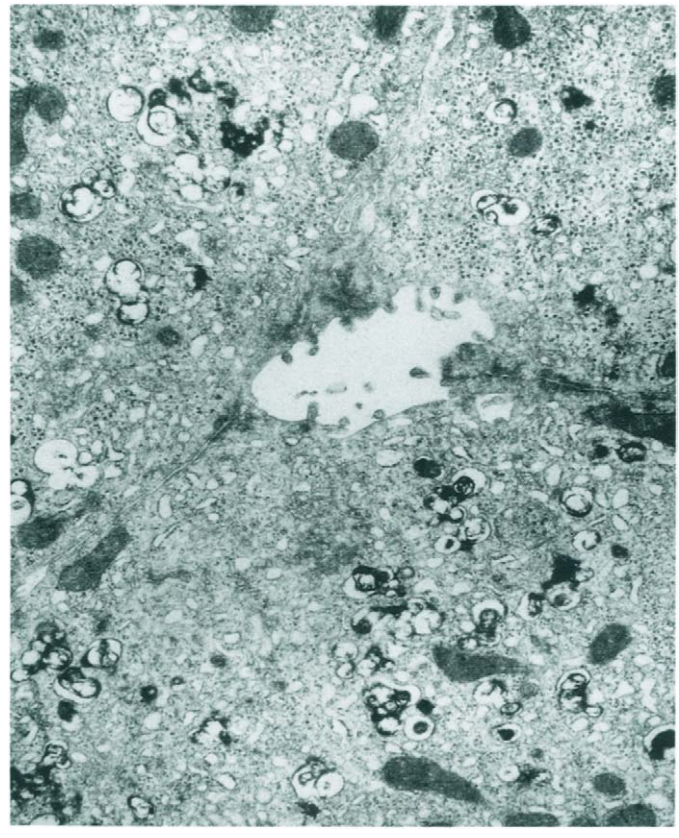


Fig. 75 Liver cells with lamellar vacuolar inclusions, ×16,400. (Reproduced from Cervós-Navarro and Goebel, 1989.)

Neuropathology *Gross appearances.* Gross appearances are extremely variable. The cerebral cortex may appear near-normal (Norman *et al.*, 1967) or generally atrophic (Harzer *et al.*, 1978). The cerebellum may appear either intact (Crocker and Farber, 1958) or obviously affected (Norman *et al.*, 1967).

Light microscopy. A similar wide range of lesions can be seen. In the cerebral cortex the neurons of the third and fifth layers show the most pronounced ballooning (Braak *et al.*, 1984), while those of the second, fourth, and sixth layers are virtually intact. Dense gliosis may be present in the molecular layer, while the deeper layers may show status spongiosus (Harzer *et al.*, 1978). The large neurons of the striatum, pallidum, and cranial nerve nuclei are severely affected, as a rule (Fig. 76). The material stored in the neurons is PAS positive, but lipids often cannot be convincingly demonstrated by histochemical methods. In the glial cells, on the other hand, fat, cholesterol, and phospholipid stains are generally positive. A neuroaxonal dystrophy may be present in the thalamus and the dentate nucleus.

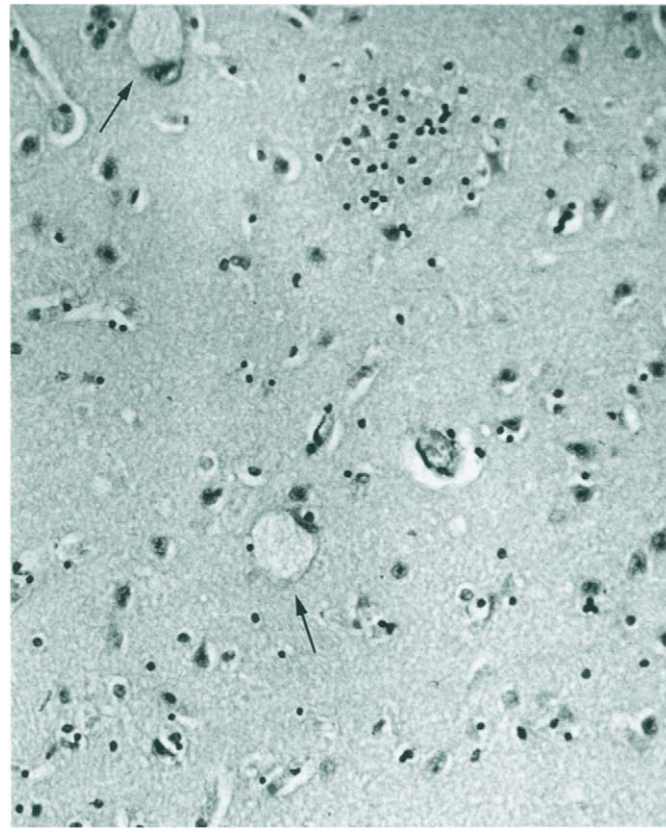


Fig. 76 Same case shown in Fig. 75. Swollen nerve cells in the striatum (arrows). Periodic acid–Schiff stain, ×240.

In the cerebellar cortex the lesion may range from severe atrophy with ballooning of the surviving Purkinje and Golgi cells (Norman *et al.*, 1967) to a focal loss of Purkinje cells with ballooning of the Golgi cells (Harzer *et al.*, 1978) or isolated involvement of the dentate nucleus. Axonal swellings may be present in the granular layer and the cerebellar white matter. A loss of myelin of variable severity can be found in the cerebral and cerebellar white matter, accompanied by perivascular aggregations of sudanophilic cells. The loss of myelin may be almost total and may be associated with dense gliosis (Harzer *et al.*, 1978). Demyelination of the posterior columns of the spinal cord has also been reported.

In the vascular endothelia an accumulation of glycosphingolipids has been demonstrated histochemically, together with small amounts of sphingomyelin and cholesterol (Elleder *et al.*, 1985). Foam cells are rarely seen in the choroid plexuses and the leptomeninges. Retinal changes are less pronounced than in type A or may be absent altogether.

In an infantile case with severe sensorimotor polyneuropathy, Hahn *et al.* (1994) found thin myelin sheaths with globular expansion, evidence of chronic demyelination, axonal spheroids, and lipid inclusions in the Schwann cells, endoneurial fibroblasts, macrophages, pericytes, and endothelial cells.

Electron microscopy. Concentric lamellar bodies may be found in neurons and histiocytes. They are smaller than those seen in GM_2 gangliosidosis and contain only a few lamellae. They have therefore been called "oligomembranous cytoplasmic bodies" by Harzer *et al.* (1978). In addition, inclusions may be found, 0.5–1.5 μm in diameter, containing lipofuscin intermingled with lamellar and vesicular structures (Gilbert *et al.*, 1981). The axonal swellings are tightly packed with concentric lamellar bodies. Lamellar bodies were also found in the basal ganglia and in the spinal cord of a 21-week fetus.

Lamellar bodies with multiple membranes have been seen in rectal neurons (Fig. 77A and B) Cervós-Navarro and Goebel, 1989). They also occur in the retina (Palmer *et al.*, 1985).

Pathogenesis Niemann–Pick disease type C differs from types A and B in the normal activity of ASM and in the variable, usually insignificant, elevation of sphingomyelin levels. It is doubtful that it is related to Niemann–Pick disease at all, but until the genetic and enzyme defects have been elucidated, it has been conventionally retained in this group.

The main biochemical abnormalities are impaired LDL cholesterol esterification (Bowler *et al.*, 1990; Argoff *et al.*, 1990, 1991) and intracellular translocation of exogenous cholesterol (Vanier *et al.*, 1991a,b). The result is an accumulation of nonesterified cholesterol in the cytoplasm of various cell types. Endogenous cholesterol is metabolized normally. Other abnormalities appear secondarily. Hyperlipidemia may be severe and may lead to deposition of xanthomas in the respiratory and gastrointestinal tracts (Filling-Katz *et al.*, 1992). In these cases there may be some increase in sphingomyelin and other phospholipids, particularly bis-monoacylglyceryl phosphate. Accumulation of sphingosine and sphinganine has also been recorded (Rodriguez-Lafrasse *et al.*, 1994). There may be an increase in the content of "lower gangliosides" (GM_2 and

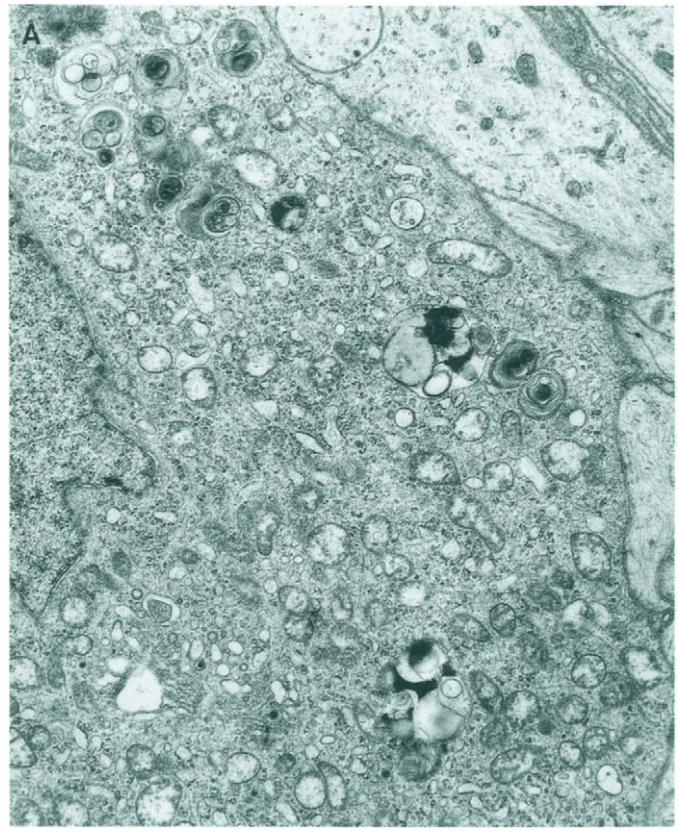


Fig. 77 Same case shown in Fig. 75. (A) Lamellar inclusions in the rectal neurons, ×8000. (B) Single inclusions containing multiple membrane whorls, ×28,000.

GM_3) (Philippart *et al.*, 1983). A certain heterogeneity in group C and syndromes related to it has been emphasized (Martin and Ceuterick, 1988).

A similar metabolic defect may be produced iatrogenically by the use of psychotropic drugs, particularly chlorpromazine and related compounds (Masson *et al.*, 1992).

Lipidoses Related to Niemann–Pick Disease Type C

A number of cases in which foam cells have been demonstrated in the bone marrow and other organs and in which membranous cytosomes have been found ultrastructurally have been allocated to type C. In these cases, however, an accumulation of sphingomyelin or an impairment of sphingomyelinase activity has not always been found. This group therefore consists of ill-defined neurovisceral lipidoses that do not fit exactly into any of the well-defined entities (Elleder *et al.*, 1983; Martin *et al.*, 1984). Although it is generally classified as an independent variant, type D can be subsumed into this group.

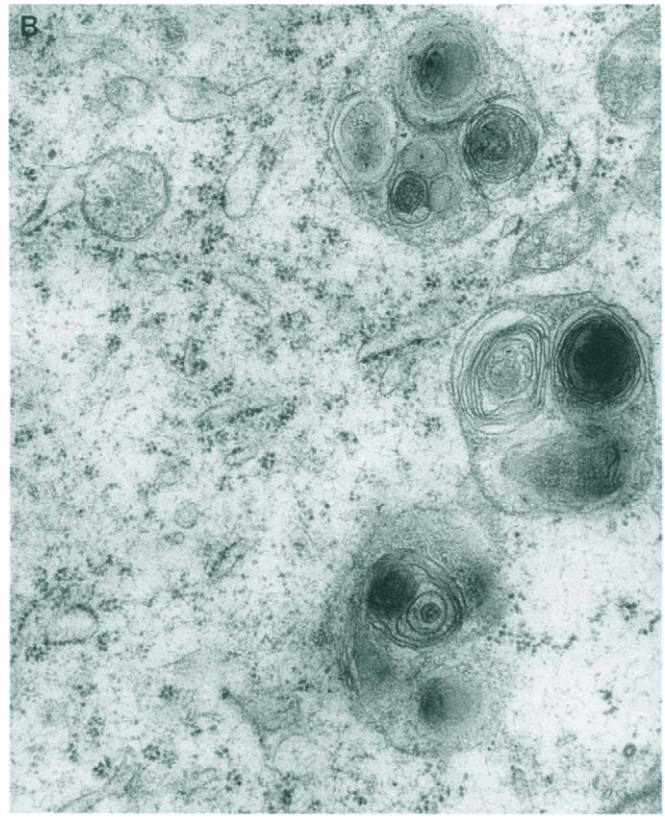


Fig. 77 Continued.

Dystonic Infantile Lipidoses (Kidd–Elfenbein Disease; Dystonic Infantile Idiocy without Amaurosis; Neurovisceral Lipidoses with Supranuclear Ophthalmoplegia; Neville's Sphingomyelinosis Type III)

Kidd (1967) described the first case of this disorder as an atypical cerebral lipidosis. Elfenbein (1968) coined the term *dystonic juvenile lipidosis* and included the condition among the sphingolipidoses. Further cases were reported and these were separated from other chronic variants of Niemann–Pick disease on the strength of their neurological symptoms and the presence of "sea blue" histiocytes in the bone marrow. The clinical picture of all of these cases resembles that of type D, with the reservation that all type D patients came from Nova Scotia. Martin *et al.* (1984) included this clinical syndrome under type C of Niemann–Pick disease.

Clinical Picture About one half of the patients suffered from transient neonatal jaundice and had impairment of growth. Splenomegaly appears only occasionally during the first year of life and hepatomegaly is even rarer, but both almost invariably appear later. Splenomegaly appearing between the ages of 2 and 5 years is often the first symptom. Sea

blue histiocytes are always present in the spleen and the bone marrow (Yan-Go *et al.*, 1984). The neurological symptoms vary from case to case. The most constant ones are dementia and ataxia as well as a characteristic supranuclear ophthalmoplegia with impairment of vertical eye movements. Most patients suffer from generalized seizures and cerebellar ataxia. Patients in whom neurological symptoms appear before the age of 5 generally die within 3–5 years from the onset of symptoms.

In those patients in whom the symptoms appear toward the end of the first or during the second decade, the disease runs a more protracted course (Martin *et al.*, 1984). In addition to dementia, the patients develop dystonic movements in the legs and the hands. Seizures occur in some patients. During the second decade dysarthria, dysphagia, spasticity, and urinary incontinence supervene (Elfenbein, 1968; Horoupian and Yang, 1978). These patients die during the second or third decade. The inheritance is autosomal recessive. An adult form with a course of about 20 years has also been reported (Longstreth *et al.*, 1982).

Pathology *Gross appearances.* Hypertrophy of the spleen is usually present; hepatomegaly is not always evident.

Light microscopy. Two types of foam cells with transitional forms are found in the bone marrow, liver, spleen, and kidneys. Most of them have a large coarsely vacuolated cytoplasm with dense dark blue inclusions and, occasionally, phagocytized erythrocytes. They stain weakly with PAS and Sudan black. In the other type the cytoplasm is studded with smaller bluish gray granules that stain strongly with PAS and Sudan black. In Giemsa staining they resemble Niemann–Pick cells or sea blue histocytes. They show a positive histochemical reaction for sphingomyelin. The skeletal muscles frequently show neurogenic atrophy (Horoupian and Yang, 1978).

Electron microscopy. Membranous cytoplasmic bodies and pleomorphic inclusions are seen in the kidneys, hepatocytes, and Kupffer's cells. The histiocytes of the bone marrow contain lamellar cytosomes, large inclusions with granules and fragments of membrane, and pleomorphic residual bodies. Transitions between the lamellar and pleomorphic residual bodies are recognizable (Longstreth *et al.*, 1982). These are larger and more irregular than other inclusions and may contain highly electron-dense material. In the hepatocytes most of the inclusions appear empty.

Neuropathology *Gross appearances.* The brain is generally severely atrophic, particularly in the frontal lobes. The cortex and the white matter are equally affected. The basal ganglia, brain stem, cerebellum, and spinal cord are unremarkable, as a rule. The patients reported on by Kornfeld (1978), however, showed only mild to moderate atrophy of the cerebrum and pronounced atrophy of the cerebellum.

Light microscopy. Nerve cells with ballooned cytoplasm and swollen processes are seen throughout the cerebral cortex. They are also seen in the basal ganglia, particularly the striatum, in the substantia nigra, and in the reticular formation (Martin *et al.*, 1984). Horoupian and Yang (1978) found numerous Alzheimer's NFTs in the frontal and temporal cortex, in the hippocampus, striatum, and locus coeruleus.

Storage is also prominent in the cranial nerve nuclei and the nuclei pontis. Only a few Purkinje cells are ballooned. In the spinal cord the anterior horn cells are predominantly affected. Some of the anterior horn cells show central chromatolysis with displacement of the nucleus to the periphery. The cells of the autonomic nervous system are conspicu-

ously ballooned. Axonal spheroids can be seen focally in the CNS. The nerve fibers of the peripheral nervous system contain yellowish green fluorescent particles. Limited segmental demyelination is also seen in the peripheral nerves.

The cytoplasm of the ballooned cells has a foamy and granular appearance (Elfenbein, 1968). The stored material shows regionally different staining properties. The PAS reaction is strongly positive in the basal ganglia, but only weakly positive in the cerebral cortex and the spinal cord. Otherwise, the material is weakly sudanophilic. The neuronal cytoplasm shows a yellowish green autofluorescence under ultraviolet light. There is a strong reaction for acid phosphatases in the inclusions. Golgi impregnation shows a fusiform expansion of the proximal axons with some thick-set spines on their surface.

Horoupian and Yang (1978) found a moderate astrocytosis in the third cortical layer, subcortical white matter, and basal ganglia. The number of retinal neurons is considerably reduced.

Electron microscopy. The cytoplasm of the ballooned neurons contains numerous pleomorphic inclusions, 2–3 μm in diameter, with light electron-lucent centers, surrounded by several concentric lamellae. Granular or amorphous material may be present in the center of the inclusions (Martin *et al.*, 1984). The lamellae show a periodicity of about 5 nm. In other neurons the inclusions are smaller and have dense osmiophilic centers separated by a clear halo from the surrounding membrane. In addition, membranous cytoplasmic bodies, zebra bodies, and ceroidlike lipopigment may be present.

The NFTs consist of paired helical filaments, as seen in Alzheimer's disease (Wisniewski *et al.*, 1976). In peripheral nerves the Schwann cells and the endoneurial fibroblasts contain residual bodies with electron-dense granular contents, sometimes associated with electron-lucent vacuoles. Membranous cytoplasmic bodies are rare here. Considerable thickening of the subendothelial basement membranes was described in the cortical vessels (Elfenbein, 1968).

Baar–Wiedemann Disease (Phospholipidosis Type II: Phosphoglyceridosis)

Baar and Hickmans (1956) described a disease in two siblings which, clinically and histopathologically, closely resembled Niemann–Pick disease. Upon biochemical analysis, however, accumulation was found of the glycerophosphatide phosphatidylethanolamine and cholesterol. Sphingomyelin was only slightly increased. Additional cases were reported by Wiedemann *et al.* (1972). The latter authors called the condition *phospholipidosis type II*, as opposed to phospholipidosis type I, in which sphingomyelin is the stored lipid. Subsequently, however, they have accepted the syndrome as belonging to Niemann–Pick disease type C (Elleder and Jirasek, 1981).

Clinical Picture The symptoms appear usually after the age of 2 years, occasionally even after the age of 5 years. However, in families in which the disease has already affected older siblings, a diagnosis could be made in subsequent children soon after birth by demonstrating the presence of storage cells in the bone marrow (Wiedemann *et al.*, 1972). At the time of the onset of symptoms, the children have a conspicuously large abdomen, a thrombocytopenic hemorrhagic tendency, and some psychomotor retardation. This is followed by ataxia, choreoathetosis, epileptic seizures, and dementia. In

some cases, however, these patients may remain reasonably normal well into the second decade, aside from developing splenomegaly. Death may occur in the first decade, however, usually as a result of pseudobulbar disturbances. Storage cells may also be detected in the bone marrow of heterozygotes (Wiedemann *et al.*, 1972).

Pathology *Gross appearances.* The main features of this disease are gross splenomegaly, moderate hepatomegaly, and enlargement of the lymph nodes. The bone marrow is pale grayish red and shows, in places, gelatinous atrophy. The skeletal muscles are also atrophic.

Light microscopy. Storage cells are found in the splenic pulp, in the sinuses of the lymph nodes, and in the tonsils, bone marrow, and liver. The affected macrophages are very large and resemble Niemann–Pick cells. They are PAS positive, and the various fat stains reveal an abundance of alcohol-insoluble lipids. Ceroidlike pigments are also present, particularly in the lymph nodes.

Electron microscopy. Numerous inclusions are scattered throughout the cytoplasm of hepatocytes, Kupffer's cells, and vascular endothelia. Their size is approximately that of mitochondria, with occasional larger ones, up to 2 μm in diameter. They are membrane bound and contain numerous myelin figures, the fusion of which leads to the formation of pleomorphic structures. Similar inclusions are also found in the tonsillar macrophages, bone marrow, and fibroblasts.

Neuropathology *Gross appearances.* Severe cerebral atrophy is present. The consistency of the cerebrum, cerebellum, and spinal cord is firm.

Light microscopy. Changes are present in the nerve cells, particularly of the third and fourth cortical layers. These changes are most severe in the occipital lobes, followed by the parietal, temporal, and frontal lobes, in descending order. The putamen is also affected, while the changes in the caudate and amygdaloid nuclei and in Ammon's horn are relatively slight. Less pronounced changes are also seen in the globus pallidus, thalamus, and some cranial nerve nuclei of the brain stem.

The affected neurons show ballooning of the cytoplasm with displacement of the nucleus to the periphery. The proximal parts of the dendrites may also be expanded. The Nissl substance is either displaced to the periphery or disintegrated into fine dust. The cytoplasm is foamy or honeycombed, and its contents are strongly PAS positive and react strongly with Sudan black, Nile blue sulfate, and oil red O. In various cortical areas a focal loss of neurons is apparent, with reactive gliosis. Here and there some deposition of homogeneous, partially granular, material may be seen in the astrocytes. An extensive, but incomplete, disintegration of myelin sheaths is found in the cerebral white matter. Some perivascular macrophages in the white matter show lipid storage in their foamy or honeycombed cytoplasm.

Electron microscopy. The ballooned neurons contain multiple membrane-bound inclusions of various sizes. Their contents consist either of concentric irregularly spaced lamellae or of a dense homogeneous substance that shows a lamellar structure in places. Zebra bodies are less numerous, as are other inclusions with a fine filamentous structure. The inclusions are also found in the dendrites and the proximal segments of the axons.

The ganglion cells of the autonomic system also show prominent storage. Inclusions have also been seen in Schwann cells of the peripheral nerves.

Pathogenesis Histochemical investigations have shown that the stored material consists primarily of phosphoglycerides. Baar and Hickmans (1956) identified the lipid as phosphatidylethanolamine (cephalin). A strong phosphatidylinositol component is responsible for the PAS positivity. The discrepancy of the results probably reflects the improvement in analytical techniques. No enzyme deficiency has been identified to date.

Lactosylceramidosis

Dawson and Stein (1970) found large numbers of foam cells with expanded cytoplasm in the bone marrow of a 3-year-old mentally retarded girl. Other features were hepatomegaly and epileptic seizures. A brain biopsy showed a significant increase in lactosylceramide, with traces of glucosylceramide, ceramide trihexoside, and globoside.

Light microscopy. A cerebral biopsy revealed moderate expansion of the neuronal cytoplasm and the dendrites.

Electron microscopy. Under electron microscopy the perikarya and the dendrites of the affected nerve cells contained membranous, granular, and amorphous inclusions.

Using different methods for the estimation of lactosylceramide β-galactosidase in fibroblasts of the same case, Wenger *et al.* (1975) concluded that it was not a case of lactosylceramidosis, but another variant of Niemann–Pick disease.

Bradova *et al.* (1993) studied the lipid distribution in a fetus sibling of two affected children. They found high levels of lactoceramide and glucoceramide, some elevation of GM_2 and GM_3 gangliosides, and normal phospholipids. The sphingolipid activator protein (SAP) was deficient and the defect was shown to be caused by the absence of the common saposin precursor (prosaposin).

Sea Blue Histiocyte Syndrome Moeschlin (1947) described in the spleen—and Wewalka (1950), in the bone marrow—macrophages laden with granules that stained a deep blue with the Giemsa method. Silverstein *et al.* (1970) called them "sea blue histiocytes" and considered them the hallmark of a specific syndrome. This became open to doubt when it was found that these histiocytes may store a variety of different lipids or polysaccharides, and in particular when it was shown that the blue granules consist of ceroid, which is of no specific diagnostic value.

In about half of the patients with sea blue histiocytes, one could demonstrate a sphingomyelinase deficiency. A family with nonneuropathic Niemann–Pick disease, low acid sphingomyelinase activity, and sea blue histiocytes was reported by Viana *et al.* (1990, 1992). On the other hand, sea blue histiocytes are present in several variants of type C of Niemann–Pick disease (Landas *et al.*, 1985). One can therefore conclude that within sea blue histiocyte syndrome there is a group of cases included among the sphingomyelinoses. There are several subgroups among these, and it is still uncertain whether they all belong together.

Niemann–Pick Disease Type D (Nova Scotia Variant of Sphingomyelinosis)

All patients with type D originate from Nova Scotia either directly or indirectly. Their symptomatology resembles that of type C with tremor, progressive ataxia, spasticity, and de-

mentia. Supranuclear ophthalmoplegia may also be present (Crocker and Farber, 1958). The characteristic differential from other variants is an initial or persistent jaundice with correspondingly raised bilirubin and alkaline phosphatase.

The accumulation of sphingomyelin is slight to pronounced in the spleen, slight in the liver, and absent in the brain. A slight increase in cholesterol is also present. Sphingomyelinase activity is normal (Baraton and Revol, 1977). No specific enzyme deficiency has been identified.

Under the electron microscope membrane-bound inclusions have been found in foam cells of the peripheral blood and the bone marrow. They contain membranous structures in a homogeneous matrix. The biochemical defect resembles that of type C (Byers *et al.*, 1994).

Animal and Experimental Sphingomyelinoses In mouse mutants with a foam cell reticulosis (Lyon *et al.*, 1965), changes are seen in the spleen, liver, and muscles, in which sphingomyelin is the principal stored substance. A sphingomyelinase deficiency was found only in a further mutant (Miyawaki *et al.*, 1982). A spontaneous Niemann–Pick disease was suspected in a poodle and in cats (Lowenthal *et al.*, 1990). The autosomal-recessive lysosomal cholesterol storage disorder in BALB/c mice is morphologically as well as biochemically similar, if not identical, to Niemann–Pick disease C in humans. Neuropathological features of the CNS consisted of hypomyelinization, axonal spheroids, and neuronal storage with meganeurite formation (Higashi *et al.*, 1991). In the mutants resembling type C of Niemann–Pick disease, lipid storage was present in the brain (Goldin *et al.*, 1992) and cystine levels in the tissues were greatly elevated (Butler *et al.*, 1993).

Metachromatic Leukodystrophy (Scholz–Bielschowsky–Henneberg Type of Leukodystrophy; Norman–Greenfield Type of Leukodystrophy)

In their classification of variants of Schilder's disease, Einarson and Neel (1938) drew attention to a type in which a substance was present in the white matter that stained metachromatically with basic aniline dyes; they called the condition "metachromatic leukodystrophy" (MLD). Norman (1947) described a case of MLD in which metachromatic substances were present not only in the white matter, but also in the neurons. It was therefore necessary to abandon a classification based strictly on localization. Instead of dealing with leukodystrophies as a group, we have adopted a classification based on the underlying metabolic defect. MLD is a familial progressive demyelinating disease caused by an enzyme defect affecting the catabolism of a physiological myelin constituent. Rattazi *et al.* (1978) differentiated the subtypes of MLD, according to the age at onset and the clinical course, into congenital, infantile, late infantile, juvenile, and adult forms, all of which were caused by a deficiency of arylsulfatase A (ASA). A sixth form was caused by the deficiency of all arylsufatases. In addition, Shapiro *et al.* (1979) identified a clinically and morphologically typical form of MLD without arylsulfatase deficiency.

Metachromatic Stored Substances

In spite of enzymatic differences and various recently described ultrastructural findings, the basic criterion for inclusion in this group remains the metachromasia of stored substances. As alcohol dissolves the metachromatic substances, they can be demonstrated only in frozen sections, rarely in paraffin sections, and never in celloidin-embedded material. The product of storage can be stained metachromatically with basic aniline dyes (e.g., toluidine blue), as discovered by Greenfield (1933).

A specific histochemical reaction was developed by Hirsch and Peiffer (1955) using acetic cresyl violet (Fig. 78). Holländer's (1964) method is based on the orange–red staining of sulfatide anions with acriflavine. This method can also be used to demonstrate fluorescence. Benz and Harzer (1974) used pseudoisocyanin, a chemically purer substance than cresyl violet, and obtained reddish violet metachromasia (Fig. 79) in a precisely defined wavelength

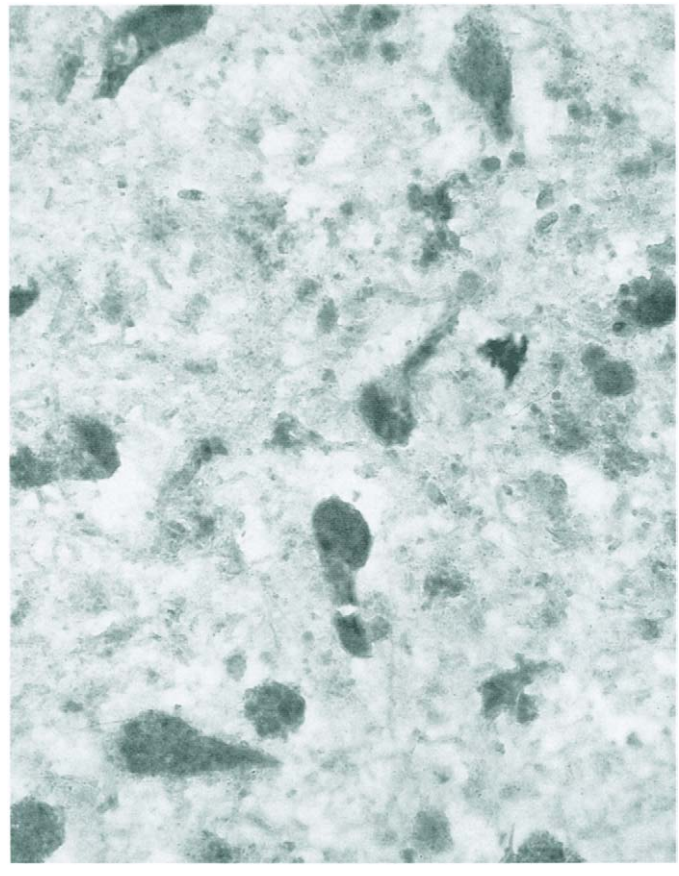


Fig. 78 Metachromatic deposits demonstrated with Hirsch and Peiffer's acetic cresyl violet stain. Original magnification ×300. (Courtesy of H. J. Peiffer, Tübingen, Germany.)

(538 nm). Further evidence of the presence of an acid glyco-lipid is furnished by the positive reaction with PAS. In contrast with the case in gangliosides (see p. 304), the results of Bial's test with orcein are negative. The metachromatic material is birefringent. This may appear in the form of linear stacks or aggregates of birefringent granules. These are present at all sites where deposits of metachromatic material occur, with the exception of deposits in neurons that are not birefringent.

Congenital Form

Some patients in whom MLD was diagnosed histologically died soon after birth. In all of these cases, no biochemical confirmation was available, and therefore the diagnosis remains open to doubt. The biochemically confirmed cases (Meyermann *et al.*, 1982) were fetuses examined for prenatal diagnosis. As it is uncertain at what age the disease would

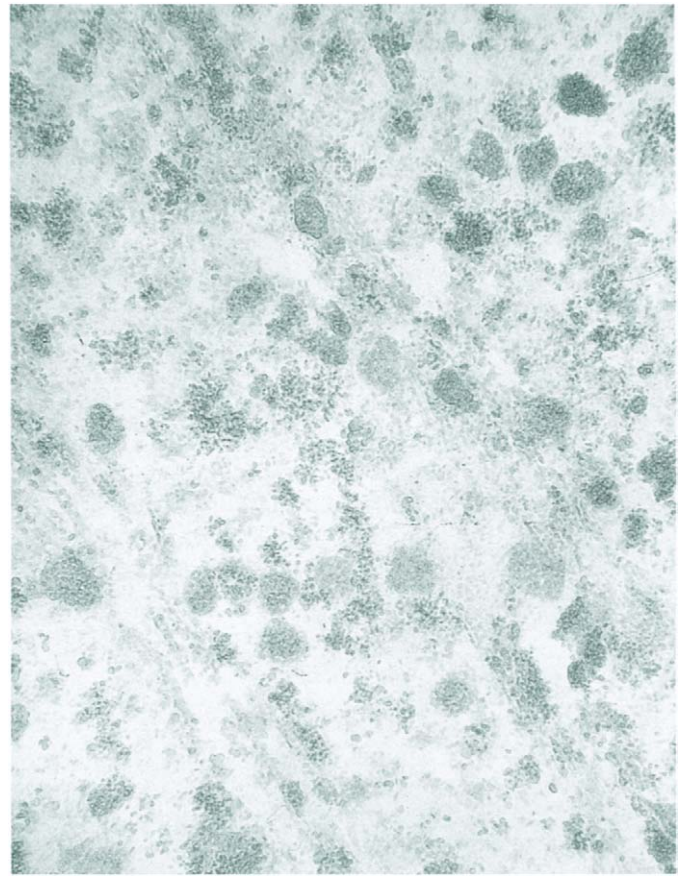


Fig. 79 Storage material demonstrated with Benz and Harzer's pseudoisocyanin stain, ×300. (Courtesy of H. J. Peiffer, Tübingen, Germany.)

have manifested itself had the infants survived, these cases cannot, with certainty, be allocated to the congenital form. Eto *et al.* (1982) separated the congenital form from other forms on the basis of enzymatic investigations.

Clinical Picture The infants with this disorder presented with episodes of apnea and cyanosis, bradycardia, and clonic movements of the extremities. They died within hours or days of birth.

Pathology Morphological observations are scanty. Metachromatic material was seen in the fetal kidneys or was demonstrated by fluorescence microscopy in the kidneys and the liver.

Electron microscopy. Prismatic inclusions and lamellar bodies could be demonstrated in the kidneys and the liver.

Neuropathology *Gross appearances.* Externally, the brain is normal. Upon slicing, the white matter appears dull, dry, and granular and may contain multilocular cysts. The U-fibers appear normal.

Light microscopy. In the fetal brain some lipid storage is present in the arachnoidal cells. The cerebral cortex appears normal. In the white matter an increase of glial cells is seen, as well as numerous foam cells laden with metachromatic material. Prominent metachromasia is present in Schwann cells of the peripheral nerves. Meyermann *et al.* (1982) found no metachromasia in the peripheral nerves of a 22-week fetus, only vesicular demyelination (Fig. 80).

In the infants who died shortly after birth, metachromatic material was found in the neurons of the cerebral cortex and the basal ganglia, but not in the myelinated white matter, which showed only eosinophilic products.

Electron microscopy. The perikarya and processes of neurons in the cerebral and cerebellar cortices and in the brain stem contained numerous lysosomes with circumscribed lamellar structures within a finely granular matrix. The lamellar parts were better developed in oligodendroglial cells and showed the structure of typical tuffstone bodies. Here and there concentric lamellar structures could be seen. Various types of inclusions were present in not precisely identifiable glial cells. The abnormal lysosomes were particularly abundant in the cytoplasm of clearly identifiable oligodendrocytes in the spinal cord. More than 10% of the Schwann cells showed osmiophilic inclusions of the tuffstone type.

Infantile and Late Infantile Forms

The infantile and late infantile forms are identical in their classical symptomatology and differ only in their age at onset. The infantile form is rare and manifests itself between the ages of 6 and 12 months. The late infantile form accounts for about two thirds of all reported cases of MLD and its symptoms appear between the ages of 1 and 4 years.

Clinical Picture The appearance of neurological manifestations may sometimes be preceded by symptoms arising from other organs, such as the gallbladder (Ries and Deeg, 1993).

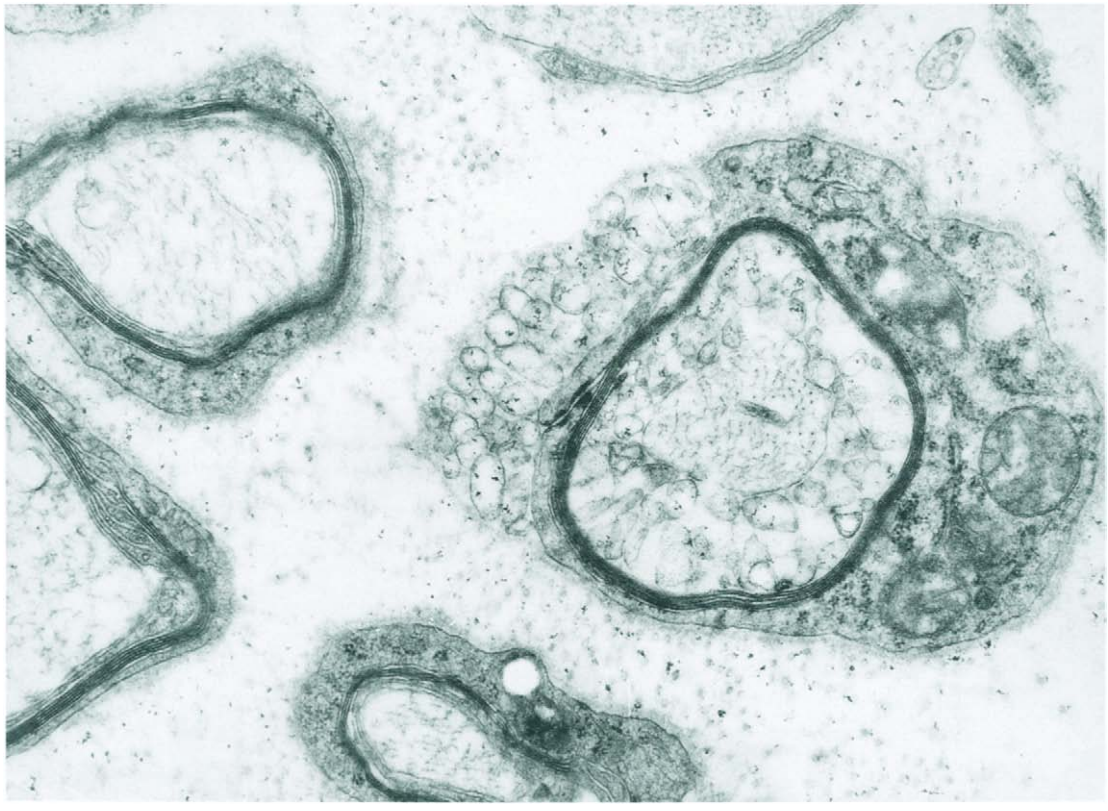


Fig. 80 Congenital form of metachromatic leukodystrophy. Vesicular demyelination in a peripheral nerve, ×12,000. (Reproduced from Meyermann *et al.*, 1982.)

The clinical course can be divided into four stages (Hagberg, 1962). In the first stage, lasting about 18 months, weakness and hypotonia of the musculature predominate, sometimes associated with ataxia and slight disturbances of speech. In some cases the first symptoms are those of a polyneuropathy. In the second stage, of about 6 months' duration, rapid deterioration sets in, with increasing quadriparesis, dysarthric speech, ataxia, nystagmus, and painful limbs. It is during this stage that psychomotor retardation becomes apparent. In stage III, which may last between a few months and 3 years, the patients suffer from spastic quadriplegia and painful muscle spasms. Continuous mental deterioration is accompanied by bulbar symptoms and optic atrophy with losses of vision and pupillary reactions. Stage IV, which can last for years, is characterized by blindness, deafness, muscular rigidity, and occasional epileptic seizures. Partial seizures, affecting any part of the body, have been recorded (Fukumizu *et al.*, 1992). Death is caused by intercurrent infections or hyperpyrexia of cerebral origin. The total duration of the late infantile form of the disease ranges between 3 and 5 years, occasionally up to 8 years.

In almost all cases the protein content of the CSF is considerably raised. The cells in the CSF may contain metachromatic substances. Less commonly, these may appear in the circulating blood leukocytes. CT confirms the diagnosis. MRI shows the area of demyelination more clearly, but neither CT nor MRI can differentiate it from other leukodystrophies (Demaerel *et al.*, 1991).

Pathology Metachromatic substances are found in the liver in hepatocytes, Kupffer's cells, and epithelia of the bile ducts (Brain and Greenfield, 1950; Toga *et al.*, 1972). In the gallbladder the epithelia laden with stored material may form papillomatous excrescences (Norman, 1947). In the kidneys the epithelia of the distal tubules are involved in the storage process (Brain and Greenfield, 1950). The changes in the kidneys allow a diagnosis by renal biopsy or by finding metachromatic substances in desquamated renal epithelia in the urine. The reticuloendothelial cells in the spleen, the cells of the anterior pituitary, and those of the testes may occasionally contain metachromatic material. The variation in staining properties of the metachromatic material in various organs has already been noted by Brain and Greenfield (1950).

Electron microscopy. Under the electron microscope all affected cells contain inclusions identical to those seen in the CNS and the peripheral nervous system (see page 260).

Neuropathology *Gross appearances.* Narrowing of the gyri and variable widening of the sulci are apparent in both the cerebrum and the cerebellum. Upon coronal slicing, a tough consistency of the white matter is noted; in a fresh unfixed brain it feels rubbery or lardaceous. In cases with a very prolonged course, the central white matter is yellowish brown and spongy, yet tough. As a rule, the U-fibers are preserved.

This sclerosing process is often accentuated in the parietal and occipital lobes, and sometimes in the temporal lobes or the basal regions of the brain. Brain and Greenfield (1950) pointed out the relative escape of some areas. The outlines of the basal ganglia appear blurred. The corpus callosum is thin. Isolated softening of the claustrum and of the adjacent external and extreme capsules has repeatedly been recorded (Norman *et al.*, 1960). The ventricular system is moderately dilated.

Light microscopy. The appearance of the white matter in myelin stains may be deceptive. There is a generalized slight pallor with rarefaction of the myelinated fibers and an accumulation of myelin balls and buttons.

Only in the most severely affected areas is the disintegration of myelin sheaths obvious. Total demyelination, albeit with sparing of the U-fibers, is seen only in cases of long-term survival in which the breakdown of myelin is seen even in the granular layer of the cerebellum and in the basal ganglia. The optic radiation is preserved in all cases (Brain and Greenfield, 1950). A dense gliosis can be seen in Holzer-stained sections, even in areas showing only pallor of myelin. The glial fibers often form baskets around areas of "honeycomb" rarefaction filled with macrophages. The number of axons is generally reduced; they are often broken up or swollen with spherical or fusiform expansions. Their neurofibrils are tangled, as in Alzheimer's neurofibrillary changes. Numerous axonal torpedoes may be seen in the granular layer of the cerebellum (Brain and Greenfield, 1950). The macrophages stain a weak smoky gray in myelin stains.

Staining with Sudan red reveals only scanty sudanophilic fat granule cells around the blood vessels. Their contents are doubly refractile with Maltese cross formation. Sudanophilic fat granule cells are present in the end plate and the pyramidal cell band of Ammon's horn; otherwise, they are confined to the white matter. The very numerous macrophages in the white matter stain yellowish orange with Sudan stains and are only weakly birefringent under polarized light. The extent of the myelin breakdown is revealed by the PAS reaction, which is strongly positive in macrophages throughout the white matter. These do not cluster around the blood vessels, but remain in their original position alongside the myelinated fibers. These are round cells, tightly packed with granules so that they often obliterate the nucleus. In Hirsch and Peiffer's (1955) acetic cresyl violet stain they show brown metachromasia (Fig. 81). Here and there the larger intracerebral veins are surrounded by a wide metachromatic halo. Metachromatic material can also be abundant in the vascular endothelia (Osetowska and Zelman, 1964).

Nissl staining confirms the abundance of glial cells. Apart from gemistocytic astrocytes, and occasionally binucleated ones, microglial cells predominate. There is no inflammatory reaction, but sparse perivascular lymphocytes may be seen in places.

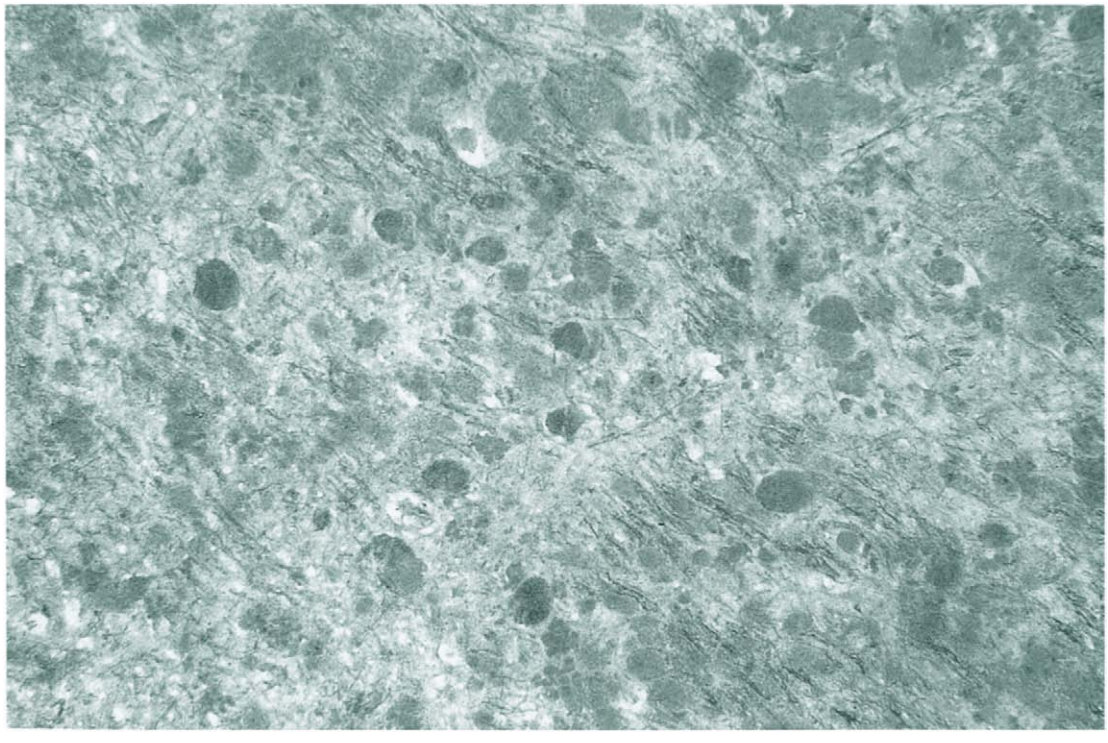


Fig. 81 Infantile form of metachromatic leukodystrophy. Macrophages with rounded cell bodies filled with metachromatic granules. The metachromatic substances aggregate around blood vessels. Acetic cresyl violet stain; original magnification ×500. (Courtesy of H. J. Peiffer, Tübingen, Germany.)

The cortical neurons are only exceptionally affected, apart from some pyknosis of the nuclei, ischemic changes, and cell loss in Ammon's horn. Ballooning of the perikarya, however, is prominent in the basal ganglia, the nuclei of the brain stem, and the spinal cord (Peng and Suzuki, 1987). With acetic cresyl violet some stain a deep burgundy–red, but most show the typical brown metachromasia (Fig. 82). The metachromatic inclusions may be present in areas in which the surrounding white matter is intact. In PAS-stained sections one can see that the intraneuronal granules are identical to those seen in the glial cells of the white matter (Fig. 83). The sites of predilection of neuronal storage are, in the first place, the dentate nuclei, followed by the brain stem and the spinal nuclei as well as the thalamus and the globus pallidus (Norman *et al.*, 1960; Peiffer, 1970).

Demyelination is also prominent in the cerebellum. Purkinje cells often show axonal "torpedoes." In the optic nerve and the ganglion cells of the retina, identical metachromatic substances are deposited as in the CNS (Hagberg *et al.*, 1962; Libert *et al.*, 1979). A considerable loss of myelinated fibers is apparent in the peripheral nerves (Fig. 84).

Electron microscopy. Intracytoplasmic inclusions of variable appearance are present in astrocytes, oligodendrocytes, and affected neurons in the CNS and the retina. They can be classified into three groups: (1) pleomorphic inclusions (Fig. 85) consisting of concentric

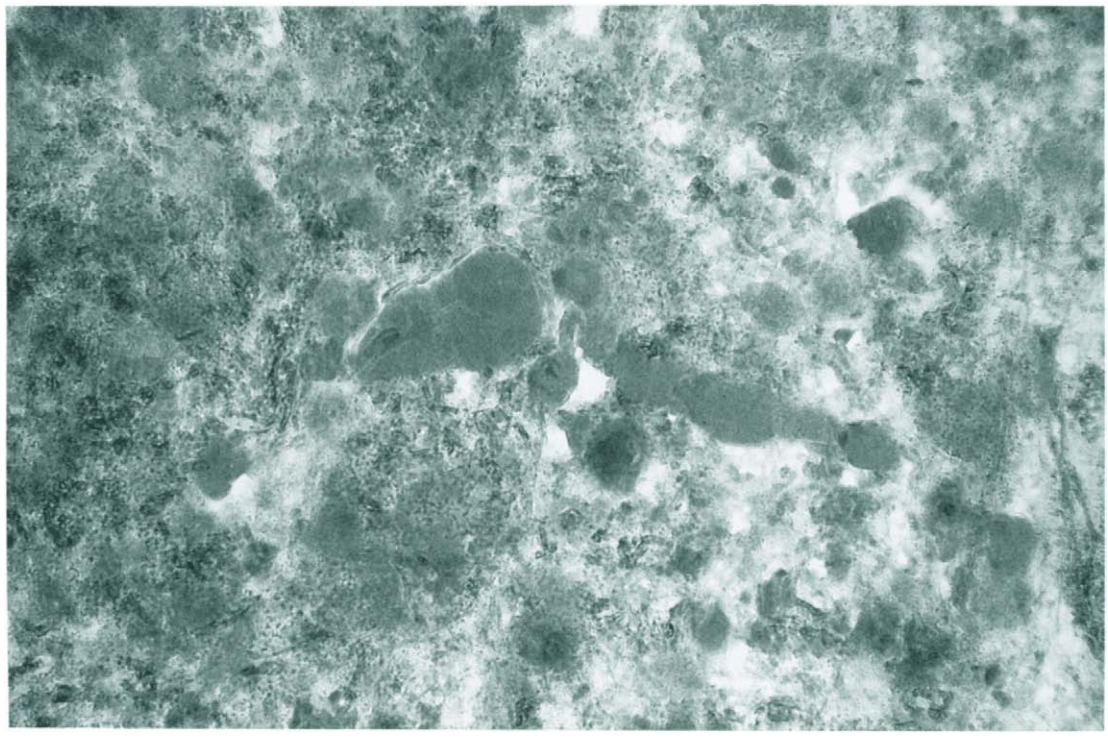


Fig. 82 Neurons in the cerebral cortex with metachromasia in the perikaryons. Acetic cresyl violet stain, ×500. (Courtesy of H. J. Peiffer, Tübingen, Germany.)

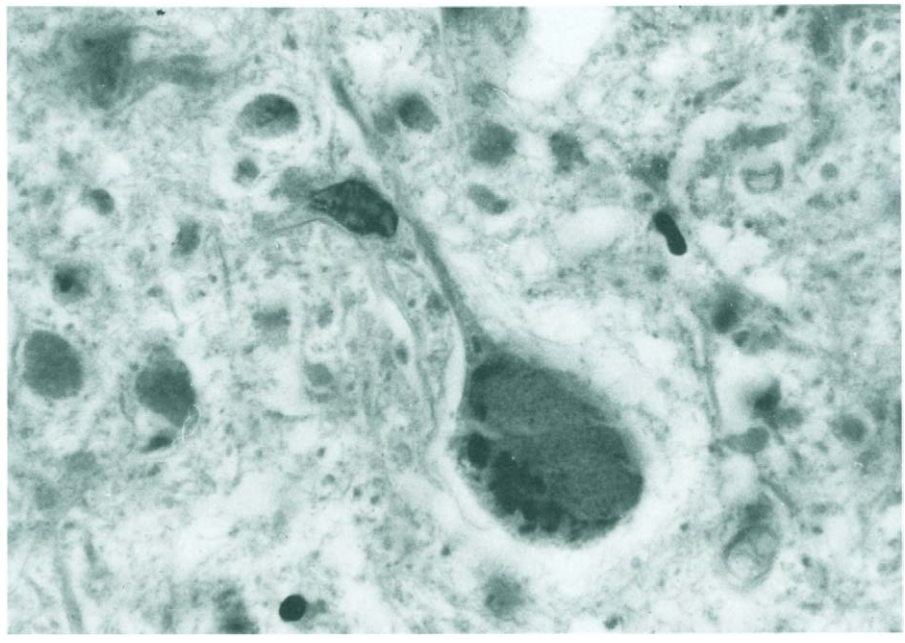


Fig. 83 Infantile form of metachromatic leukodystrophy. The cytoplasm of a pontine neuron. Paraffin section, ×700.

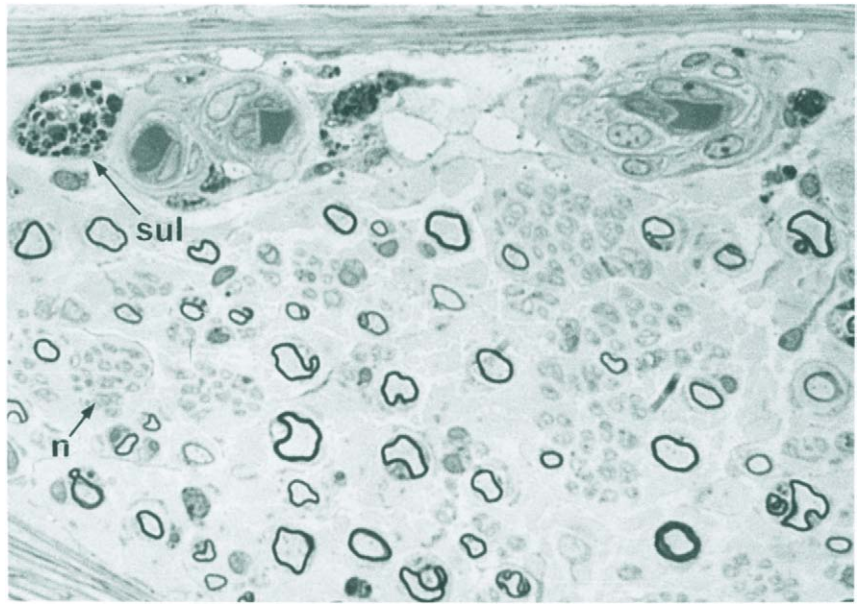


Fig. 84 Infantile form of metachromatic leukodystrophy in a peripheral nerve. A loss of myelinated fibers and a preponderance of unmyelinated fibers. Storage material appears in a perivascular endoneurial macrophage (sul). Semithin section. Nissl stain, ×200. (Reproduced from Weller and Cervós-Navarro, 1977.)

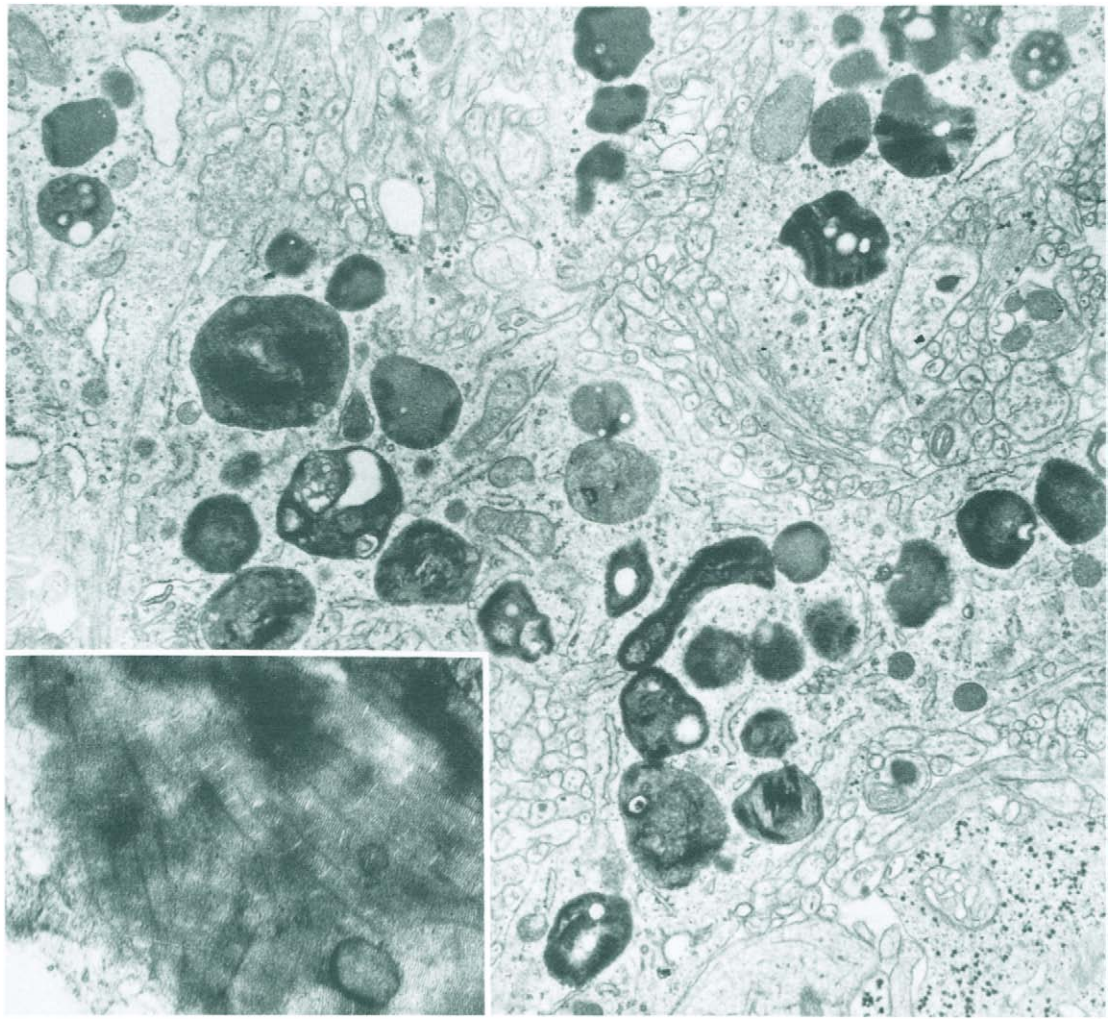


Fig. 85 Infantile form of metachromatic leukodystrophy. Ultrastructure of the intracellular stored sulfatides, ×30,000 (inset ×120,000). (Reproduced from Cervós-Navarro and Goebel, 1989.)

lamellar structures, densely osmiophilic bodies, and granular material (Terry, 1970; Peng and Suzuki, 1987), (2) tuffstone bodies (Luijten *et al.*, 1978), and (3) prismatic inclusions (Libert *et al.*, 1979). The prismatic structures consist of bands of lipids, separated by spaces that appear empty in sections stained with uranyl–lead acetate. The lipid bands in the prisms are laminated with a characteristic periodicity of 5–6 nm (Fig. 86A and B). In material fixed in glutaraldehyde without osmication and stained with phosphotungstic acid in watery solution, the apparently empty spaces are seen to contain an electron-dense matrix suggestive of the presence of amino groups. This material can be dissolved by treatment with hyaluronidase.

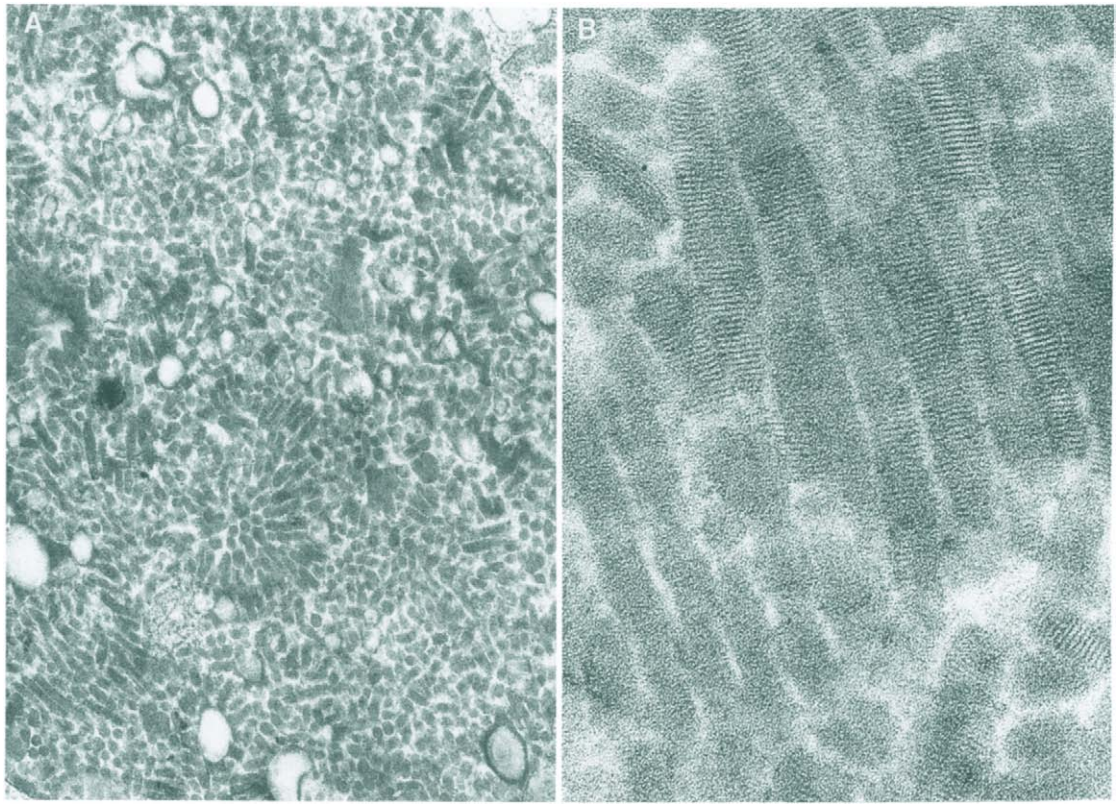


Fig. 86 Infantile form of metachromatic leukodystrophy. Ultrastructure of laminated storage material with characteristic periodicity, (A) ×40,000 and (B) ×200,000. (Courtesy of R. O. Weller, Southampton. Hampshire, England.)

The tuffstone bodies, 1 μm in diameter, are moderately osmiophilic and consist of vesicular and solid parts, with a mosaic structure built up of adjacent plates, prisms, and concentric rings (Fig. 87). They correspond to the pleomorphic structures and the "spider web" or honeycomb structures (Luijten *et al.*, 1978).

The inclusions with concentric lamellae may be found side by side with the tuffstone bodies, are about the same size, and are equally membrane bound. Their periodicity is 4–5 nm. Both the tuffstone and concentrically laminated structures seem to be carriers of the metachromatic reaction. When isolated by ultracentrifugation, they stain metachromatically. They evidently contain sulfatides, even if their morphology is indistinguishable from that of the gangliosides.

The cytoplasm of Schwann cells in the peripheral nerves contains—aside from concentric lamellar, tuffstone (Fig. 88A and B), and prismatic inclusions—also zebra bodies (Weller and Cervós-Navarro, 1977; Luijten *et al.*, 1978). In cases of long duration, increasing changes may be seen in the myelin. Inclusions are also found in the Schwann cells of unmyelinated fibers. In the eye Goebel *et al.* (1992) found typical MLD residual

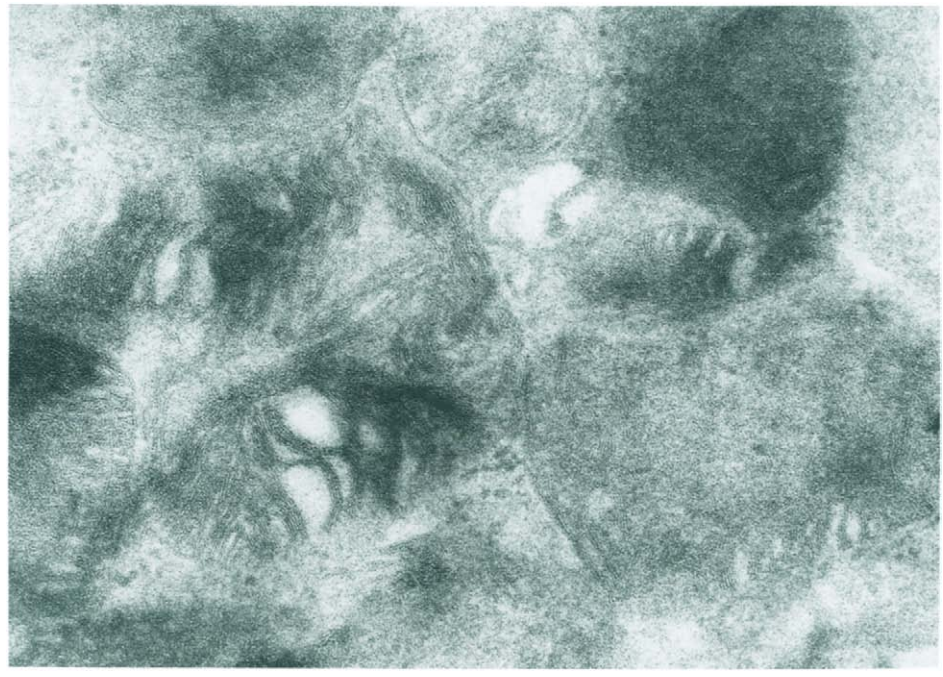


Fig. 87 Infantile form of metachromatic leukodystrophy. A neuron in the cerebral cortex, showing a tuffstone inclusion with homogeneous and irregular membranous parts, ×100,000.

bodies in ganglion cells of the retina, but not in bipolar or photoreceptor cells. The optic nerve was demyelinated.

Juvenile Form

The first symptoms of the juvenile form of the disease appear between the ages of 4 and 19 years and resemble those of the late infantile form. Genealogical studies and investigation of the residual activity of arylsulfatase reveal differences, however, between the two forms.

Clinical Picture After a normal initial development scholastic difficulties are the first manifestation of the disease. In contrast with the late infantile form, extrapyramidal symptoms (tremor, rigidity, and hyperkinesia) and cerebellar disturbances are prominent. Dysarthria, incontinence, and compulsive laughter also occur. Epileptic seizures occur in two thirds of the cases (Haltia *et al.*, 1980). Disturbances of vision may precede the motor phenomena. The duration of the illness averages 6 years, but may be as long as 12 years (Holländer, 1964).

Pathology The gallbladder is atrophic and fibrotic. Abundant storage of metachromatic granules is present in the kidneys, less so in the liver and the adrenals, and minimally in the pancreas and the testes.

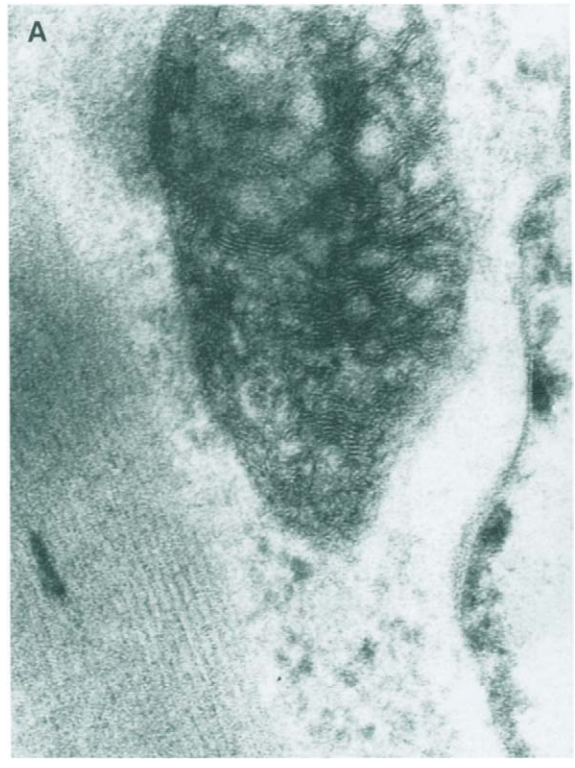


Fig. 88 Late infantile form of metachromatic leukodystrophy. A tuffstone inclusion in a Schwann cell of a myelinated axon, (A) ×80,000 and (B) ×150,000.

Neuropathology *Gross appearances.* The cerebrum and the cerebellum are atrophic and firm. The leptomeninges show a milky opacity. The ventricles are dilated. The white matter is slightly to moderately (Haltia *et al.*, 1980), occasionally extremely, atrophic. Accordingly, the demyelination is variable, but always conspicuous and recognizable on the CT scan. In the juvenile form the frontal lobes are most severely affected, followed by the temporal and the basal and lateral parts of the occipital lobes. The U-fibers are spared.

Light microscopy. Under light microscopy abundant metachromatic granules are present in the U-fibers. If the central white matter is severely atrophic, it contains only sparse metachromatic material. The nerve fibers are reduced in number, with frequent swellings in the surviving ones. Gliosis is dense throughout the white matter.

The cerebellum is diffusely demyelinated; the number of Purkinje cells, reduced. Moderate demyelination is found in the peripheral nerves. Storage of metachromatic material is present in the Schwann cells and the perivascular macrophages (Luijten *et al.*, 1978).

Electron microscopy. Concentric lamellar, zebralike, and dense homogeneous inclusions are seen in both types of glial cells. Prismatic inclusions were seen in only one case, both in the CNS and in the peripheral nervous system. All other types of inclusions were seen in the Schwann cells of myelinated fibers and unmyelinated fibers in all cases

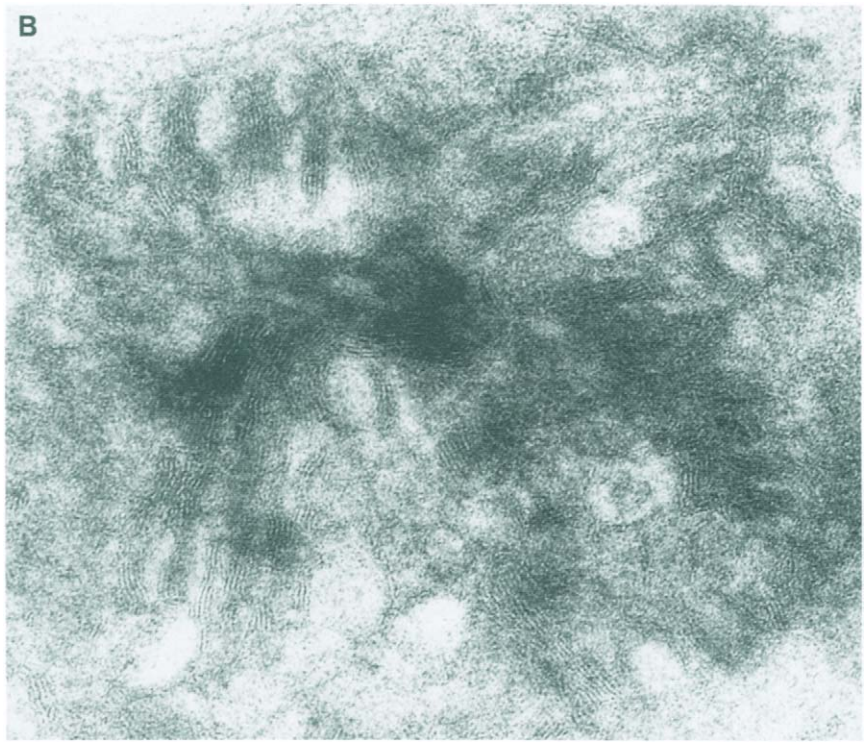


Fig. 88 Continued.

(Luijten *et al.*, 1978). Onion bulb formation, as an expression of recurrent segmental demyelination, is observed occasionally (Haltia, *et al.*, 1980).

Adult Form

The adult form of MLD is unique in that nothing in the clinical course of the disease suggests a metabolic disorder. Its incidence is not very rare, and the classical accounts of Alzheimer (1910) and Witte (1921) should be included in this group.

Clinical Picture The first symptoms appear after the age of 20 years, occasionally before the end of the second decade (Luijten *et al.*, 1978). The symptomatology is nonspecific, and the advanced age is not suggestive of a metabolic disorder, all the more so in that most cases are sporadic and not familial. Only rarely is a diagnosis made during the patient's life (Waltz *et al.*, 1987).

In contrast with other forms, the disease usually begins with mental peculiarities, proceeding to definite mental disorders and finally to a dull dementia (Waltz *et al.*, 1987; Baumann *et al.*, 1991; Minauf *et al.*, 1993; Sadovnick *et al.*, 1993; Perez Sempere *et al.*, 1992). Neurological symptoms are scanty, and are more prominent in cases with an earlier

onset and relatively rapid course than in patients whose illness begins late in life (Luijten *et al.*, 1978). In early stages the only finding may be slowing of the motor and sensory conduction velocity (Pilz and Hopf, 1972; Pilz *et al.*, 1977). Severe peripheral neuropathy is rare as a presenting symptom (Fressinaud *et al.*, 1992; Hansen *et al.*, 1994). Dysarthric staccato speech is fairly common. Epileptic seizures occur only terminally. The duration of the disease is very variable and ranges from a few years to several decades.

MRI shows evidence of cerebral atrophy with hypodensities in the white matter, often symmetrical (Baumann *et al.*, 1991).

Pathology Guseo *et al.* (1975) detected an atrophy of all internal organs. Using light microscopy, these authors found storage of metachromatic substances in the kidneys. In cases with a prolonged clinical course, Tagliavini *et al.* (1979) failed to find evidence of visceral storage. Under electron microscopy zebra bodies and lamellar structures have been seen in the kidneys.

Neuropathology The expression of changes in the CNS depends on the duration of the clinical course. Although transitional cases may be found, the patients can be roughly divided into two groups: (1) those with a subchronic course (Luijten *et al.*, 1978) and (2) those with a chronic course of over 5 years (Guseo *et al.*, 1975).

Cases with a Subchronic Course

Gross appearances. The is atrophy of the cerebrum (Fig. 89), particularly pronounced in the basis pontis and the medullary pyramids, and less so in the spinal cord. The cerebellum is not atrophic, as a rule. The lateral ventricles are dilated. The white matter shows spongy rarefaction, is grayish yellow, and is of a leathery consistency. The lesions involve a highly atrophic corpus callosum, but spare the basal ganglia, cortex, and unmyelinated fibers.

Light microscopy. Extensive demyelination can be seen in the white matter of the cerebral hemispheres (Fig. 90A and B). It is distributed symmetrically in the frontal, parietal, temporal, and occipital lobes as well as in parts of the corpus callosum. The picture is dominated by macrophages, scattered reactive astrocytes, and isolated perivascular round cell infiltrates. The granular contents of the macrophages are strongly metachromatic. Sulfatide granules are also tightly packed in the astrocytes. The storage cells are concentrated in the neighborhood of blood vessels in the white matter, and only occasionally around vessels in the deeper cortical layers. Axons are absent in the centers of the demyelinated lesions, but nearer the edges they are swollen with spherical expansions. The axons of the unmyelinated fibers are preserved. A strong anisomorphic fibrillary gliosis can be seen in Holzer preparations in the demyelinated areas (Fig. 90C and D). The cerebellum is not demyelinated; a slight pallor can be seen around the dentate nucleus. Metachromatic material is present in the cerebellar astrocytes. The neurons of the dentate nucleus contain an excess of lipid, which, in some cells, shows a faint metachromasia. Also, in the midbrain some neurons in the oculomotor nucleus contain weakly metachromatic granules. The myelinated fibers are rarefied in the pyramidal tracts, where storage cells are abundant and intermingled with strongly sudanophilic fat granule cells.

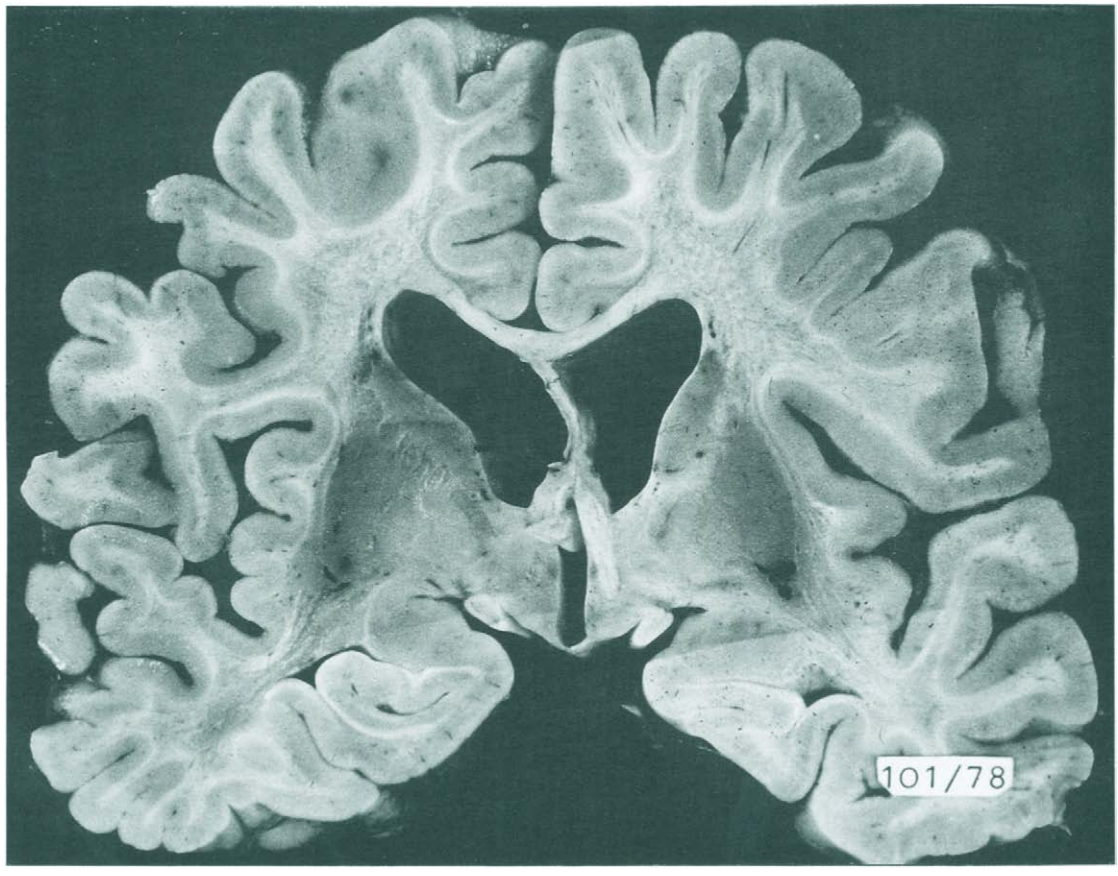


Fig. 89 Adult form of metachromatic leukodystrophy. Prominent demyelination with sparing of the unmyelinated fibers. (Reproduced from Cervós-Navarro and Goebel, 1989.)

Segmental demyelination and axonal degeneration are sometimes seen in the peripheral nerves (Luijten *et al.*, 1978). Metachromatic material is always present in the Schwann cells and the endoneurial macrophages.

Cases with a Protracted Course

Gross appearances. The brain is slightly to moderately atrophic. The brain stem and the cerebellum are unremarkable. The white matter is atrophic, particularly in the frontal and occipital lobes, shows patchy areas of brownish discoloration, and has a firm consistency. The corpus callosum is always severely atrophic.

Light microscopy. Patchy demyelination is present in the white matter, with accentuation in the frontal and occipital lobes. The U-fibers are spared. A severe loss of myelin is

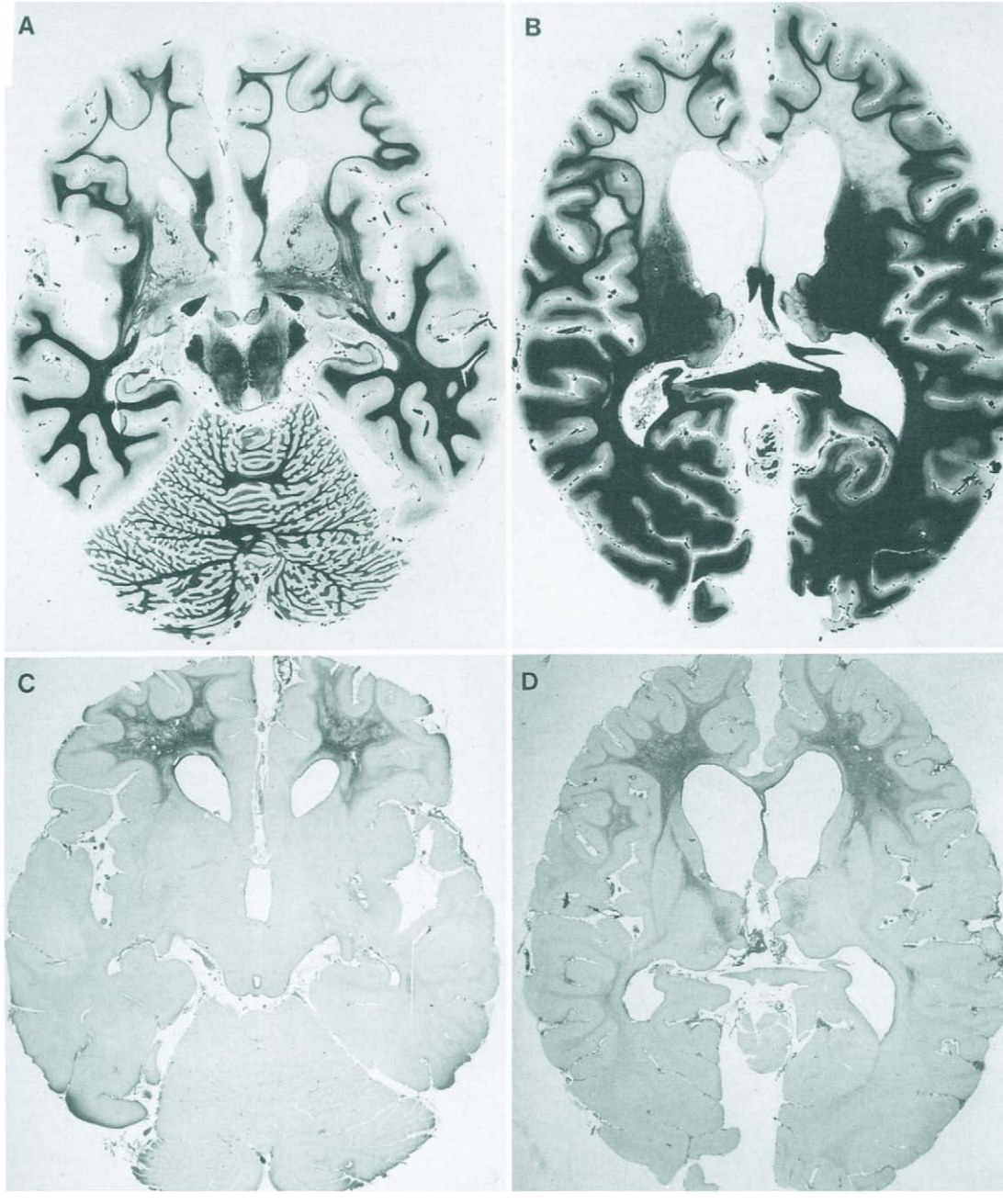


Fig. 90 Adult form of metachromatic leukodystrophy. (A and B) Demyelination in the frontal white matter. Wölcke's myelin stain. (C and D) Dense gliosis in demyelinated areas. Holzer stain.

seen in the corpus callosum. The axons are generally preserved in the demyelinated areas. Axonal swellings are present in places, often in areas without obvious demyelination. A strong isomorphic gliosis is present in demyelinated areas. Storage of metachromatic material is most pronounced at the edges of the demyelinated areas.

In some cases metachromatic material may be found in axons and in neuronal cytoplasm not only in the brain stem, but also in the cerebral cortex, thalamus, optic nerve, and retina. Sudanophilic material is more abundant in cases with a long clinical course. The prominent hypertrophic and degenerative changes in the peripheral nerves are also a reflection of the chronicity of the disease. The storage of metachromatic material in the peripheral nerves is accompanied in these patients by segmental demyelination and axonal degeneration.

Electron microscopy. Prismatic structures and zebra bodies are found mainly in astrocytes and macrophages (Guseo *et al.*, 1975). Accumulations of lipopigments, which are marked by an opaque, supposedly lipid, droplet and a granular component, have been reported by Goebel and Busch (1990) in neurons. The sparse remaining oligodendrocytes contain only scanty concentric lamellar bodies. Other authors have described these structures in the Schwann cells of myelinated fibers and U-fibers and in endoneurial macrophages (Luijten *et al.*, 1978). They can appear together with zebra bodies in nerves in which no appreciable demyelination can be seen. These changes were found on a nerve biopsy of a healthy 13-year-old boy from a family affected by the adult form of MLD. Inclusions identical to those seen in the peripheral nerves are also found in the optic nerves.

Pathogenesis MLD is characterized by an accumulation of sulfatides, which are formed from galactocerebroside by esterification of the hydroxyl group on C-3 of the galactose with sulfuric acid. The proportion of other cerebrosides to sulfatide is 3 : 1 in the normal brain. In MLD the levels of sulfatide are considerably increased and reach a proportion of 1 : 4 in the late infantile and juvenile forms and 1 : 1 in the adult form. The amount of cerebrosides can remain normal or decrease.

The accumulation of sulfatides is due to a deficiency of ASA (Austin *et al.*, 1964), which splits off the sulfate radical form sulfatide. It acts in the same way on other sulfated lipids (e.g., lactosyl sulfatide). These lipids can also accumulate in sulfatase deficiency. ASA, ASB, and ASC were distinguished by Austin *et al.* according to their optimal activity. ASA and ASB are soluble; ASC is insoluble and can be demonstrated only histochemically. As MLD can manifest itself at any age, one must assume that the various clinical forms express genetically determined peculiarities. The genetics of MLD are complex, as many different mutations have been recorded in individual patients and various ethnic groups. The ASA gene has been cloned. Its cDNA consists of eight exons and contains about 3 kb (Gieselmann *et al.*, 1991). The common mutations in white patients are a G-to-A transition on exon 2, leading to a G-to-S substitution at position 309 in late infantile MLD (Kreysing *et al.*, 1993; Barth *et al.*, 1993), and a C-to-T transition on exon 8, leading to a P-to-L substitution at position 426 in late-onset cases (Barth *et al.*, 1993; Ohshima *et al.*, 1994). In a Japanese population Hasegawa *et al.* (1993) failed to find any of the common mutants that affect white patients; instead, they found a

G-to-R substitution at point 245 in a late infantile case and a G-to-N change at position 99 in an adult case. Other unusual mutations were discovered by Fluharty *et al.* (1991), Bohne *et al.* (1991), and Kappler *et al.* (1992). Many patients are heterozygous in the sense that they carry a different mutation on each allele.

The late infantile cases show, as a rule, a total absence of ASA activity, while some residual activity is present in late-onset cases. Kreysing *et al.* (1993), however, reported a case of late infantile MLD with residual activity of the same order of magnitude as that as that observed in late-onset cases. The neurological and morphological findings, in conjunction with the clinical evolution and general neuropathological experience, allow the distinction of three pathological processes:

1. The primary storage of sulfatides
2. The breakdown of myelin sheaths
3. Phagocytosis and scarring

The gradual progression of the disease allows the observation of structures, in both biopsy and autopsy material, in which the pathological process is still in an early stage of evolution. In these areas one can demonstrate an accumulation of metachromatic material before the onset of disintegration of the myelin sheaths. Observations on peripheral nerve biopsies show that storage in oligodendroglia and the homologous Schwann cells is already present before completion of myelination and also in cells supporting unmyelinated fibers. The storage of metachromatic material in ganglion cells shows that the neuronal elements are not exempt from the process. Stern and Bornstein (1971) demonstrated that in tissue cultural neurons as well as glial cells are capable of phagocytosis of exogenous sulfatides. The striking predilection of certain neuronal groups is strong evidence against a simple phagocytic mechanism of neuronal storage, however.

Demyelination is one of the characteristic features of the disease. It is, however, difficult to separate this process from the primary storage phenomenon. The paucity of sudanophilic products of myelin degradation, characteristic of other demyelinating processes, suggests an enzyme deficiency that inhibits the normal catabolism to sudanophilic lipids. Cardona (1939) was the first to propose the view that demyelination was the result of the primary metabolic disorder.

Phagocytosis and glial scarring are phenomena that can occur in any disease of the CNS. A unique feature of this disease however, is that most of the phagocytes contain storage material, while only a few are laden with the common sudanophilic breakdown products.

Multiple Sulfatase Deficiency (Mucosulfatidosis; Austin Type of Metachromatic Leukodystrophy; Variant 0 of Metachromatic Leukodystrophy)

Mossakowski *et al.* (1961) described a disease in three Canadian siblings which they interpreted clinically and morphologically as a combination of MLD and amaurotic idiocy. Austin *et al.* (1965) described a similar syndrome as a variant of MLD with multiple sulfatase deficiency, leading to additional storage of glycolipids in the cerebral cortex and excretion of mucopolysaccharides in the urine. The lysosomal ASA and ASB

and the microsomal ASC (Austin, 1973) are involved in the process, as well as the heparan-*N*-sulfatase and the iduronide sulfatase. Synonyms include *combined metachromatic dystrophy and mucopolysaccharidosis* and *the Austin type of MLD*. Because of the deficiency of several enzymes, the generally accepted term became *multiple sulfatase deficiency* or, as an alternative, Jatzkewitz's (1972) term *enzyme variant 0 of MLD*. A congenital form was differentiated by Vamos *et al.* (1981) because of clinical and enzymatic peculiarities.

Clinical Picture The onset of symptoms and clinical course correspond with those of infantile or late infantile MLD. Additional features are microcephaly, seizures in one half of the patients, hypertelorism and ichthyosis in three quarters, and bony changes and mucopolysaccharidiuria in two thirds of the cases (Guerra *et al.*, 1990; Harbord *et al.*, 1991). A rapidly progressive cerebral disintegration leads to quadriplegia, blindness and deafness, loss of contact with the environment, and double incontinence. Death occurs 1–4 years after the onset of symptoms. Vamos *et al.* (1981) described a severe congenital form with hepatosplenomegaly, hydrocephalus, psychomotor retardation, and cloudiness of the cornea. A family with some atypical features was reported from Saudi Arabia (al-Aqeel *et al.*, 1992).

Pathology *Gross appearances.* The liver and the spleen are enlarged.

Light microscopy. Fine granules are present in skin fibroblasts and in those of internal organs, staining metachromatically with toluidine blue at pH 3.0–4.0, but showing no metachromasia with cresyl violet. The granules in hepatocytes show similar reactions. In the epithelia of the renal tubules, the stored material stains metachromatically with both toluidine blue and cresyl violet. Most authors found a striking vacuolation of the cytoplasm in lymphocytes and bone marrow cells. Abnormal lipid storage was found in the renal tubules.

Electron microscopy. Inclusions of low density are found in fibroblasts, hepatocytes, and endothelial cells. Apart from the clear ones, some inclusions with a dense osmiophilic membrane are present in the kidneys.

Neuropathology *Gross appearances.* The whole brain, particularly the cerebellum, is markedly atrophic. The ventricles are correspondingly enlarged. The consistency of the tissue is firm and feels tough during cutting.

Light microscopy. The leptomeninges are highly cellular and fibrous and contain large round histiocytes. The cerebral cortex is considerably atrophic, but the laminar structure is preserved. With a few exceptions, all ganglion cells are swollen to two to three times their normal size. The variation in the shape of the cells with abnormal storage is greater than in simple MLD. The cytoplasmic inclusions range from fine and coarse granules to massive, dense, homogeneous structures. Different types of inclusions may be present in the same cell. The inclusions may be either metachromatic or only PAS positive (Austin, 1973). The nucleus is displaced laterally or toward the apical dendrite. The astrocytes appear more numerous, particularly in the first layer, and contain finely and coarsely granular storage material. Intact myelin sheaths are barely recognizable in the cerebral cortex (Ulrich and Isler, 1971). The proliferation of astrocytes is prominent in the end plate of Ammon's horn. Storage in neurons of the claustrum resembles that of the cortex. In the striatum all neurons contain finely granular, generally nonmetachromatic, material. This is more striking in the large

cells than in the small ones. The latter appear somewhat depleted. The pallidum is less severely affected. In the basis pontis most ganglion cells are atrophic, while large clear astrocytes contain abundant metachromatic material.

The granular layer of the cerebellum is severely depleted and infiltrated by glial cells and fibers. A few Golgi type II neurons contain finely granular nonmetachromatic material. The Purkinje cells are reduced in number and contain both metachromatic and nonmetachromatic material, particularly in the dendrites, which show staghorn expansions. All authors agree that orthochromatic material predominates in the cerebral cortex and in Purkinje cells, while metachromatic material occurs in the dentate nucleus and the brain stem. Occasionally, storage is also seen in ganglion cells of the retina.

The appearance and distribution of the white matter lesions correspond generally with those seen in classical MLD. The main difference is that the nuclei of the storage cells are clearly visible, both those of the astrocytes and those of the interfascicular oligodendrocytes. Partial demyelination is present in the centrum ovale and the cerebellar white matter with an accumulation of macrophages laden with metachromatic material. In the peripheral nerves both the Schwann cells and the endoneurial fibroblasts contain fine granules of metachromatic material. Nonmetachromatic myelin debris and perivascular sudanophilic degradation products are also present.

Metachromatic Leukodystrophy with Activator Protein Deficiency (AB Variant)

Fogelson *et al.* (1968) found a normal arylphosphatase activity in patients whose disease clinically and morphologically resembled MLD. Other authors reported on patients with MLD in whom the arylsufatase activity was reduced to only 50% of the normal values. Hahn *et al.* (1981) described an additional case and called it the "AB variant" of MLD, by analogy with the current terminology of GM_2 gangliosidosis.

Clinical Picture Psychomotor development may be retarded from early childhood (Hahn *et al.*, 1981). The first symptoms usually appear after the age of 1 year or sometimes later, during the early school years. Mental deterioration is prominent, and after a few years the patients lose their speech. Increasing ataxia and motor weakness interfere with gait. Epileptic seizures may appear early in the course of the disease or may be totally absent. The sulfatide concentration in the urine may be increased 20-fold. The activity of ASA or cerebroside sulfatase in the urine, leukocytes, and fibroblasts is within normal limits or is only slightly reduced (Hahn *et al.*, 1982).

Neuropathology *Light microscopy.* In the remaining cases a nerve biopsy showed a considerable reduction in the number of myelinated fibers. Many fibers had an abnormally thin myelin sheath. Onion bulb formation was evident in the case reported by Hahn *et al.* (1981). The cytoplasm of Schwann cells contained aggregates of orthochromatic and metachromatic granules. The latter were also present in the Schwann cells of U-fibers and in endoneurial fibroblasts.

Electron microscopy. Fogelson *et al.* (1968) found inclusions in the oligodendrocytes consisting of long, stacked, parallel lamellae. In the peripheral nerves one finds a concentric

granular disintegration of the myelin sheath with preservation of the axon, indicative of segmental demyelination. Prismatic inclusions and lamellar and zebra bodies are seen in the cytoplasm of Schwann cells supporting unmyelinated fibers, as well as in endoneurial fibroblasts and macrophages. Tuffstone inclusions and clear vacuoles with floccular contents predominate in the Schwann cells of myelinated fibers (Hahn *et al.*, 1981).

Pathogenesis To explain the sulfatide storage in the presence of near-normal activity of ASA, deficiency of an activator (see p. 13) was postulated. Stevens *et al.* (1981) demonstrated that addition of an arylsufatase activator to the fibroblast culture obtained from the same patients normalized the enzyme activity. This was definite proof of a pathogenesis different from that of other forms of MLD. Schlote *et al.* (1991) found a deficiency of SAP1 protein in a 7-year-old boy with normal ASA activity.

Arylsulfatase A Pseudodeficiency

In examining a group of normal controls, some healthy individuals were found with a low activity of ASA, similar to that seen in late-onset MLD (1–10%). This phenomenon has been called "pseudodeficiency" (Gieselmann *et al.*, 1991). This finding has been amply confirmed in different populations (Wenger and Louie, 1991; Shen *et al.*, 1993). While it is impossible to predict that these individuals will not develop the disease in later life, they exhibit a specific genetic mutation not encountered in patients with MLD (*ASAp*). This consists of an A-to-G transition in the first polyadenylation signal of the *ASA* gene, which results in the loss of its major mRNA species (Nelson *et al.*, 1991). Heterozygotes for the *ASAp* gene and a mutant causing MLD also remain asymptomatic (Penzien *et al.*, 1993). Kappler *et al.* (1991) reported what they considered to be a chance association of a choreic–dystonic syndrome in three siblings with an *ASAp/ASAp* genotype.

Metachromatic Leukodystrophy in Animals Andersen and Palludan (1968) described an MLD in minks, and Wight (1976) did in Hawaiian ducks.

Globoid Cell Leukodystrophy (Krabbe's Disease; Cerebroside β-Galactosidase Deficiency)

This disease was differentiated by Krabbe (1916) from other forms of diffuse sclerosis. The name *globoid cell leukodystrophy* developed from the term used by Collier and Greenfield (1924) to describe the characteristic aggregations of macrophages. The most common and useful classification is based on age groups.

Infantile Form

After normal birth and early development of an infant, the disease manifests itself between the ages of 4 and 6 months. A few patients, however, show symptoms from the time of birth (Blackwood, 1952).

The disease begins with weakness in the legs and impairment of movements. This is followed by ataxia, progressive stiffening, contractures, and tetanic seizures. Mental deterioration and blindness are common. The protein level in the CSF is raised to above 100 mg/dl (Hofman *et al.*, 1985). The finding of a peripheral neuropathy is helpful in making the diagnosis. Hagberg *et al.* (1970) divided the course of the disease into three stages before the children die, usually during the second year. Several CT and MRI studies (Sasaki *et al.*, 1991; Farley *et al.*, 1992; Choi and Enzmann, 1993; Percy *et al.*, 1994; Bernardi *et al.*, 1994; Vanhanen *et al.*, 1994) have revealed hyperdensity in the thalamus extending into the neighboring white matter. On MRI these areas are paramagnetic; this is attributed to finely dispersed calcium. Otherwise, the appearances confirm widespread demyelination.

Pathology Austin (1962) found abnormal droplets that stained with toluidine blue in the epithelia of renal tubules. Giant cells, which appear in various organs besides the nervous system, differ from globoid cells. Rarely, globoid cells were found in the lungs, spleen, and lymph nodes.

On skin biopsies characteristic intracytoplasmic inclusions can be found in the epithelia of eccrine glands (Elleder, 1992a,b; Ceuterick and Martin, 1993; Goebel *et al.*, 1993).

Neuropathology *Gross appearances.* Considerable cerebral atrophy is present (Fig. 91A). Upon sectioning, one perceives dilated ventricles and a symmetrical atrophy of the white matter of a gray fibrous appearance and a tough consistency (Fig. 91B). The U-fibers are generally only slightly affected. The consistency of the brain stem, cerebellum, and spinal cord is also firm.

Light microscopy. Diffuse demyelination is seen (Fig. 92), with an almost total loss of myelin sheaths and only partial preservation of the U-fibers and the intracortical ones. The myelin content of the mature parts of the internal and external capsules is less severely affected (Norman *et al.*, 1961). The optic tract is usually completely demyelinated. The loss of myelin is subtotal in the cerebellum, pons, and medulla oblongata. In the spinal cord demyelination may be diffuse or focal. These areas are not sharply demarcated. The axons are also affected, depending on the severity of the demyelination.

Surrounding the blood vessels are clusters of macrophages (Fig. 93) called globoid or epitheloid cells. They form giant cells, 30–70 μm in diameter, with massive cytoplasm and multiple narrow (2–20 μm), slightly curved, and mostly peripherally placed nuclei (Fig. 94). Most of these cells lie in close apposition to the blood vessels, although some may lie free in the tissue. The latter are often particularly large and may contain vacuoles. Some perivascular histiocytes may contain droplets of sudanophilic lipid, which is never seen in the globoid cells. The globoid cells stain somewhat more darkly than the glial cells. Their homogeneous cytoplasm has a peculiar velvety appearance, and occasionally fine granules may be visible. The cells vary in size, stain bluish with azan and weakly pink with fat stains, and are PAS positive. Krabbe called them epithelioid cells and thought they were derived from glia. Ulrich

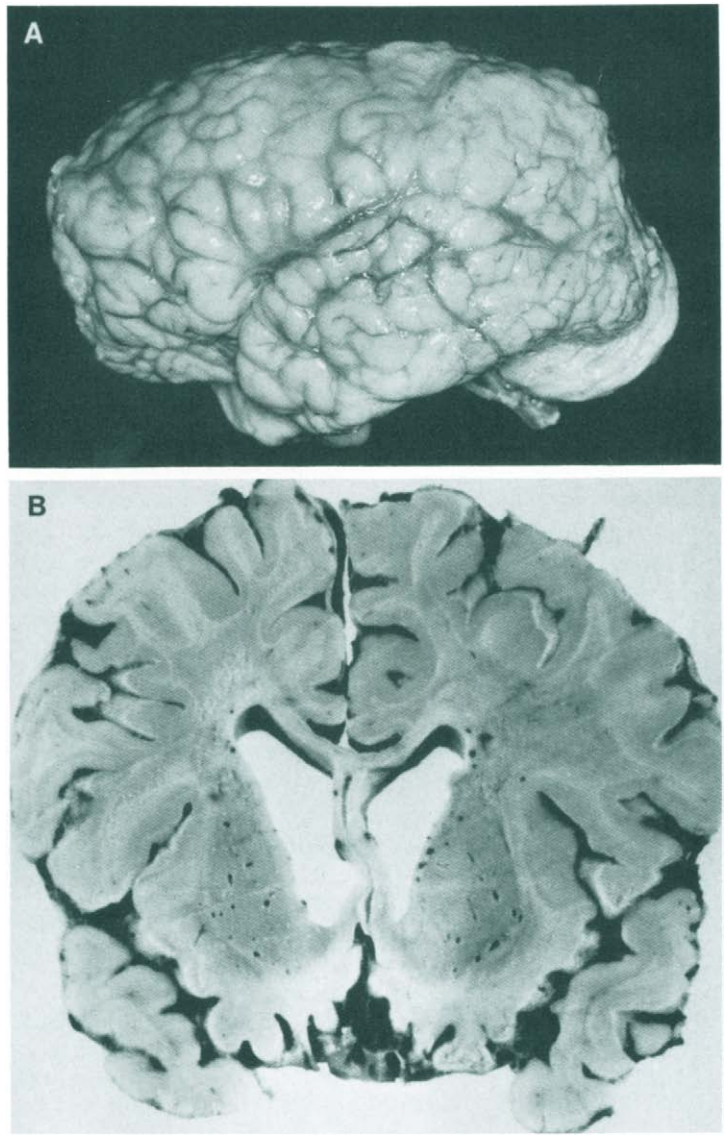


Fig. 91 Infantile form of Krabbe's disease. (A) Pronounced cerebral atrophy. (B) Dilatation of the lateral ventricles and symmetrical atrophy of the white matter, which appears darker than normal.

et al. (1983) demonstrated by immunohistochemical methods that the cells were not astrocytic in origin. Figols *et al.* (1992) demonstrated strong positive labeling of the globoid cells with lectin specific for different carbohydrates. In fetuses diagnosed prenatally globoid cells were found only in the spinal cord (Pollanen and Brody, 1990) or

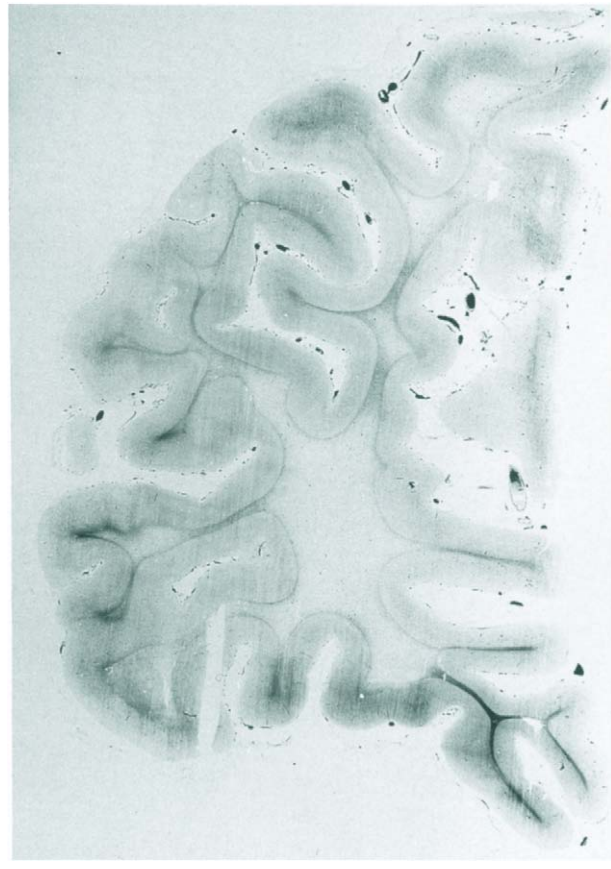


Fig. 92 A strong loss of myelin in the hemisphere's cerebral white matter. Heidenhain's stain; celloidin embedding. (Reproduced from Figols *et al.*, 1992.)

in the spinal cord, brain stem, and peripheral nerves (Martin *et al.*, 1981). In a few otherwise typical cases with prolonged survival, no globoid cells have been found (McKelvie *et al.*, 1990).

Glial cells are abundant, particularly gemistocytic, astrocytes that occasionally contain sparse fat granules. Fat catabolism in fat granule cells is always present, but is strikingly sparse even in recent lesions. A more or less dense isomorphic fibrillary gliosis is present in all demyelinated parts of the brain and the spinal cord (Fig. 95). This gliosis decreases in intensity in areas with partially preserved myelin. A superficial, subpial, and subependymal gliosis is present throughout the brain and the spinal cord. Sparse, or occasionally more abundant, lymphocytic infiltrates may be seen. The absence of plasma cells has been repeatedly emphasized.

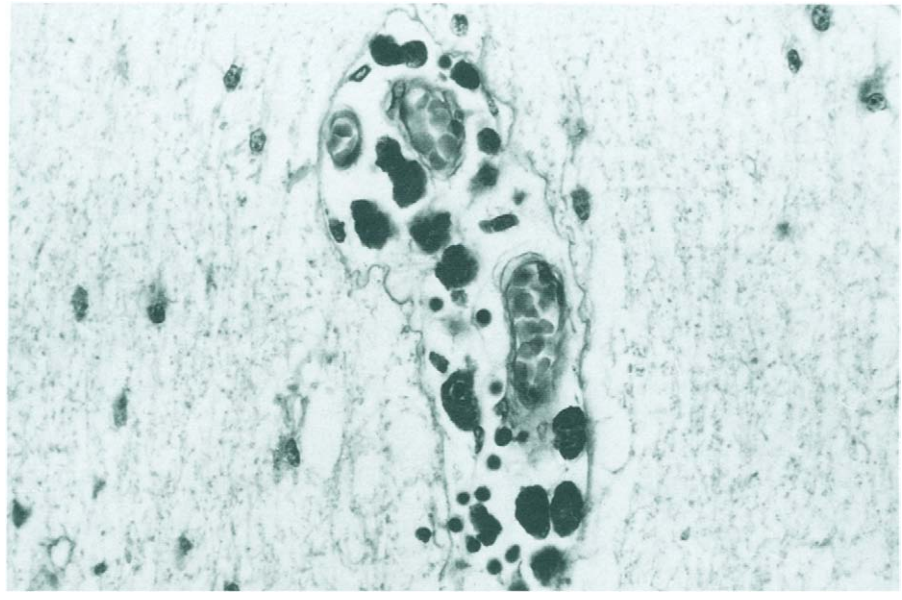


Fig. 93 Infantile form of Krabbe's disease. A perivascular aggregation of globoid cells in the white matter of the frontal lobe. Nissl stain, ×300.

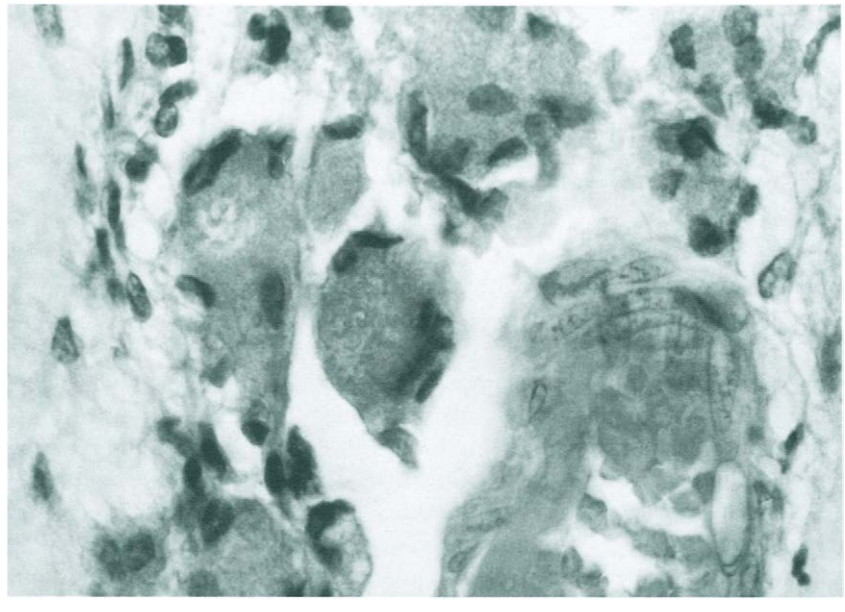


Fig. 94 Same case shown in Fig. 93, at higher magnification, showing multinucleated giant cells, ×750.

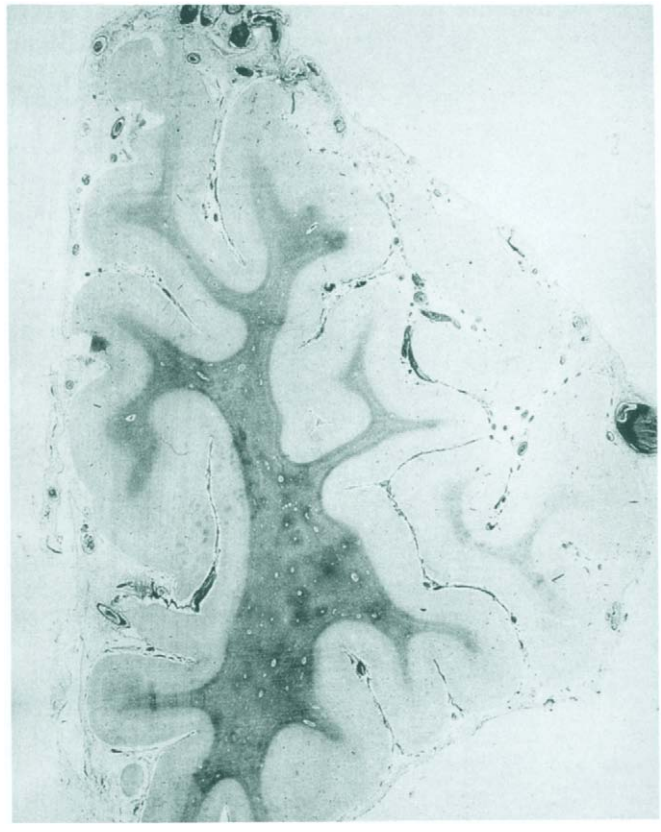


Fig. 95 Krabbe's disease. Intense fibrillary gliosis in the white matter. Kanzler's glial stain. (Reproduced from Cervós-Navarro and Goebel, 1989.)

The cerebral cortex is generally intact, although some loss of neurons may occur in some cases. In a case with prolonged survival, Hirato *et al.* (1994) found severe neuronal loss in the thalamus, pontine nuclei, inferior olives, dentate nucleus, and granular layer of the cerebellar cortex. Purkinje cells were partially preserved and contained eosinophilic inclusions in their dendrites. Astrocytes may proliferate in the deeper layers, particularly if the process has encroached on the U-fibers. Definite neuronal loss has been seen in the thalamus, and also in the nuclei gracilis and cuneatus. Segmental demyelination with some reduction in the number of large myelinated axons is found in the peripheral nerves. A high activity of lysosomal enzymes and of mitochondrial and extramitochondrial dehydrogenases has been demonstrated histochemically (Elleder, 1983).

Electron microscopy. The globoid cells are recognized as giant cells lying in the neuropil (Fig. 96), often adjacent to the basement membrane of a blood vessel. Only occasionally are they found within the perivascular space. While some cells are round or

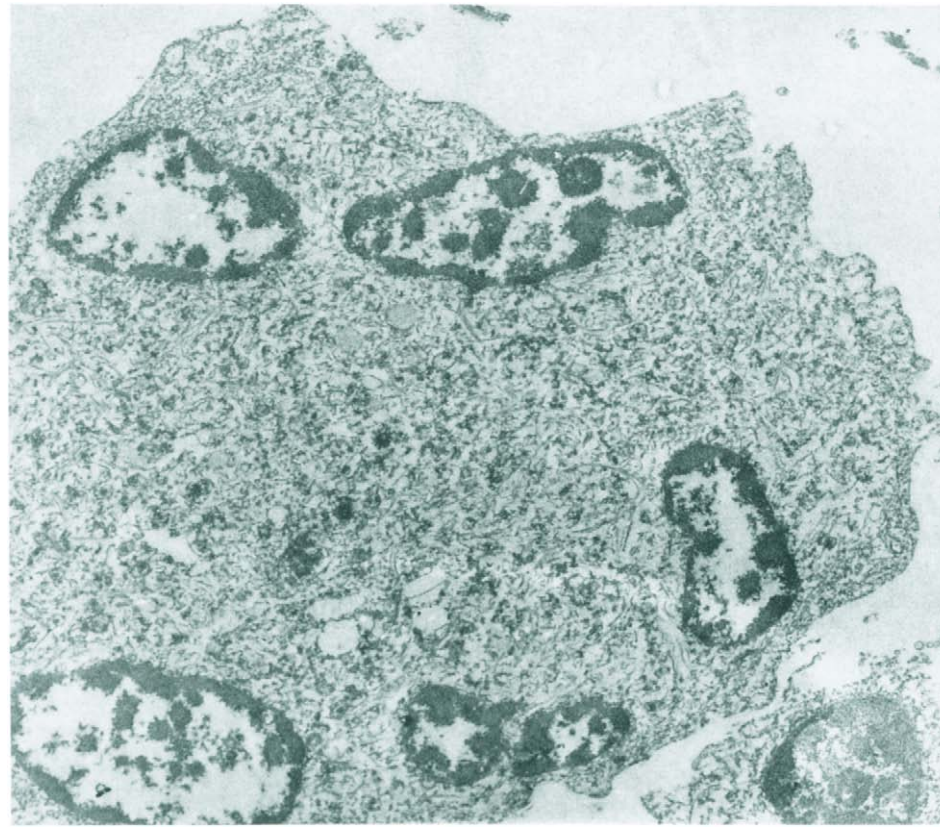


Fig. 96 Infantile form of Krabbe's disease. A multinucleated giant cell in a globoid cell infiltrate, ×3500.

oval, as under the light microscope, in others the cell membrane forms numerous fine pseudopodia that insinuate themselves between surrounding structures. Inclusions are present in the cytoplasm (Fig. 97) which, in longitudinal sections, appear as linear structures, some straight, some curved, and displaying longitudinal striation of 6-nm thickness (Schneider and Haase, 1985). In cross-sections they present a hollow polygonal profile. They have been described as "crystalloid," "tubules with angular profile," "needle and prism-like inclusions," "pleomorphic crystalline structures," and "twisted tubules." In addition, pleomorphic inclusions surrounded by myelin-like membranes may be found in the globoid bodies. Immunogold deposits of RCA-1 and WbA can be demonstrated (Fig. 98).

Hirato *et al.* (1994) found giant lamellar bodies in the Purkinje cell dendrites of their case. They interpreted this finding as a specific reaction of deafferent Purkinje cells. Inclusions are also found in Schwann cells, macrophages, and endoneurial fibroblasts (Fig. 99) in the peripheral nerves (Thomas, 1992).

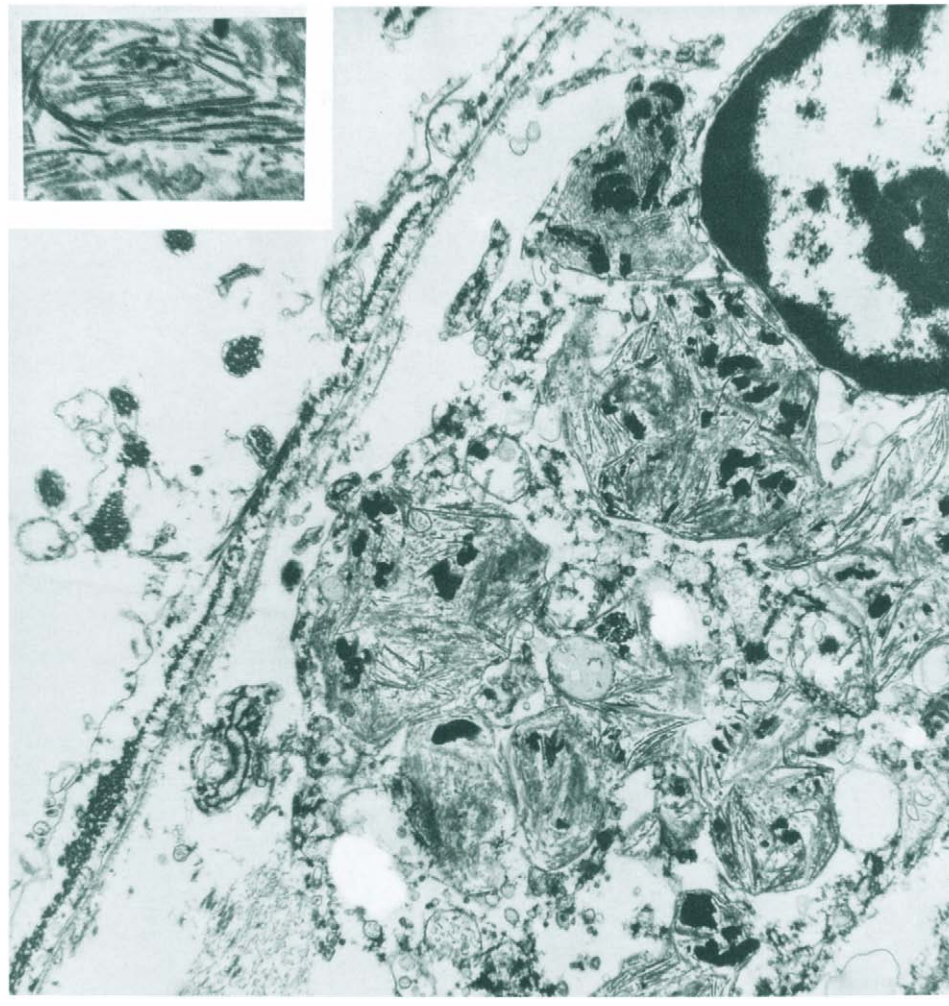


Fig. 97 A globoid cell in a perivascular space. Numerous irregular inclusions surrounded by a limiting membrane, ×6300. (Inset) High magnification of typical needlelike structures, composed of two electron-dense lamellae separated by a thin electron-lucent space, ×16,200. (Reproduced from Figols *et al.*, 1992.)

Juvenile Form

Aside from the classical infantile form, cases with globoid cell formation have been observed from time to time in older patients. Onset in the third year of life was recorded by Collier and Greenfield (1924). Hanfeld *et al.* (1973) confirmed a juvenile case both histologically and enzymologically.

Clinical Picture The later onset of blindness, disturbances of gait, and slowly progressive dementia, on the one hand, and the absence of peripheral neuropathy and of CSF

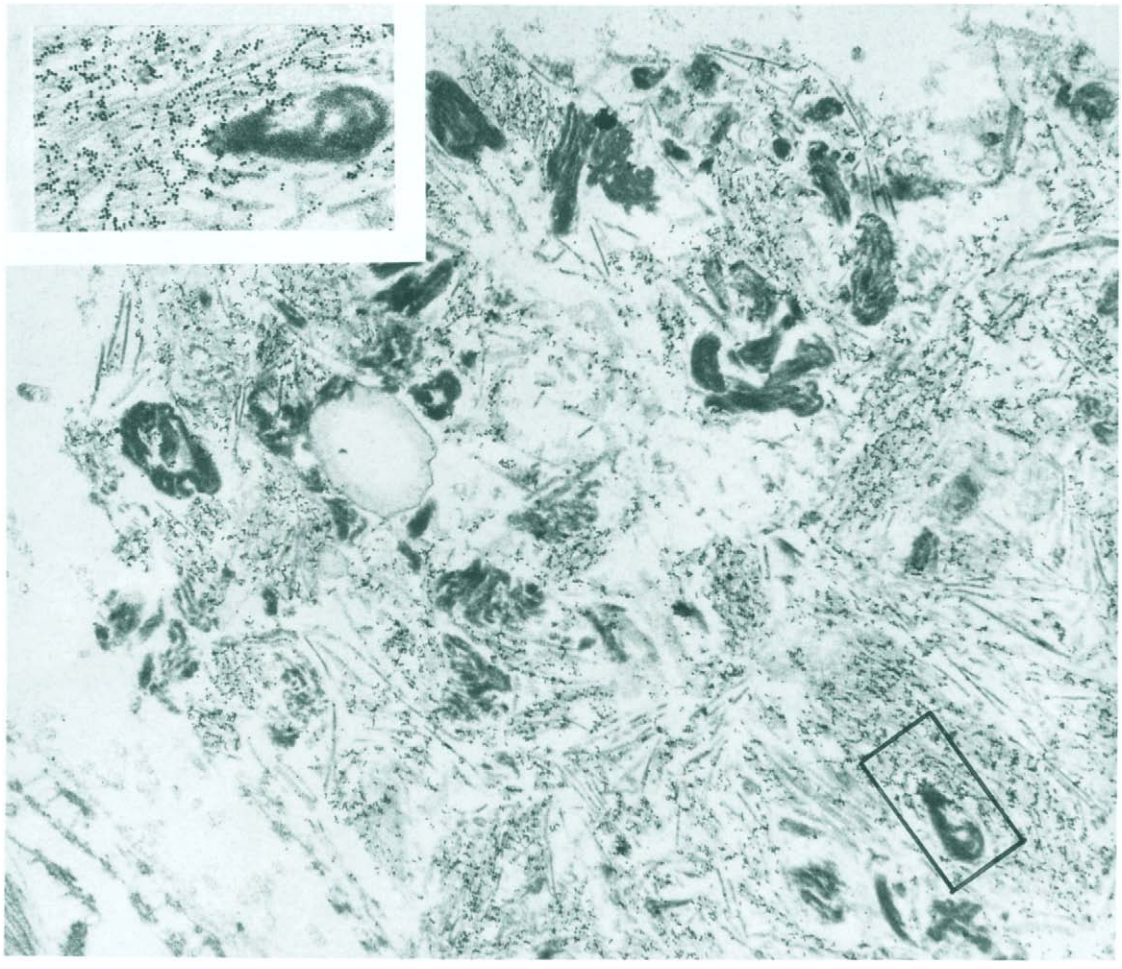


Fig. 98 Cytoplasma of a globoid cell. Selective labeling with wheat germ agglutinin (WGA). Gold-labeled WGA stain, ×12,000. (Inset) Detail of an inclusion of a globoid cell. Gold particles localized in the needlelike spiculae and in the matrix. Gold-labeled WGA stain, ×30,000. (Reproduced from Figols *et al.*, 1992.)

abnormalities, on the other, differentiate the juvenile from the classical infantile form of Krabbe's disease (Lyon *et al.*, 1991; Phelps *et al.*, 1991). Nevertheless, occasional patients with a juvenile course may show signs of a peripheral neuropathy (Goebel *et al.*, 1990; Phelps *et al.*, 1991). Occasionally, the disease may run a remitting course, marked by seizures and ataxia (Goebel *et al.*, 1990). The juvenile form of Krabbe's disease appears to be relatively common in Sicily (Lyon *et al.*, 1991).

Neuropathology The atrophic brain shows definite evidence of demyelination, typical globoid cells, and a conspicuous proliferation of perivascular macrophages. The nests

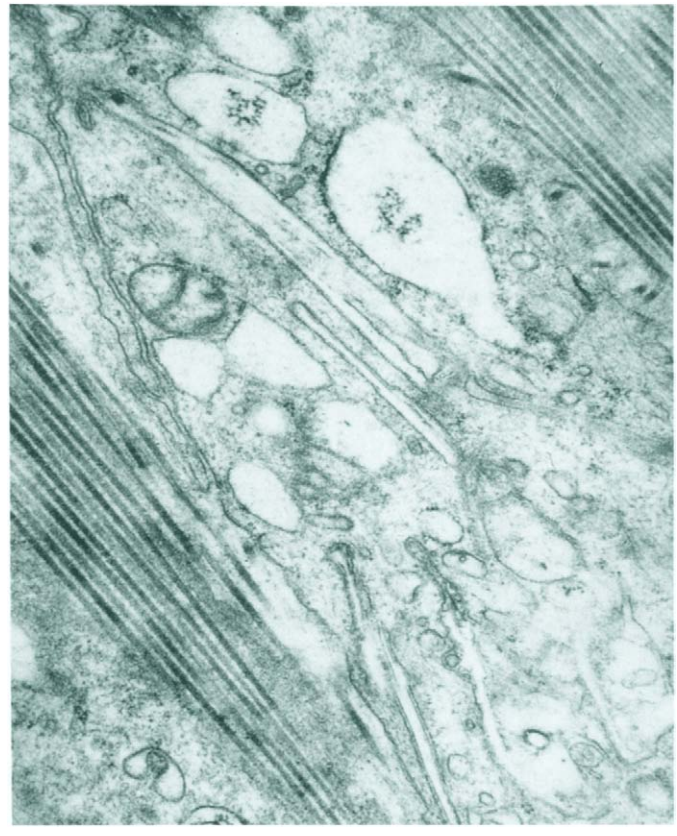


Fig. 99 Krabbe's disease. Typical needle-shaped inclusions in an endoneurial cell, ×32,000.

of globoid cells stain positively with PAS, but weakly with fat stains. They show signs of a high activity of lysosomal enzymes, as demonstrated by acid phosphatase and β-glucuronidase (Hanefeld *et al.*, 1973). In some cases the typical needlelike inclusions may be absent in Schwann cells (Goebel *et al.*, 1990).

Adult Form

Verhaart (1931) first described this disease in adults.

Clinical Picture In a series of late-onset cases, ranging in age from 4 to 73 years, Kolodny *et al.* (1991) found pes cavus, optic disk pallor, progressive spastic tetraparesis, and demyelinating neuropathy. Intellect was preserved in more than half of the cases. The course of the disease may resemble that of multiple sclerosis. In the case of Guillain *et al.* (1944), the cranial nerves were primarily affected. About 2 years before death, the patient developed a right facial palsy, difficulties in swallowing, and disturbances of speech, fol-

lowed by further cranial nerve palsies, cerebellar manifestations, and spastic paraparesis. The disease can masquerade as a spinocerebellar degeneration (Thomas *et al.*, 1984). Clinical evidence of a demyelinating sensorimotor neuropathy was found in some cases (Thomas *et al.*, 1984; Kolodny *et al.*, 1991).

Neuropathology *Light microscopy.* Clearly demarcated foci of demyelination resemble the plaques of multiple sclerosis. These foci are present in Ammon's horn, in the amygdaloid nucleus, symmetrically on the border between the putamen and the pallidum, and in the pons and the medulla oblongata, particularly in the region of the cranial nerve nuclei. Occasionally, cerebellar foci may also be present. The spinal cord was affected only in the case of Verhaart (1931). In all lesions a significant number of globoid cells was seen side by side with astrocytic proliferation, fibrillary gliosis, and a prominent inflammatory reaction. The globoid cells were tightly packed around the blood vessels, forming mulberry-like structures. They show strong positivity in the immunostain for monoclonal antigalactocerebroside (Cruz *et al.*, 1991).

Pathogenesis The disease is inherited as an autosomal-recessive trait and is due to a deficiency of the enzyme cerebroside β-galactosidase (Ellis *et al.*, 1973). The gene coding for the enzyme has been located on chromosome 14q31 (Cannizzaro *et al.*, 1994). A nonsense mutation (GAA to TAA) was found on codon 369 in the coding sequence of cDNA, amplified from mRNA obtained from a patient's fibroblasts (Sakai *et al.*, 1994). This causes an accumulation of cerebroside in the brain. As this cannot be catabolized, it accumulates in perivascular mesodermal cells, which form the globoid bodies.

Lectin and immunohistochemical investigations have shown that globoid cells are fundamentally different from astrocytes and cannot be derived from them (Schröder and Klein, 1984). Vanier and Svennerholm (1976) pointed out that in the myelinization phase a high concentration of psychosin (galactosylsphingosin) appears. This highly toxic substance is, in normal individuals, immediately taken up by lysosomes and broken down. It is a powerful inhibitor of the mitochondrial cytochrome-C oxidase (Cooper *et al.*, 1993). If allowed to accumulate, it destroys the oligodendrocytes and inhibits further myelinization. If a residual activity of galactosylceramidase remains, the stimulus to form globoid cells disappears. These patients can also survive for longer periods.

Gaucher's disease and Krabbe's disease show many morphological and biochemical similarities. The distribution of lesions, primarily in the viscera in the former and exclusively in the nervous system in the latter, accounts for the different clinical symptomatology. The differences between the different forms of Krabbe's disease may possibly be accounted for by different genetic mutations of galactosylceramidase.

Globoid Cell Leukodystrophy in Animals Leukodystrophy of the Krabbe type has been observed in dogs (Johnson *et al.*, 1975) and cats (Johnson, 1970). The ultrastructural changes (Yajima *et al.*, 1977) and the enzyme deficiency (Suzuki *et al.*, 1974) correspond with those seen in the human disease. A mouse mutant (*twitcher*) also closely resembles the human Krabbe-type leukodystrophy (Suzuki, 1994b).

Gaucher's Disease (Glucosylceramidase Deficiency)

Gaucher's disease was the first lipidosis to be described. Admittedly, Gaucher (1882) himself did not recognize the nature of the disease, and ascribed the splenomegaly to neoplasia. Marchand (1907) first attributed the cellular changes to storage of foreign material.

According to the clinical course, two types were originally recognized, the infantile and the adult, with genetic differences between them. The discovery of an intermediate juvenile type led to the present classification:

Type 1: Chronic adult form
Type 2: Acute, malignant, infantile form with neurological symptoms
Type 3: Subacute juvenile form with neurological symptoms

This arrangement facilitates the allocation of individual cases, even if it does not rest on a sound biological foundation (Erikson, 1986).

Type 1 (Chronic, Adult, Nonneuropathic Form)

Type 1 is the most common form of the disease. In the United States there are about 5000 patients with this classical form of Gaucher's disease. The rarity of neurological symptoms qualifies this form as nonneuropathic, although intracerebral reticuloendothelial elements may participate in the process and may be indistinguishable from Gaucher cells in other organs.

Clinical Picture Hepatosplenomegaly and a raised level of acid phosphatase in the serum are constant features. Another typical feature is the presence of ochre–yellow or brown slightly raised patches in the conjunctiva. The skin shows, in most cases, a yellowish, bronzed, or lead gray pigmentation, most obvious in parts exposed to light. It is rarely symmetrical and may also affect the mucous membranes.

In the rare cases with neurological manifestations, these appear in the late stages of the disease, many years after the onset of the typical visceral and bony changes (McKeran *et al.*, 1985). Hypertonia, hyperreflexia, myoclonus, and dementia are the main symptoms. McKeran *et al.* (1985) also noted a tapetoretinal degeneration in one patient. Psychotic manifestations predominate in some patients (Neil *et al.*, 1979). Two siblings without previous neurological symptoms developed glioblastomas (Lyons *et al.*, 1982). Compression of the spinal cord may be caused by vertebral involvement (Neau *et al.*, 1993). The adult type of Gaucher's disease occasionally may manifest itself in childhood or adolescence.

Pathology *Gross appearances.* The liver and the spleen are enlarged. The surface of the spleen is knobby. The cut surfaces of the spleen, liver, lymph nodes, and bone marrow present a variegated appearance due to the juxtaposition of transparent foci for Gaucher cells with areas of necrosis, hemorrhage, and fibrosis.

Light microscopy. Abundant storage cells are seen in the spleen (Fig. 100) and the liver. In the liver the histiocytes of Glisson's capsule and the adventitial cells of both arteries

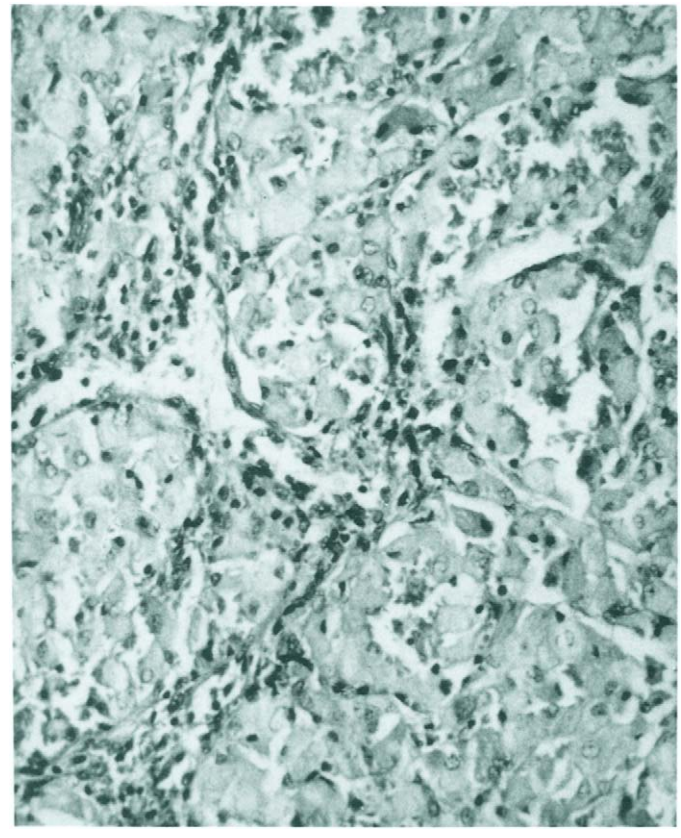


Fig. 100 Gaucher's disease. Gaucher cells in the spleen, ×200.

and veins are involved in the process. The Gaucher cells are between 20 and 100 μm in diameter. In unfixed preparations their cytoplasm appears homogeneous and hyaline. Multinucleated cells are not uncommon. The pale yellow cytoplasm is surrounded by a network of fibers of various lengths and thicknesses. Histochemically, the contents of the cells consist of cerebroside–protein complexes. Two cell types may be distinguished: type I, the typical Gaucher cell, has a fibrillary structure; type II has a granular or amorphous cytoplasm. One cell type may transform into the other as a result of the crystallization of cerebrosides (Elleder, 1992a,b). Small quantities of neutral fat can be demonstrated with oil red O. A negative Schiff reaction points to the absence of unsaturated fatty acids, but the PAS reaction is positive. A high activity of acid phosphatase has been mentioned repeatedly.

Thickened nodules and strands, consisting of Gaucher cells, are found in the lung parenchyma. Gaucher cells may also appear in the sputum. The pigmentation of the skin is due mainly to melanin, with an admixture of fatty pigments and hemosiderin. The con-

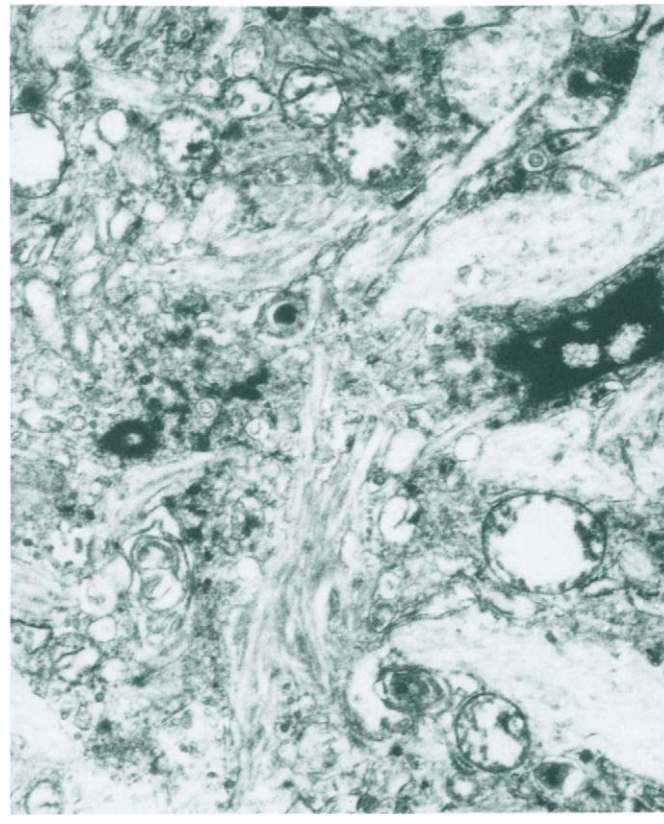


Fig. 101 Same case shown in Fig. 100. Convoluted needle-shaped inclusions in a Gaucher cell. Original magnification ×29,000. (Reproduced from Cervós-Navarro and Goebel, 1989.)

junctival patches consist predominantly of Gaucher cells. Gaucher cells can be found in the myocardium, thyroid gland, and thymus. They form nests and well-demarcated foci. A phenocopy of Gaucher cells has been observed in macrophages of the bone marrow, liver, and spleen in patients with chronic leukemia.

Electron microscopy. Characteristic inclusions are present in the cytoplasm (Fig. 101). They consist of tubular structures embedded in a pale matrix (Elleder, 1992a,b). Their diameter ranges from 12 to 75 nm and varies from cell to cell. They may be up to 5 μm. Each tubule contains 10–12 fibrils, wound around in the form of a dextroverted helix. The distance between the fibrils is about 8 nm. It is possible to produce typical Gaucher cells in tissue cultures by adding glucocerebrosides to the medium.

Biochemically, the tubular structures consist of protein (10%), cholesterol (10%), phospholipids (10%), and glycolipids (70%).

Neuropathology *Light microscopy.* Sleeves of cells are arranged around arterioles, capillaries, and venules. The cells have round, most eccentric, nuclei, a broad cytoplasm with a round or polygonal profile, and a foamy or striated appearance. They are PAS positive. They are accompanied by a proliferation of collagen fibers. Gaucher cells may also be seen in the neurohypophysis and the hypothalamus.

Electron microscopy. The perivascular cells show the characteristic tubular structures of Gaucher cells (Soffer *et al.*, 1980).

Type 2 (Acute Malignant Form with Neurological Symptoms; Cerebral Form; Infantile Form)

The first clinical observation of this form was that by Rusca (1921). Oberling and Woringer (1927) defined the condition on the basis of their clinical and morphological observations of four siblings. De Lange (1940) coined the term *malignant form of Gaucher's disease.*

Clinical Picture Hepatosplenomegaly may appear soon after birth, but is generally not obvious until the age of 3–5 months. Retarded growth, feeding and swallowing difficulties, and loss of weight are prominent symptoms. These are followed by paralysis of external ocular movements, generalized rigidity with opisthotonos, laryngospasm, dysphagia, and vomiting. Trismus, spasticity with bent arms, and generalized seizures develop in severe cases as an expression of brain stem and extrapyramidal lesions. Mental retardation to the level of total idiocy completes the picture. Skin pigmentation and conjunctival patches are rare in type 2. Superficial lymphadenopathy, on the other hand, is far more common than in the other forms. Neonatal ichthyosis was reported by Lui *et al.* (1988). The children die by the age of 2 years of respiratory paralysis or aspiration pneumonia as a result of pseudobulbar palsy.

Pathology *Gross appearances.* A massive hepatosplenomegaly is present in all cases. The cut surface of the liver, spleen, and lymph nodes show a gray discoloration, which is also focally apparent in the lungs and the vertebral bodies.

Light microscopy. Gaucher cells are seen in all affected organs. They are particularly abundant in the liver and the spleen and may also be present in the adrenal cortex. Type 2 is generally free of bony and cutaneous involvement (Oberling and Woringer, 1927).

The main biochemical features in all three types is the accumulation of monohexose ceramide in the internal organs, which may reach levels 700 times that of normal values.

Neuropathology *Gross appearances.* The unremarkable brain may be slightly underweight.

Light microscopy. Some ganglion cells may be swollen; others are shrunken or deformed. They may occasionally contain PAS-positive material (Norman *et al.*, 1956; Banker *et al.*, 1962). The degeneration of Nissl bodies is striking (Oberling and Woringer, 1927). Parenchymal damage with neuronal loss and neuronophagia is found in the deeper cortical layers, thalamus, basal ganglia, brain stem, and cerebellum, affecting both Purkinje cells and the dentate nucleus, as well as in the spinal cord (Grafe *et al.*, 1988).

Changes are also present in the subcortical and central white matter, most pronounced in the occipital lobes (Leech *et al.*, 1985; Kaye *et al.*, 1986), but occasionally in the frontal lobes (Grafe *et al.*, 1988). The basal ganglia and the brain stem are less commonly affected. Several authors have drawn attention to the degeneration of the superior cerebellar peduncles, secondary to the cell loss in the dentate nucleus (Norman *et al.*, 1956).

In the earlier publications only parenchymal lesions were mentioned. Debré *et al.* (1951) were the first to draw attention to the proliferative changes in the adventitia of intracerebral and meningeal blood vessels. These observations were amply confirmed by subsequent authors (e.g., Hernandez and Bueno, 1973). The adventitial cells are swollen and contain PAS-positive material. Typical Gaucher cells with a striped cytoplasm are scattered among the adventitial cells. Endothelial cells may also be involved. A heterotopic gliosis in the adventitia of blood vessels and in the leptomeninges has been reported.

Electron microscopy. The adventitial cells (Fig. 102A and B) contain typical tubular structures in their cytoplasm, as well as spindle-shaped inclusions and isolated tubules in a finely granular matrix (Cervós-Navarro and Zimmer, 1990) (Fig. 102C). Inclusions with parallel membranes, resembling zebra bodies, were far less common than Gaucher-type structures in the neuronal cytoplasm (Hernandez and Bueno, 1973; Leech *et al.*, 1985).

Biochemically, early authors could not demonstrate any deviation in the normal lipid spectrum in the brains of patients with type 2. Svennerholm (1967), however, found an increase in glucocerebrosides in the brain. These contain C_{20} sphingosine and large quantities of C_{18} fatty acids. On the other hand, galactocerebrosides are reduced in proportion with the progressive demyelination.

Type 3 (Subacute Juvenile Form with Neurological Deficit)

Type 3 is an uncommon form, although the first case was already described by Evans in 1916. Even before the identification of the deficient enzyme, several further cases were reported (Maloney and Cumings, 1960). In spite of this, doubts were expressed about the existence of form 3. The condition has been subdivided into two subtypes: 3a and 3b (Brady *et al.*, 1993). Patients of subtype 3a have mild to moderate hepatosplenomegaly and slowly progressing neurological deterioration. Those with 3b have prominent hepatosplenomegaly, but the only neurological sign is supranuclear horizontal gaze paresis. A subgroup of type 3 was reported by Hillborg (1959) in a cluster of patients from the Norrbotten Province in Sweden. The characteristic features of this group consisted of a congenital oculomotor apraxia and the frequent occurrence of retinal infiltrates.

Clinical Picture Generalized and myoclonic seizures are often the first symptoms (Maloney and Cumings, 1960). Conspicuous disturbances in external ocular movements have been described. Neurological symptoms may appear in early childhood or later. Although the general course of the disease resembles that of type 2, it exhibits certain peculiarities. Aside from strabismus, trismus, laryngospasm, and dysphagia, symptoms include cerebellar disturbances of coordination, hyperkinesia, and hyperreflexia as well as difficulties in speech and writing. A tapetoretinal degeneration may accompany the neurological symptoms (McKeran et al, 1985). There may be a striking rigidity of facial expression. Behavioral disturbances may amount to psychotic episodes. Intellectual deterio-

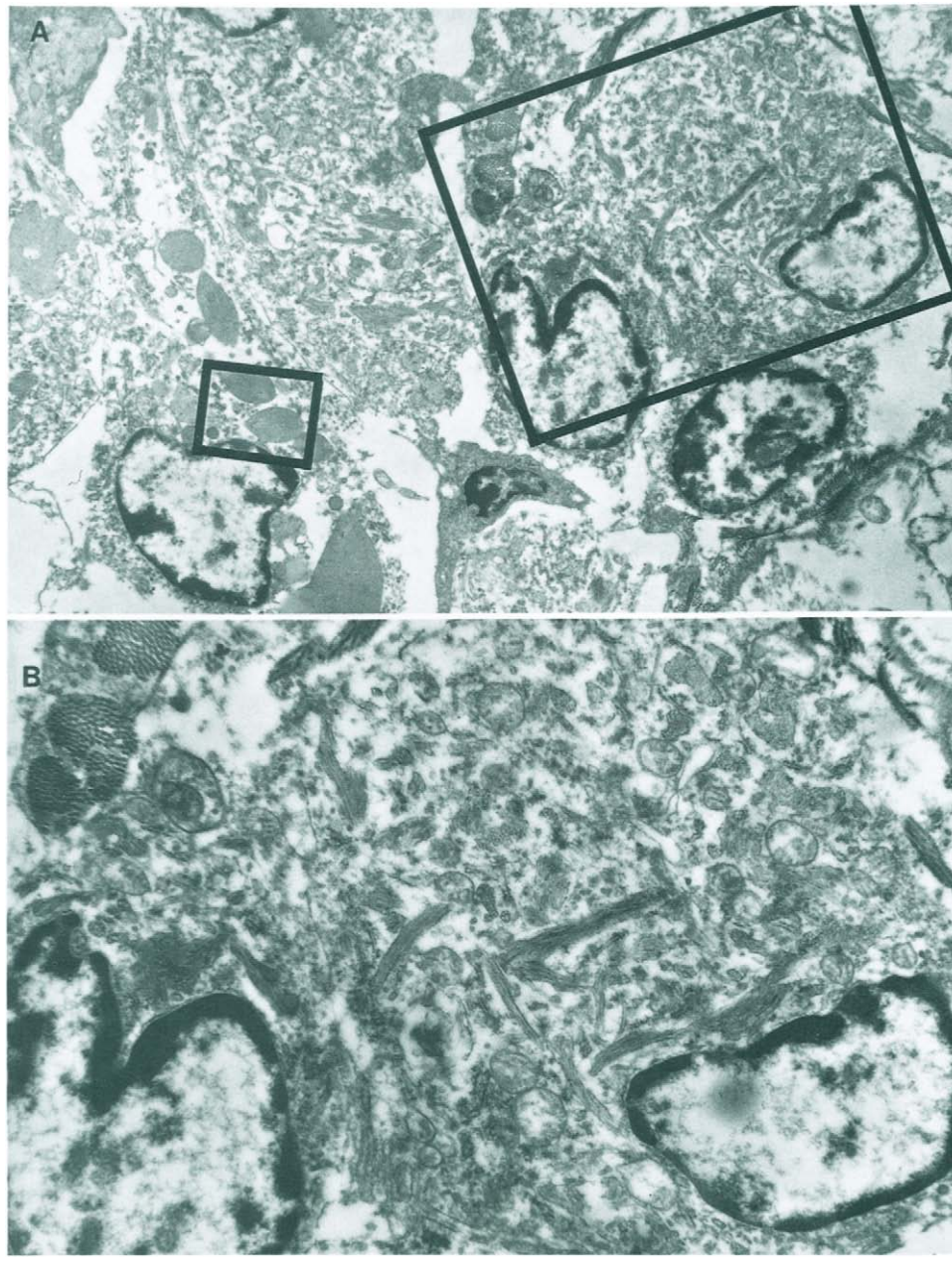


Fig. 102 Acute malignant form of Gaucher's disease. Adventitial cells of a venule in the frontal cortex. (A and B) Elongated and tubular structures in the cytoplasm, (A) ×2500 and (B) ×8000. (C) An inclusion with finely granular matrix and scattered tubules, ×40,000.

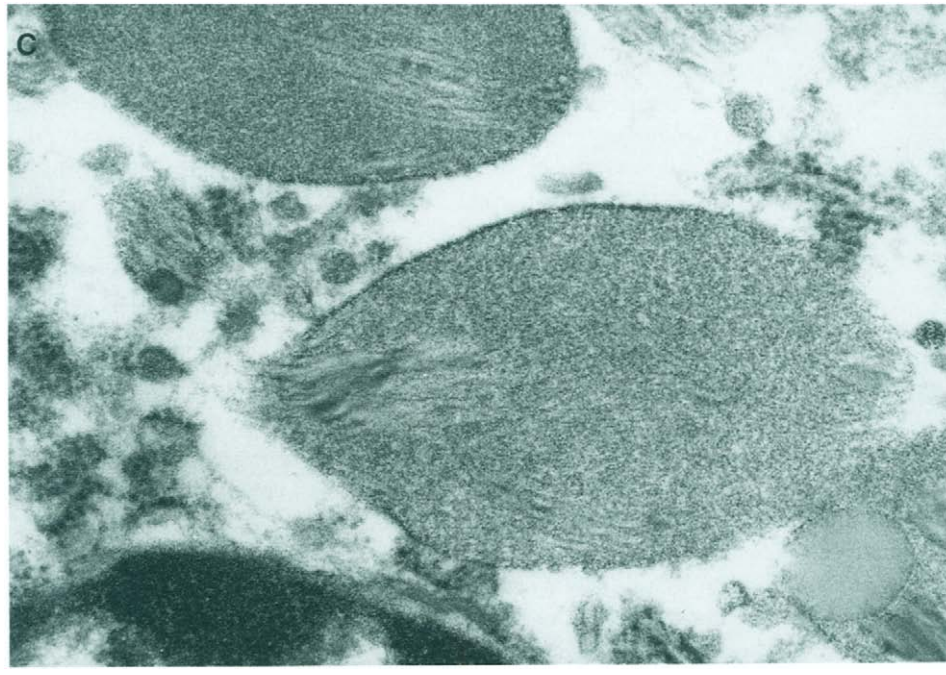


Fig. 102 Continued.

ration develops rapidly and ends in a profound dementia. Most patients die in later childhood, but some reach the age of 30 years. Splenectomy may cause deterioration of the patient's condition and accelerate the progress of the disease (Kyllerman *et al.*, 1990).

Pathology *Gross appearances.* Skeletal abnormalities affect preferentially the phalanges of the fingers and the toes, the mandible, and, to a lesser extent, the long bones, vertebrae, and pelvis. Splenomegaly is conspicuous (Maloney and Cumings, 1960).

Light microscopy. The splenic pulp is infiltrated with lipid-laden histiocytes. Similar cells can be found in the lungs, less so in the liver and the bone marrow. Galactocerebroside storage may occur outside the nervous system (Maloney and Cumings, 1960). Dihexoseceramides and glycoproteins (Elleder and Jirasek, 1981) may also be stored.

Neuropathology *Light microscopy.* Ballooning of the neurons is apparent, particularly in the brain stem (Brain, 1954).

The stored substances do not stain with lipid stains. Some are weakly PAS positive, but many, particularly in the most distended cells, are PAS negative. In many areas a definite loss of nerve cells may be observed, accompanied by gliosis (Maloney and Cumings, 1960). The glucocerebrosides are not increased in the brain (Svennerholm, 1967). On the other hand, there is an increase in dihexoseceramides.

In the Norrbotten type glycosylceramide accumulates in the adventitial cells of blood vessels in the cerebral and cerebellar white matter. Zones of demyelination surround the

aggregations of perivascular storage cells. The neuronal loss–in places, accompanied by neuronophagia or satellitosis–varies from case to case. Histochemically, lipofuscin and complex lipid, but no glycolipids, can be demonstrated in the neurons. Dense gliosis can also be seen around the Gaucher cell infiltrates. In a child presenting with oculomotor apraxia, myoclonus, and prominent bulbar signs, Conradi *et al.* (1991) found an accumulation of Gaucher cells in lamina IV of the cerebral cortex, in the thalamus, and in the brain stem. A focal loss of granule cells and a total loss of neurons in the dentate nucleus were found in the cerebellum.

Electron microscopy. Double membrane-bound inclusions are seen in neurons of the cerebral cortex, dentate nucleus, and pons in the Norrbottnian type. The perivascular cells show granular deposits reacting with antibodies to muramidase and α-antichymotrypsin. They are surrounded by a reticulin network that stains with antibodies to collagen types III and IV and laminin (Conradi *et al.*, 1988).

Pathogenesis The chemical nature of the lipids stored in Gaucher's disease was recognized by Lieb (1927) as the cerebroside kerasin. Further and more complete analyses of the internal organs were carried out by Klenk (1940).

The first step in the degradation of glucocerebrosides is a hydrolytic cleavage of the β-glucopyranoside link. This is catalyzed by the hydrolase β-glucosidase, the activity of which is considerably reduced in Gaucher's disease. As a result of this enzyme deficiency, glucocerebrosides accumulate in the tissues. In addition, there are activators of glucosylceramidase which are not specific for this enzyme, however (Christomanou *et al.*, 1986).

Aside from possibly locally formed cerebral glucosylceramidases, the main source of this enzyme is leukocytes and erythrocytes. By their shedding, sphingolipids and gangliosides are attacked and glucocerebrosides are formed. The pathological accumulation of glucocerebrosides leads to the transformation of cells with a high phagocytic potential. The storage of pure glucocerebrosides, or galactocerebrosides, in Gaucher's disease explains the different appearance of the inclusions from those of the gangliosidoses (Terry, 1971).

The brain reacts somewhat differently from the extracerebral organs. Svennerholm (1967) suggested that cerebral glucocerebrosides could be a product of the hydrolytic breakdown of some gangliosides. The reduced activity of glucosylceramidase and a disturbed biochemical balance would then lead to an accumulation of glucocerebrosides within the neurons. The differences in the maturity of neurons and their reaction to the accumulating products would explain the differences between types 2 and 3, in that the more mature neurons in the juvenile type could deal with the pathological storage for longer periods. The activities of aryl-β-glucosidase and β-xylosidase are far more reduced in late infantile than in adult cases. Increased activities of β-hexosaminidase and mannosidase in type 2 were reported by Chitayat *et al.* (1987).

The glucosylceramides taken up by macrophages in the CNS appear to consist partly of a neuronal component and partly of a component originating in other parts of the body. The fact that psychosin is present in a higher concentration in the gray matter than in the white matter supports the neuronal origin of the stored substance. In type 2 there is good correlation between the organic lesions and the functional deficits. The rapid clinical course corresponds with the progressive destructive process. There are divergent opinions about the nature of the parenchymal damage. Norman (1958) suggested that in acute cases the metabolic

disorder is so overwhelming that the neurons die before the storage becomes apparent. In the more slowly progressive cases intraneuronal storage may develop. In an intermediate group, as illustrated by Norman *et al.* (1956), both types of lesions may exist side by side. In fact, these lesions are obvious in the most acute cases.

The disease occurs worldwide, with a high prevalence of type 1 among Ashkenazi Jews. All types are inherited as autosomal-recessive traits. The structural gene for glucosylceramidase has been localized in chromosome 1q9.21–9.32 (Devine *et al.*, 1982; Ginns *et al.*, 1985). Over 35 mutations have been documented (Beutler, 1993). These include missense and nonsense point mutations, splicing mutations, deletions and insertions, a fusion gene, and examples of gene conversion. In type 1 the most common abnormality in Ashkenazi Jews is the 1226 mutation (Zimran *et al.*, 1991). A single base mutation (adenosine to guanidine) in exon 99 with an N-to-S substitution has been found in the same ethnic group (Isuji *et al.*, 1988). In two Israeli brothers two mutated alleles were found (Levy "AA" 1991). One allele had a G-to-C transversion at nucleotide 3119 (N to H at set 140). The other had two base pair changes: A to C at nucleotide 3170 (K to G at position 157) and G to A at nucleotide 5309 (Q to K at position 324). In neuropathic Gaucher's disease (types 2 and 3) the most common mutation is that of L to P at point 444 (Tsuji *et al.*, 1987; Patterson *et al.*, 1991), although it is not always associated with neurological involvement. A case of an L-to-P mutation at position 444 without neurological symptoms was reported by Glew *et al.* (1991). Patients with an S-to-N substitution at amino acid 370 do not develop neurological symptoms (Patterson *et al.*, 1993). The mutation in Norrbottnian patients is remarkably constant and consists of a single base substitution in exon 10 of the glucosylceramidase gene (Svennerholm *et al.*, 1991).

Gaucher's Disease in Animals Hartley and Blakemore (1973) described neurovisceral storage of glucocerebroside in a Sydney silky terrier.

Ceramidase Deficiency (Disseminated Lipogranulomatosis; Farber Disease)

Farber *et al.* (1957; Farber, 1952) described altogether three cases of disseminated lipogranulomatosis as a specific entity. A combination with β-hexosaminidase deficiency (see p. 327) was reported by Roggendorf *et al.* (1987).

Clinical Picture In the first, infantile, form the patients show general marasmus and swollen joints a few months after birth. Later, firm skin granulomas develop, freely mobile in relation to the surrounding tissues. Aphonia is a common symptom. Finally, severe dyspnea, hepatosplenomegaly, lymphadenopathy, and cardiac symptoms supervene. The psychomotor development is severely impaired from an early stage. A few months after the onset of symptoms the patients lie in bed immobile and apathetic. Death occurs between the ages of 1 and 2 years.

In a second group the symptoms appear later and are less pronounced. In these cases with a protracted course, the patients may survive into the second decade. An intermediate form was described by Burck *et al.* (1985).

Pathology *Gross appearances.* The granulomatous deposition of stored substances leads to enlargement of the tongue and the vocal cords. Granulomas are present in the tendons and in the capsules of major joints. The liver is enlarged.

Light microscopy. The walls of arteries, particularly the coronary vessels, contain mucoid substances and cellular infiltrates in the intima and the media, with splitting of the elastic lamina. The basement membrane of the renal glomeruli is thickened. In the periportal areas of the liver, solid masses surround the blood vessels. The nodules in the tongue, vocal cords, and skin consist of homogeneous masses, staining weakly with glycogen stains and positively with PAS. In the joints and the tendons the deposits are accompanied by cellular infiltrates, consisting of lymphocytes, histiocytes, and foam cells.

Electron microscopy. The hepatocytes contain both electron-lucent and electron-dense inclusions. The endothelia of the skin vessels contain zebra bodies (Fusch *et al.*, 1989). Kuppfer's cells and the histiocytes of the skin, thymus, and lungs contain, aside from clear banana bodies (Fig. 103), osmiophilic inclusions with curvilinear tubules (Burck *et al.*, 1985).

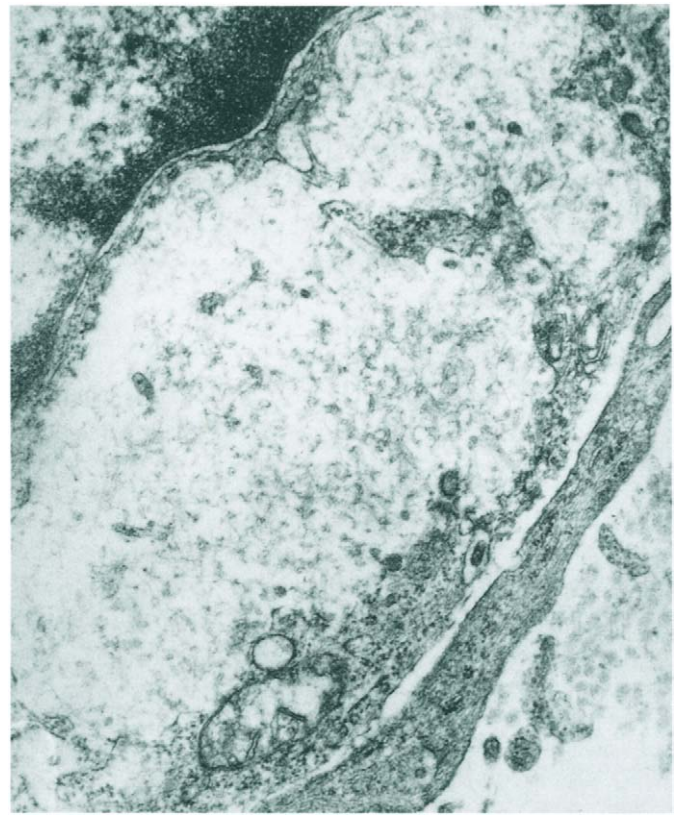


Fig. 103 Farber's disease in the skin. A large lysosomal vacuolar inclusion body in a histiocyte. (Courtesy of H.-H. Goebel, Mainz, Germany.)

Neuropathology *Gross appearances.* The brain may appear normal (Moser *et al.*, 1969) or may show moderate to severe atrophy with internal hydrocephalus.

Light microscopy. Loss of neurons, particularly in the second and third layers, and astrocytic proliferation are characteristic lesions in the cerebral cortex (Rivel *et al.*, 1977). Fibrillary gliosis and microglial proliferation are seen in the subcortical white matter. Demyelination of the internal capsule and the pyramidal tracts is found occasionally (Rivel *et al.*, 1977). Cerebellar cortical lesions in the form of swelling of the molecular layer, a partial loss of Purkinje cells, and, frequently, rarefaction of the granular layer can be found.

From cortical to spinal regions, some neurons show increasing storage of glycolipid. These neurons are rarely seen in the allocortex, and are more frequent in the isocortex and the basal ganglia. In the substantia nigra, the oculomotor nuclei, and the subthalamic nuclei large numbers of ballooned cells can be seen (Rivel *et al.*, 1977). The nuclei of the pons and the medulla oblongata are equally affected. The Purkinje cells are stuffed with stored substance, but are less expanded than other storage cells. The neurons of the spinal cord, particularly the anterior horn cells, are ballooned by the stored substance (Fig. 104). The Nissl bodies have largely disappeared and the cytoplasm is filled with a finely granular substance, staining weakly with hemalum and with PAS, but positively with alcian blue.

In some neurons the stored substance occupies only part of the cytoplasm, forming a sector extending from the surface to the centrally placed nucleus. In sections stained with H&E, a colorless strip is clearly demarcated from the eosinophilic cytoplasm. In most cells, however, the eosinophilic cytoplasm has largely disappeared, the nucleus is dis-

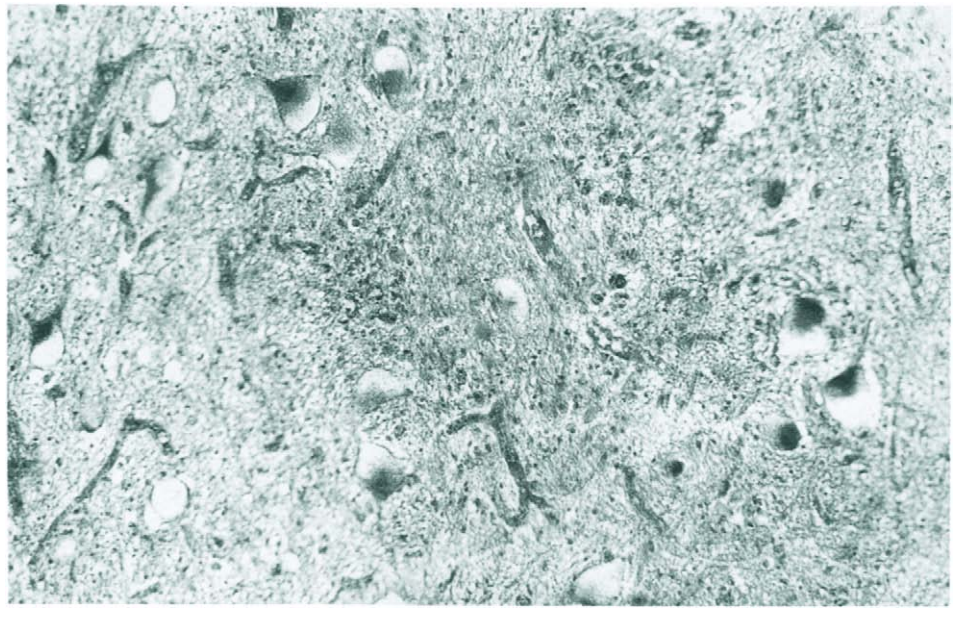


Fig. 104 Farber's disease. Marked ballooning of the anterior horn cells in the spinal cord, ×500. (Courtesy of C. Vital, Bordeaux, France.)

placed toward the apical dendrite, and the cell body is enlarged, rounded, and filled with storage material.

The cytoplasm of the retinal ganglion cells is expanded and filled with birefringent material (Zarbin *et al.*, 1985). The cells of the autonomic nervous system show a variable degree of storage. The cells of Auerbach's plexus in the gut are clearly enlarged and filled with storage material, and their nuclei are pyknotic and displaced to the periphery. In peripheral nerves some Schwann cells are expanded (Chanoki *et al.*, 1989), and the capillaries are surrounded by clumps of a weakly basophilic deposit. The endoneurium appears wide and filled by elongated deposits separating the fibers.

Electron microscopy. Zebra bodies are present in the endothelia of the cerebral and cerebellar blood vessels, and occasionally also in the neurons (Zarbin *et al.*, 1985). In the Schwann cells of skin nerves, Zappatini-Tommasi *et al.* (1992) observed banana-shaped inclusions up to 1.6 μm long and 0.2 μm wide. Similar inclusions in Schwann cells (Fig. 105) were illustrated by Rivel *et al.* (1977). Schmoeckel and Hohlfeld (1979) described them as "spindle-shaped bodies"; Burck *et al.* (1985), as needlelike inclusions. The homogeneity and the localization of the banana bodies have never been documented in other spingolipidoses.

Pathogenesis Farber *et al.* (1957) interpreted this condition as a link between the histiocytoses and the inborn errors of metabolism. It has since been shown that it is, in fact, a neurolipidosis with autosomal-recessive transmission. The enzymatic defect concerned is a lack of an acylsphingosine deacylase that carries out hydrolysis of ceramide into sphingosine and fatty acids.

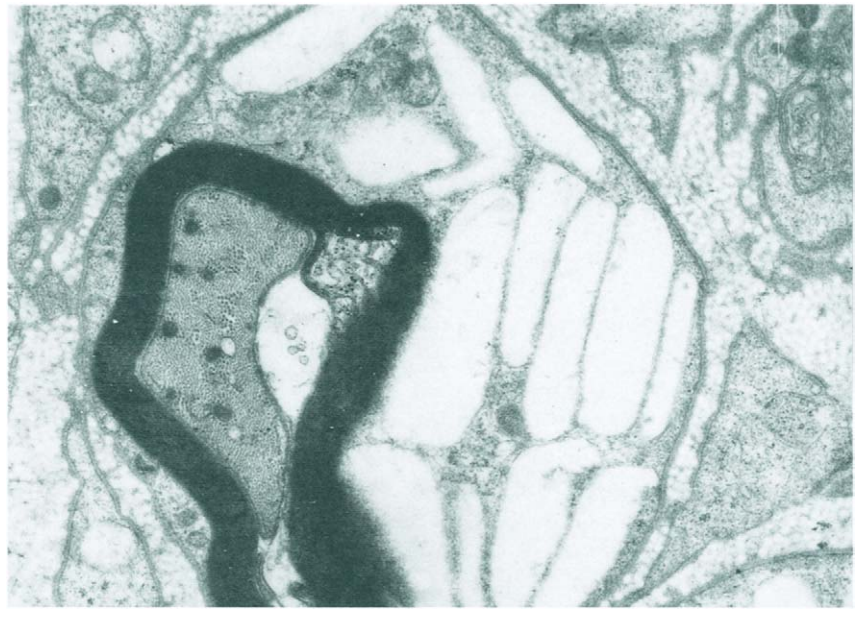


Fig. 105 Same case shown in Fig. 104. The sural nerve, showing banana-shaped inclusions in a Schwann cell, ×9000.

The participation of the neurons in the storage process was decisive for classification of the disease among the metabolic disorders. Moser et al. (1969) were the first to demonstrate ceramide in the stored material. Sugita *et al.* (1972) showed deficient activity of the lysosomal acylsphingosine deacylase.

The ceramidase deficiency leads to an accumulation of ceramide in the cytoplasm. The storage of gangliosides and other glycolipids is secondary and is due to the fact that ceramide is involved in the degradation of these lipids. The formation of granulomas and the histocytic reaction are secondary to the accumulation of ceramide and can be reproduced experimentally (Moser *et al.*, 1969). The neuronal storage is caused by a high ceramide turnover in the nervous system. The curved tubular profiles seen on electron microscopy resemble, but are not identical to, those seen in Gaucher's disease. The reason for this is that the glucocerebroside of Gaucher's disease differs from ceramide only by an additional glucose molecule. Also, the galactocerebroside, which accumulates in Krabbe's disease, forms similar needle-like inclusions in Schwann cells, resembling the ceramide of this cell population.

The variable clinical expression of the disease has not yet been explained. There is no correlation between the degree of the enzyme deficiency and the severity of the symptoms.

Globotriosylceramidosis (α-Galactosidase A Deficiency; Fabry's Disease; Anderson-Fabry Disease; Angiokeratoma Corporis Diffusum)

This disease was described in its dermatological manifestations by Fabry (1898) as "purpura haemorrhagica nodularis" and by Anderson (1898) as "angiokeratoma." The first description of neurological symptoms was published by Archer (1927). Opitz *et al.* (1965) established the incomplete sex-linked recessive mode of inheritance.

Clinical Picture In male monozygotes the disease manifests itself in childhood or adolescence by the presence of cutaneous angiokeratomas that increase in number and size with time, as well as by burning pains in the hands and the feet. Variants without angiokeratomas occur occasionally. Angiokeratoma corporis diffusum has been reported in various other enzyme deficiency disorders, including fucosidosis, GM_1 gangliosidosis type 1, aspartylglycosaminuria, and sialidosis (Sashamma and Graham-Brown, 1994). With increasing age renal failure and cardiovascular insufficiency supervene, being the common causes of death.

The neurological symptoms usually appear after the age of 20 years in the form of fleeting ischemic episodes, causing hemiplegia, aphasia, or cerebellar symptoms. In later stages the deficits fail to regress. Dementia has been observed occasionally. The absence of sweating, sometimes recorded as the first symptom of the disease, is a reflection of changes in the autonomic nervous system. Abnormalities of cutaneous thermal sensation are common, with unique predilection for cold sensitivity (Morgan *et al.*, 1990). The fluctuating course of the neurological disorder may lead to an erroneous diagnosis of multiple sclerosis. An exceptionally early onset of neurological symptoms in the second year was reported by Schröder (1984). Vascular disorders and orthostatic hypotension are rare (Mutoh *et al.*, 1988; Inagaki *et al.*, 1992). Cardiac and renal insufficiencies may develop

in advanced age. MRI reveals multiple focal lesions in males, both with and without overt cerebrovascular disease. Such abnormalities are not detected in female carriers (Morgan *et al.*, 1990).

Female heterozygotes display less pronounced symptoms, such as clouding of the cornea, occasional paresthesias, and other neurological symptoms.

Pathology *Gross appearances.* The heart valves and the papillary muscles are thickened. Occasionally, myocardial hemorrhages and necroses have been seen.

Light microscopy. Lipid storage is found in fibroblasts of the heart valves and in myocardial cells. The vascular endothelia and the smooth muscle cells are also laden with lipid inclusions, leading to stenosis of the lumen, as well as vascular dilatation in cutaneous angiokeratomas. Lipid storage is prominent in the renal glomeruli, as well as the proximal and distal tubules. It is also seen in the epithelial cells of the cornea. The inclusions stain positively for acid phosphatase.

Electron microscopy. The inclusions show a concentric multilamellar structure with a periodicity of 6–7 nm. In freeze-fractured specimens the multilamellar deposits exhibited a large periodicity of 14–15 nm (Simon *et al.*, 1990). Muscle cells, renal and other epithelia, and, above all, vascular endothelia contain pleomorphic inclusions (Fig. 106), some in the form of zebra bodies.

Neuropathology *Gross appearances.* The leptomeninges, particularly of the convexity, are thickened. The basal vessels show pronounced arteriosclerotic changes. The gyri are moderately atrophic, particularly in the frontal lobes. Extensive infarcts have also been described.

Light microscopy. On light microscopy the severe involvement of all blood vessels is confirmed. In the leptomeningeal arteries the endothelia are swollen and finely vacuolated. The intima is thickened and interspersed with macrophages and collagen fibers. Degeneration of the elastic lamina may be present. The smooth muscle cells of the media are also vacuolated.

Similar changes in the intracerebral arterioles, capillaries, and venules may lead to vascular occlusion. Vascular tangles are frequently seen. The material stored in the vacuoles stains with Sudan black, orthochromatically with thionin, intensely with methylene blue, and weakly with PAS. Part of the storage material shows a yellowish green autofluorescence under ultraviolet light. Storage is also present in the leptomeningeal cells, and a chronic meningitis has been described (Dubost *et al.*, 1985).

Even in cases in which no infarcts are seen macroscopically, numerous microinfarcts can be seen in the cortex and the white matter. The neurons frequently show ischemic changes. Moderate astrocytic proliferation is present, with an anisomorphic fibrillary gliosis in older infarcts. The neurons of the cerebral and cerebellar cortices, thalamus, and basal ganglia contain intracytoplasmic accumulations of granular material with the same tinctorial properties as the inclusions in the vascular endothelia and the smooth muscle cells. Neuronal storage may be absent in patients who died young.

Various authors have described glycolipid storage in various areas of the thalamus, hypothalamus, striatum, midbrain, and allocortex (Kaye *et al.*, 1988). Others have failed to confirm these observations. In the spinal cord Sung (1979) found neuronal storage exclu-

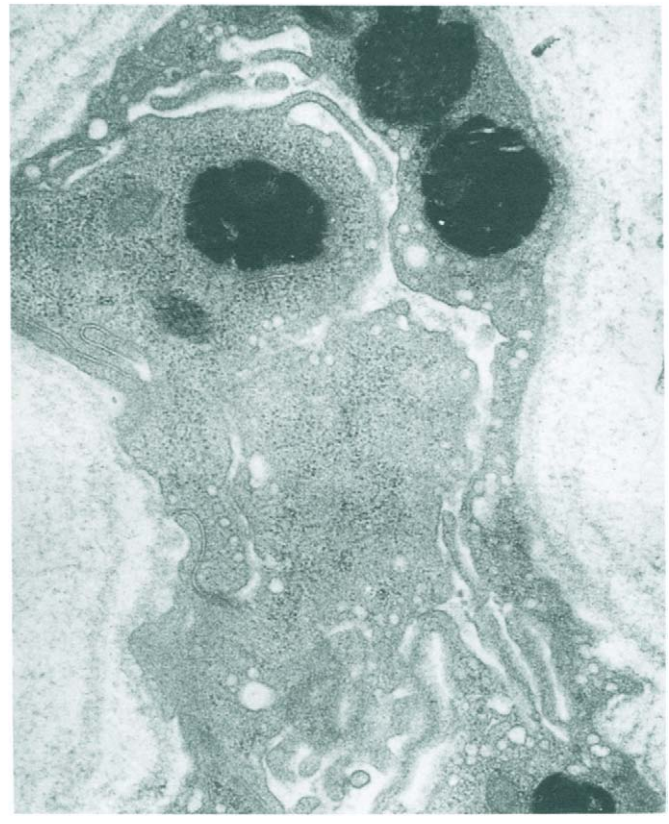


Fig. 106 Fabry's disease. A lysosomal residual body in a capillary endothelium in the skin, ×30,000. (Reproduced from Cervós-Navarro and Goebel, 1989.)

sively in the autonomic centers of the thoracic and sacral segments. Using a monoclonal antibody reactive with ceramide trihexoside, DeVeber *et al.* (1992) found more extensive neuronal deposition than was evident by luxol fast blue staining and new areas of neuronal storage in the spinal cord and the cerebral cortex. The neuronal cytoplasm of the spinal and autonomic ganglia is laden with lipids, also found in symptomatic female heterozygotes (Hozumi *et al.*, 1990).

A selective reduction in the number of myelinated and thinly myelinated fibers was found in the peripheral nerves (Sung, 1979; Gemignani *et al.*, 1984). Rarely, a loss of large thickly myelinated fibers has been observed. Vascular endothelia and smooth muscle cells, as well as perineurial cells, contain intracytoplasmic granules staining strongly with toluidine blue. The vessels of the choroid plexuses are also involved in the storage process.

Electron microscopy. On electron microscopy concentric laminar structures of 1- to 2-μm diameter are present in the endothelia and the smooth muscle cells of intracerebral

blood vessels. These can coalesce to form larger conglomerates. No storage has been found in neurons or glial cells to date.

In the peripheral nerves the vascular endothelia and the perineurial cells contain concentric or parallel, straight or slightly curved, lamellae with a periodicity of about 5 nm (Vital *et al.*, 1984). The concentric lamellar inclusions in the perineurial cells have a periodicity of 6–7 nm. Similar inclusions are seen occasionally in myelinated and unmyelinated axons, and rarely in Schwann cells. The population of nerve fibers is reduced. Evidence of demyelination and remyelination may also be present.

Pathogenesis Sweely and Klionsky (1963) identified the lipid nature of the stored substance as trihexosylceramide. Brady *et al.* (1967) discovered the absence of a lysosomal ceramide trihexosidase, characterized later as α-galactosidase A (Coppola *et al.*, 1994). The presumed B form of α-galactosidase turned out to be an α-*N*-acetylgalactosaminidase, the deficiency of which causes Schindler's disease (Schindler *et al.*, 1988), the morphology of which is similar to that of infantile neuroaxonal dystrophy (see p. 511). The activity of the α-galactosidase is reduced in female carriers of Fabry's disease, and totally abolished in male monozygotes. The enzyme deficiency leads to storage of several glycosphingolipids with a terminal galactose radical linked by an α-glycosidic binding. The reduction in α-galactosidase activity in fibroblast cultures from patients and most of the female carriers was demonstrated using both natural and artificial substrates. The results were more clear-cut in a ceramide trihexoside loading test in which uptake of substrate by the fibroblast cultures was studied over a fixed period. The uptake was 2.1% in Fabry's disease patients, 47.1% in carriers, and 82.0% in normal controls. It is assumed that trihexosylceramides released from aging erythrocytes reach the vascular endothelia and the glomerular epithelia from the bloodstream. Storage in the brain occurs exclusively in the blood vessels, as the trihexosylceramides cross the blood–brain barrier with difficulty and are therefore present only in small quantities. The fact that no foam cells appear in Fabry's disease, in contrast with other sphingolipodoses, has been attributed to the different degrees of polymerization of the various sphingolipids. The gene coding for α-galactosidase A has been localized on the long arm of the X chromosome in the region Xq21.33–q22 (Vetrie *et al.*, 1994). Several mutations have been described (Brady, 1992). These affect particularly the first of seven exons (Davies *et al.*, 1993). The abnormalities consist of various nucleotide base transitions and deletions (Ishii *et al.*, 1991; Davies *et al.*, 1993; Kornreich and Desnick, 1993).

Gangliosidoses

British ophthalmologist Warren Tay reported in 1881 the case of a 12-month-old infant in whom the fundus oculi showed a cherry-red spot at the macula. The child also suffered from neurological symptoms. Independently of these observations, American neurologist Bernard Sachs (1887) described the clinical and pathological findings in the same disease. He characterized it as a heredodegenerative disorder, of which the changes in the fundus represented only one manifestation. He called the disorder "amaurotic family idiocy." In the following 50 years a number of conditions were included in the concept of *amaurotic idiocy*, with different clinical manifestations, particularly with regard to age at

onset. These various manifestations were graced with a number of eponyms. Conditions resembling Tay–Sachs disease were found to occur in later childhood (Spielmeyer, 1905; Vogt, 1905). Further observations led to classification of these disorders by age at onset, clinical manifestations, and duration of the clinical course. Histologically, the following forms were recognized: congenital, infantile (Tay–Sachs), late infantile (Jansky–Bielschowsky), juvenile (Vogt–Spielmeyer), and adult (Kufs–Hallervorden). This classification was rendered obsolete by advances in biochemistry.

Klenk (1942) was the first to investigate the biochemistry of autopsy material obtained from cases of Tay–Sachs disease. He found some hitherto unknown water-soluble glycolipids, also present in small quantities in normal brains, and called them "gangliosides." After Norman *et al.* (1959) isolated a special subgroup of the amaurotic idiocies ("Tay–Sachs' disease with visceral involvement"), the identification of various gangliosidoses followed within a few years. These differ from each other in terms of the nature of the stored substance and the underlying enzyme defect.

Biochemistry of Gangliosides

The gangliosides are lipids typical of various membrane components of the nervous system. Like some other membrane lipids, gangliosides have a polar structure. They have a hydrophobic and a hydrophilic part. The hydrophobic part consists of ceramide, which, in turn, is built up from long-chain fatty acids and the long-chain amino alcohol sphingosine. The hydrophilic part contains sugars, amino sugars, and sugarlike substances in straight or branched chains. A characteristic component of gangliosides is sialic acid (*N*-acetylneuraminic acid). The gangliosides thus belong to the group of glycosphingolipids. Gangliosides are present in a mixture and their separation is difficult by classical analytical methods. Their purification and identification had to await the introduction of advanced methods, such as thin-layer chromatography and improved column chromatography. In the early 1960s the separation of gangliosides was achieved by Svennerholm (1964). The results obtained depend largely on the method of separation used. The terminology proposed by Svennerholm (1962) has received general acceptance. It is based on the number of sugar molecules and sialic acid radicals. To the initial *G* (for *ganglioside*) is added the letters *M* (for *monosialic*), *D* (for *disialic*). *T* (for *trisialic*), or *Q* (for *quadrisialic*), followed by a figure denoting the number of sugar molecules in the chain. This is based on results obtained by thin-layer chromatography.

The number for sugars is derived by deducting the values obtained by analysis from 5. Thus, GD_2 has three sugar molecules ($5 - 2 = 3$) in its chain. This particular ganglioside therefore contains two sialic acid and three sugar residues. In normal circumstances gangliosides form about 5% of the total lipids in gray matter, and about 0.6% of the lipids in white matter. Of these, GD_1 accounts for 20–25% and GM_1, for 35–42%.

The ganglioside GM_1 (tetrahexoside) is the principal monosialide of the normal cerebral cortex. The trihexoside GM_2 and dihexoside GM_3 are present only in traces. The more abundant tetrahexosides of di- and trisialides are not considered further here, as they are not involved in pathological storage. Most of the gangliosides are localized in the membranes of nerve endings, where they may have receptor functions similar to those of glycoproteins (e.g., for cholera toxin).

Enzyme Pathology of Gangliosides

The biosynthesis of gangliosides begins with the synthesis of the hydrophobic ceramide from sphingosine and a fatty acid. Subsequently, the various monosaccharides are added. They must present in the active form as sugar nucleotides and require the presence of the enzyme glycosyltransferase. The formation of gangliosides takes place in the endoplasmic reticulum and in the Golgi apparatus. The exact mechanism and its control have not been fully elucidated. The catabolism of gangliosides takes place in the acid environment of lysosomes, where the hydrolases display their maximum activity. They shorten the oligosaccharide chain step by step, until ultimately the ceramide is broken down into sphingosine and fatty acids. Nearly all of the hitherto recognized disorders of ganglioside metabolism are due to faults in this breakdown mechanism. This, in turn, is caused by the absence of an enzyme or its activator protein (Sandhoff and Conzelmann, 1984). The substrate of the missing or inactive enzyme accumulates in the form of storage.

GM_1 Gangliosidoses (β-Galactosidase Deficiency)

Norman *et al.* (1959) described a case that combined the features of Tay–Sachs disease with those of Hurler syndrome (see p. 112). Landing *et al.* (1964) added to the literature eight similar cases, on the basis of which he was able to define the syndrome. Because of the nature of the substances stored in the viscera, some authors classified GM_1 gangliosidosis among the mucolipidoses (see p. 137).

In describing a variant with later onset, Derry *et al.* (1968) divided GM_1 gangliosidosis into types 1 and 2. Later, an adult form was added as type 3 (Suzuki *et al.*, 1977). The three types differ from each other in both their phenotype and their genotype. Further cases of β-galactosidase deficiency (Stevenson *et al.*, 1978) could not be classified accurately for lack of knowledge of their genetic background. Depression of β-galactosidase activity can also occur as a secondary phenomenon in the MPSs I and II (see p. 121) and in sialidoses (see p. 70). The patients originally reported as having variant O of the GM_1 gangliosidosis were subsequently allocated to the category of sialooligosaccharidoses with sialidase deficiency (see p. 69).

Type 1 (Norman–Landing Type; Systemic Infantile GM_1 Gangliosidosis; Generalized GM_1 Gangliosidosis)

The majority of reported cases of GM_1 gangliosidosis are of type 1.

Clinical Picture The disease is already apparent at birth. Motor development is virtually nonexistent and the infants remain motionless, usually asleep. A hyperplasia of subperiosteal bone, similar to that of MPS II, is recognizable at birth, particularly in the long bones and the ribs, and later also in the vertebral bodies (Landing *et al.*, 1964). O'Brien (1970) refused to accept cases without bony changes as examples of GM_1 gangliosidosis. Some patients with bony lesions, but without neurological symptoms, are phenotypically indistinguishable from those with MPS IV (see p. 127). Fifty percent of the patients exhibit a cherry-red spot in the retina. It may disappear if the course of the disease is prolonged (Kivlin *et al.*, 1985). Hepatosplenomegaly is present in all cases. The initial hypo-

tonia changes to spasticity with hyperreflexia, to which generalized tonic–clonic seizures may be added. The final stage is characterized by decerebrate rigidity, and the children die between the 18th and 24th months of age, usually of bronchopneumonia (Rey-Pias *et al.*, 1979).

Pathology *Gross appearances.* The organs may appear atrophic in some cases (Suzuki *et al.*, 1968), in spite of hepatosplenomegaly.

Light microscopy. The reticuloendothelial system in various organs contains histiocytic cells with foamy cytoplasm. The parenchymal cells of the liver, pancreas, and anterior pituitary may be vacuolated or foamy (Landing *et al.*, 1964; Petrelli and Blair, 1975). The glomerular endothelia of the kidneys are also involved in the storage process, leading to a swollen appearance of the glomeruli (O'Brien *et al.*, 1971). In the renal tubules one can also find vacuolated endothelial cells. The material stored in the reticuloendothelial cells and in the renal glomeruli is distinctly PAS positive.

Electron microscopy. The hepatocytes, particularly those near the bile ducts, contain large numbers of intracytoplasmic, irregularly formed, multivacuolar bodies. Some inclusions contain parallel membranes and granules (Petrelli and Blair, 1975). Occasionally, bundles of fine, tightly packed, tubular structures were found in the macrophages of the liver and the spleen. The glomerular endothelia of the kidneys contain numerous large confluent vacuoles, bound by a single membrane. The occurrence of vacuoles in the circulating lymphocytes and monocytes is of diagnostic importance, as is the finding of histiocytes containing finely granular material in the bone marrow. Smaller multivesicular bodies may also be present. The vacuolation of fibroblasts (Fig. 107) and of endothelial and epithelial cells in skin biopsies may also be helpful in making the diagnosis (Goebel, 1984). In the conjunctiva membranous inclusions may be found in the vascular endothelia, and vacuolar ones appear in the epithelial cells (Schmitt-Gräff, 1988).

Neuropathology *Gross appearances.* The brain weight may be moderately reduced or somewhat increased (Landing *et al.*, 1964). The cerebral and cerebellar cortices appear thin. The ventricles are somewhat dilated. The white matter has a chalky white appearance.

Light microscopy. The arachnoid contains scattered foam cells. The neurons of the cerebral cortex, basal ganglia, and spinal cord are ballooned, and the nuclei are pyknotic and displaced to the periphery.

The neuronal cytoplasm contains a finely granular weakly eosinophilic material. There is usually some proliferation of astrocytes and an increase in microglial cells (Landing *et al.*, 1964). The white matter shows a moderate loss of myelin in the cerebrum, cerebellum, and pyramidal tracts. The granule cell layer of the cerebellum is rarefied. The Purkinje cells, reduced in number, show a ballooned cell body, as well as axonal and dendritic swellings. The neurons in the cerebral cortex and the basal ganglia are only weakly PAS positive, and the reaction is not altered by glycolytic enzymes. The PAS reaction is different in the Purkinje cells and in neurons of the spinal cord (Landing *et al.*, 1964).

The intracytoplasmic storage material stains only moderately with Sudan black, but reacts positively with alcian blue. Hale's colloidal iron, Bial's orcein, and luxol fast blue. In Mallory's aniline blue trichrome stain the stored material stains either diffusely or only at

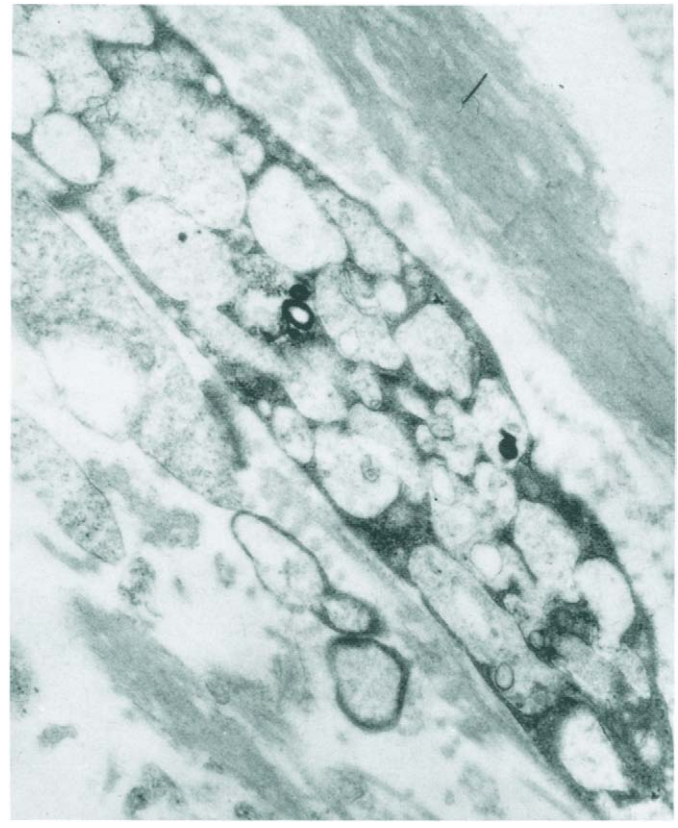


Fig. 107 GM_1 gangliodisosis type 1. Skin, showing striking lysosomal vacuolation in a fibroblast, ×30,000. (Courtesy of H.-H. Goebel, Mainz, Germany.)

the periphery of the vacuoles. In silver impregnations meganeurites and secondary neurites can be seen, with simultaneous atrophy of the dendrites (Purpura and Walkey, 1981). Storage of granular material is present in the neurons of the retinal ganglion cell layer, with preservation of the remaining layers. The neurons of the autonomic nervous system and of the myenteric plexus of the gut participate in the storage process.

Enzyme histochemistry reveals increased acid phosphatase activity in the neuronal perikarya, axons, and dendrites, and also in some glial cells. The activity of oxidative enzymes (e.g., NADH-diaphorase or succinate dehydrogenase) is limited to a perinuclear zone or to the periphery of the cell.

Electron microscopy. Round or oval multilamellar bodies are present in the neuronal cytoplasm, similar to those seen in GM_2 gangliosidosis type 1 (Patel *et al.*, 1974). Their diameter ranges from 0.5 to 3 μm. In the centers of these membranous cytoplasmic bodies, finely vesicular and granular structures may be present (O'Brien *et al.*, 1972). Some perikarya and processes also contain pleomorphic membrane-bound lipid inclusions, con-

sisting of parallel or circular lamellae and granular material of lower density (Fig. 108). Neuronal inclusions were found in the cerebellum, spinal ganglia, and retina in fetuses of 17, 18, and 22 weeks' gestational age (Bieber *et al.*, 1986).

The glial cells contain generally three types of intracytoplasmic inclusions:

1. Pleomorphic lipid bodies
2. Membranovesicular bodies, 0.5–2 μm in diameter, consisting predominantly of multiple vesicular myelin figures with circular membranes of a periodicity of 6 nm
3. Large intracytoplasmic deposits, 3.5–5.5 μm in diameter, consisting of irregularly disposed, mostly curved, lamellae, an amorphous matrix of low density, and a surrounding membrane. The ganglion cells of the retina also contain multilamellar bodies or zebra bodies.

The endothelial cells and pericytes of blood vessels contain membrane-bound inclusions, consisting of a variable number of small vesicles. In the Schwann cells and nerve fibers of cutaneous and cardiac nerves, pleomorphic lipid bodies may be found (Contraires *et al.*, 1981).

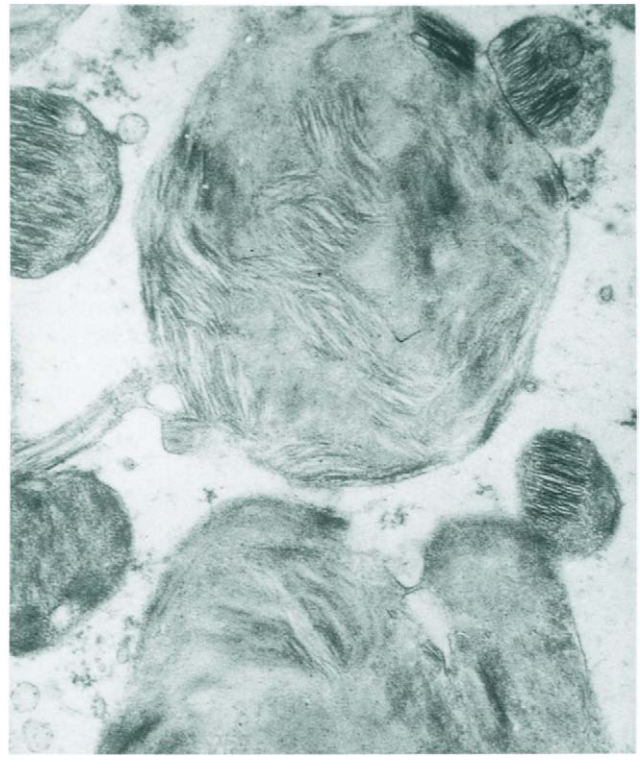


Fig. 108 Same case shown in Fig. 107. Lamellar membrane-bound lysosomal residual bodies in a retinal ganglion cell, ×44,000. (Courtesy of H.-H. Goebel, Mainz, Germany.)

Type 2 (Derry's Syndrome; Late Infantile GM_1 Gangliosidosis; Juvenile GM_1 Gangliosidosis)

Clinical Picture This disease begins between the ages of 7 and 14 months after an initial normal development. Irritability and motor disturbances are the first symptoms. Myoclonus epilepsy and hyperacusis may be present (Gascon *et al.*, 1992). Dystonia is observed occasionally (Nardocci *et al.*, 1993). The disease progresses slowly and leads to dementia within a few years. There is no hepatosplenomegaly or skeletal abnormality. Pallor of the optic disk may be seen in the fundus, but there is no cherry-red spot. Epileptic seizures occur in late stages of the disease (Patel *et al.*, 1974). Harden *et al.* (1982) pointed out the peculiarities of the EEG. The patients die generally between the ages of 7 and 10 years. Longer survival has been recorded, but these cases may well belong to type 3.

Pathology No macroscopic or microscopic changes are found in the viscera, with rare exceptions. Vacuolation of the histiocytes or of the retinal glomerular epithelium has been seen occasionally (O'Brien *et al.*, 1971). The degree of visceral storage is also less pronounced on electron microscopy than it is in type 1. The diagnostic value of lymphocytic vacuolation is less reliable. By contrast, vacuolation is always prominent in the skin fibroblasts.

Neuropathology *Gross appearances.* The cerebrum is moderately—the cerebellum, severely—atrophic. The optic nerves are thin and grayish. The gray matter appears reduced, while the white matter shows no atrophy, only a firm consistency.

Light microscopy. Neurons in all gray areas, with the exception of the granular layer of the cerebellum, show evidence of storage. The intensity of storage and the number of involved neurons vary from one region to another, and even in the same area both normal and ballooned cells may be found side by side (Patel *et al.*, 1974). Severe losses of both Purkinje and granule cells are seen in the cerebellum (Fig. 109). In Golgi impregnations Fujisawa and Nakamura (1982) found aberrant Purkinje cell dendrites remote from sites of lipid storage.

Electron microscopy. The affected neurons, and also some glial cells, contain multilamellar bodies with concentric arrangement of the membranes. Here and there structures are found consisting of tightly packed parallel membranes. In the spinal ganglia and the retina the range of variation is much wider (Patel *et al.*, 1974). Next to some electron-lucent bodies one can find circumscribed packets of membranes and dense homogeneous inclusions embedded in a loose granular matrix.

Type 3 (Chronic GM_1 Gangliosidosis; Adult GM_1 Gangliosidosis)

Suzuki *et al.* (1979) and Wenger *et al.* (1980) each described two siblings suffering from an adult type of GM_1 gangliosidosis with a protracted clinical course. The first anatomopathological investigation was published by Goldman *et al.* (1981).

Clinical Picture The patients develop normally up to the age of 3–4 years, occa-

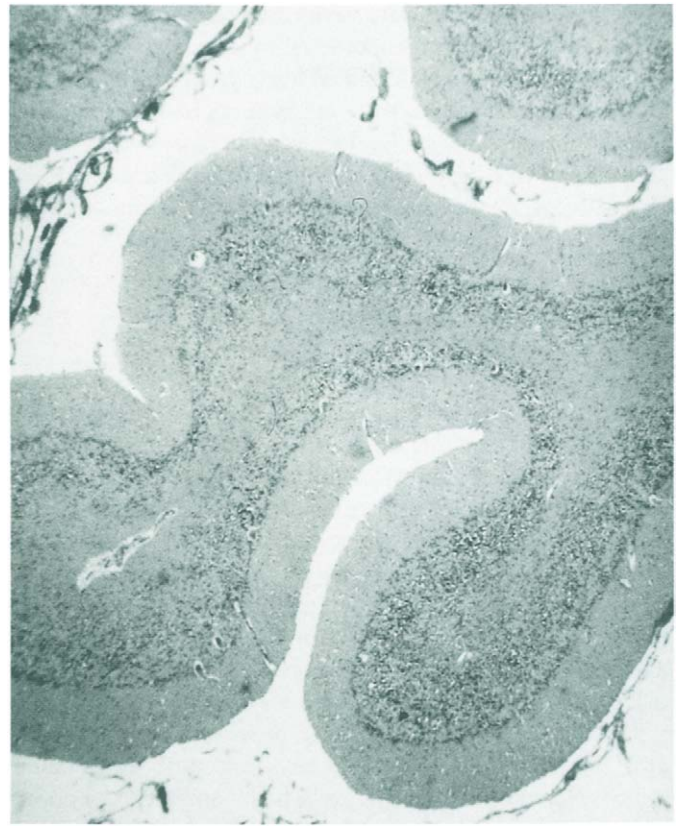


Fig. 109 GM_1 gangliosidosis type 2. The cerebellum, showing a loss of Purkinje and granule cells. Hematoxylin–eosin stain, ×80. (Reproduced from Cervós-Navarro and Goebel, 1989.)

sionally even to 8 years (Nakano *et al.*, 1985). The first symptoms are unsteadiness of gait and a slowly progressive loss of motor control. Over the years dystonia becomes the most prominent feature (Inui *et al.*, 1990). This feature may be associated with disturbances of ocular movements, difficulty in swallowing, respiratory complaints, and a total anarthria with retention of the power of communication in writing. The dystonic movements are particularly pronounced in the facial musculature. Three sisters with choreoathetoid movements began to develop dementia toward the end of the first decade (Guazzi *et al.*, 1988). Nakano *et al.* (1985) observed an atrophy of the caudate nucleus on CT. MRI (T_2 weighted) shows symmetrical hyperintensive lesions in both putamina (Inui *et al.*, 1990; Uyama *et al.*, 1992). The patient reported on by Goldman *et al.* (1981) died at 27 years. Most patients reach a higher age (Ikeda *et al.*, 1986).

Pathology In the only autopsied case to date, intracellular storage was present throughout the reticuloendothelial system. PAS-positive and more or less oil red O-positive material was found in the cytoplasm of Kupffer's cells, histiocytes in the spleen and the bone marrow, and lamina propria of the intestinal mucosa.

Electron microscopy. On electron microscopy multiple membrane-bound inclusions were found in Kupffer's cells. Some of them appeared empty; others contained fibrillary profiles, about 8 nm in diameter, with a central electron-lucent zone.

Neuropathology *Gross appearances.* The frontal lobes were slightly atrophic. Upon sectioning the brain, the caudate, putamen, and globus pallidus appeared shrunken, firm, and discolored a yellowish brown.

Light microscopy. Neuronal storage is almost exclusively limited to the basal ganglia (Suzuki, 1991). The neurons of the basal ganglia showed ballooning of the cytoplasm, the contents of which were eosinophilic and faintly granular. In Golgi preparations swelling of the proximal axon was seen in some cells. The basal ganglia, particularly their posterior parts, showed a distinct loss of neurons with corresponding gliosis. The contents of the cytoplasm were strongly PAS positive, but stained only weakly with Sudan black or oil red O. In semithin sections stained with toluidine blue, the cytoplasmic inclusions ranged in size between 0.5 and 2.5 μm. In other parts of the brain, occasional swellings of the proximal axons were seen in cells of the second and third cortical layers. Swelling of the Purkinje cell dendrites (megadendrites) without changes in the perikarya or the axons was the only abnormality in the cerebellum.

Electron microscopy. A variety of inclusions was seen in the cells of the basal ganglia. Some neurons contained only concentric membranous bodies, while others contained pleomorphic inclusions which, apart from concentric lamellae, consisted of granular material and curvilinear profiles. Occasionally, larger membrane-bound aggregates of various inclusions were seen. Apart from a proliferation of glial fibrils, the astrocytes contained membrane-bound inclusions of a vesicular or membranous nature. Conspicuous inclusions of stacked lamellae were seen in the astrocytes of the granular layer of the cerebellum. Lamellar inclusions were also present in the neurons on rectal biopsies (Nakano *et al.*, 1985; Ikeda *et al.*, 1986).

GM_1 Gangliosidosis in Animals Cases of GM_1 gangliosidosis resembling the human disease were reported in cats (Hanna *et al.*, 1982), in Friesian calves (Sheahan *et al.*, 1978), and in dogs (Saunders *et al.*, 1988). These cases correspond clinically, morphologically, and biochemically to the findings in human patients with GM_1 gangliosidosis of both type 1 and type 2. Investigations on cortical neurons in cats with GM_1 gangliosidosis have shed important light on the role of gangliosides in the structure and function of synapses. In Golgi impregnations meganeurites and aberrant neurites were found in the cerebral cortex, hippocampus, thalamus, caudate, and cerebellum. The regional differences in these changes parallel the differences in GM_1 concentrations (Byrne and Ledeen, 1983).

Singer *et al.* (1987) developed an *in vitro* model of GM_1 gangliosidosis by the application of a specific inactivator of the β-galactosidase.

In cats with GM_1 gangliosidosis, an accumulation of lamellar inclusions in the neurons does not seem to impair the electrophysiological properties of the CNS (Purpura *et al.*, 1980).

An immunocytochemical study directed at localizing glutamic acid decarboxylase in feline GM_1 gangliosidosis indicates that the axonal spheroids involve axons of GABAergic neurons (Walkley *et al.*, 1991).

Pathogenesis The GM_1 gangliosidoses are caused by a deficiency of the enzyme β-galactosidase. This enzyme splits off the terminal β-glycoside–bound galactose radical. Its principal substrate, hence its principal stored substance, is GM_1 ganglioside. Certainly, this enzyme breaks down other oligosaccharide structures containing β-glycoside–bound galactose, such as the asialic GA_1 ganglioside, as well as glycoproteins and mucopolysaccharides. The neuronal content of GM_1 increases 10-fold in all types of the disease. Admittedly, in type 3 this applies only to the neurons of the basal ganglia (Kobayashi and Suzuki, 1981).

Rushton and Dawson (1977) localized the gene of the enzyme defect on chromosome 12. Other authors found two loci for β-galactosidase activity on chromosome 22 (De Witt *et al.*, 1977) and chromosome 3 (Bootsma and Galjaard, 1979).

Farrell and Ochs (1981) found both infantile and juvenile forms of the disease in a single family. They concluded that all genes may be responsible for the phenotypic variants.

Several mutations of the β-galactosidase gene have been recorded. The common point mutations in Caucasians are *K577R*, *R590H*, *E632G*, and *R208C* (Boustany *et al.*, 1993). A C-to-T mutation at nucleotide 425 coding for a T-to-M substitution was found in an adult family (Chakraborty *et al.*, 1994). In addition, abnormal splicing due to a 20-bp insertion from the 5′ end of intron 1 between nucleotides 75 and 76 was present in a few cases (Chakraborty *et al.*, 1994; Morrone *et al.*, 1994). Different mutations were found in Japanese patients. Two mutations, *R49C* and *R457T*, were present in infantile cases. In the juvenile form the common mutation was *R20sC*; in the adult, *I51T* (Nishimoto *et al.*, 1991). Yoshida *et al.* (1992) confirmed the common occurrence of homozygotes *I51T* in adults and recorded a compound heterozygote of *I51T* with *R<8457E*.

In gel filtration of the β-galactosidase, one can separate three fractions. All three are greatly reduced in type 1, while in types 2 and 3 the third fraction is largely preserved (Orii *et al.*, 1975; Kikuchi *et al.*, 1982). In the viscera of type 1, the GM_1 increase is less pronounced than in the nervous system. The biochemical differences account for defective myelinization in type 2 (Kasama and Taketomi, 1986).

The patient's age at onset or at death in GM_1 gangliosidosis could not be correlated with the residual activity of the enzyme or the number of remaining isoenzymes of β-galactosidase (Stevenson *et al.*, 1978).

GM_2 Gangliosidoses

Biochemical and enzymological differences enable us to differentiate five different forms of GM_2 gangliosidosis. There are also morphological differences, but these are

not clearly defined, due to the limited number of cases examined at autopsy. These forms are classified as types 1–5. Sandhoff (1969) introduced a new terminology based on the differences in lack of activity of the various isoenzymes of β-hexosaminidase (see p. 329). The variants are called after the remaining isoenzyme; thus variant B denotes the lack of isoenzyme A, variant O indicates the lack of both isoenzymes, and variant AB represents the lack of an activator factor in the presence of both isoenzymes A and B. O'Brien (1978) proposed a terminology based on the various loci responsible for the structure of the α- and β-subunits of the enzyme (see p. 329). Thus, type 1 of GM_2 gangliosidosis is $\alpha_2\alpha_2$, type 2 is $\beta_2\beta_2$, and type 3 is $\alpha_3\alpha_3$. The alleles for type 4 are unknown; for type 5 $\alpha_2\alpha_5$ or $\alpha_2\alpha_6$ is possible (Johnson, 1981).

Congenital Form: Cases described in the earlier literature as examples of congenital amaurotic idiocy with onset of symptoms at, or soon after, birth cannot be classified with the GM_2 gangliosidoses with any degree of certainty. In fetuses with GM_2 gangliosidosis, inclusions are present containing granular or amorphous material, and occasionally also some loose membranous structures (Suchlandt *et al.*, 1982). Sometimes they resemble zebra bodies (Fig. 110A and B). The inclusions show no acid phosphatase activity, which suggests immaturity of the enzyme systems in early stages of development (Adachi *et al.*, 1978).

Type 1 (Tay–Sachs Disease; Infantile Form of Amaurotic idiocy; GM_2 Gangliosidosis Variant B; Hexosaminidase A Deficiency)

Type I is the classical type of amaurotic idiocy. It may be assumed, however, that some of the cases formerly diagnosed as infantile amaurotic idiocy belong to the group of ceroid lipofuscinoses.

Clinical Picture The clinical features were already fully characterized in Sachs' (1896) classical description. The disease begins in the first year with psychomotor retardation or loss of previously acquired functions, progressive impairment of vision leading to blindness, and paralysis, at first flaccid, and later spastic. The steadily progressive course leads to total decerebration and death within 2–3 years. Epileptic seizures and episodes of compulsive laughter occur in the later stages of the disease (O'Brien, 1983). Macrencephaly appears occasionally. The characteristic changes in the fundus include the cherry-red spot at the macula and optic atrophy. On the CT scan alternating hypodense and hyperdense foci can be seen in the cerebral cortex in later stages of the disease (Watanabe *et al.*, 1985).

The disease is inherited as an autosomal-recessive trait. It occurs predominantly, but not exclusively, in children of Jewish origin. The frequency of heterozygote carriers is 1 : 40 in Ashkenazi Jews, 1 : 380 in others.

Pathology Cases in the earlier literature in which extraneural storage in the viscera was reported (Diezel, 1957) are unlikely to be examples of type 1 GM_2 gangliosidosis.

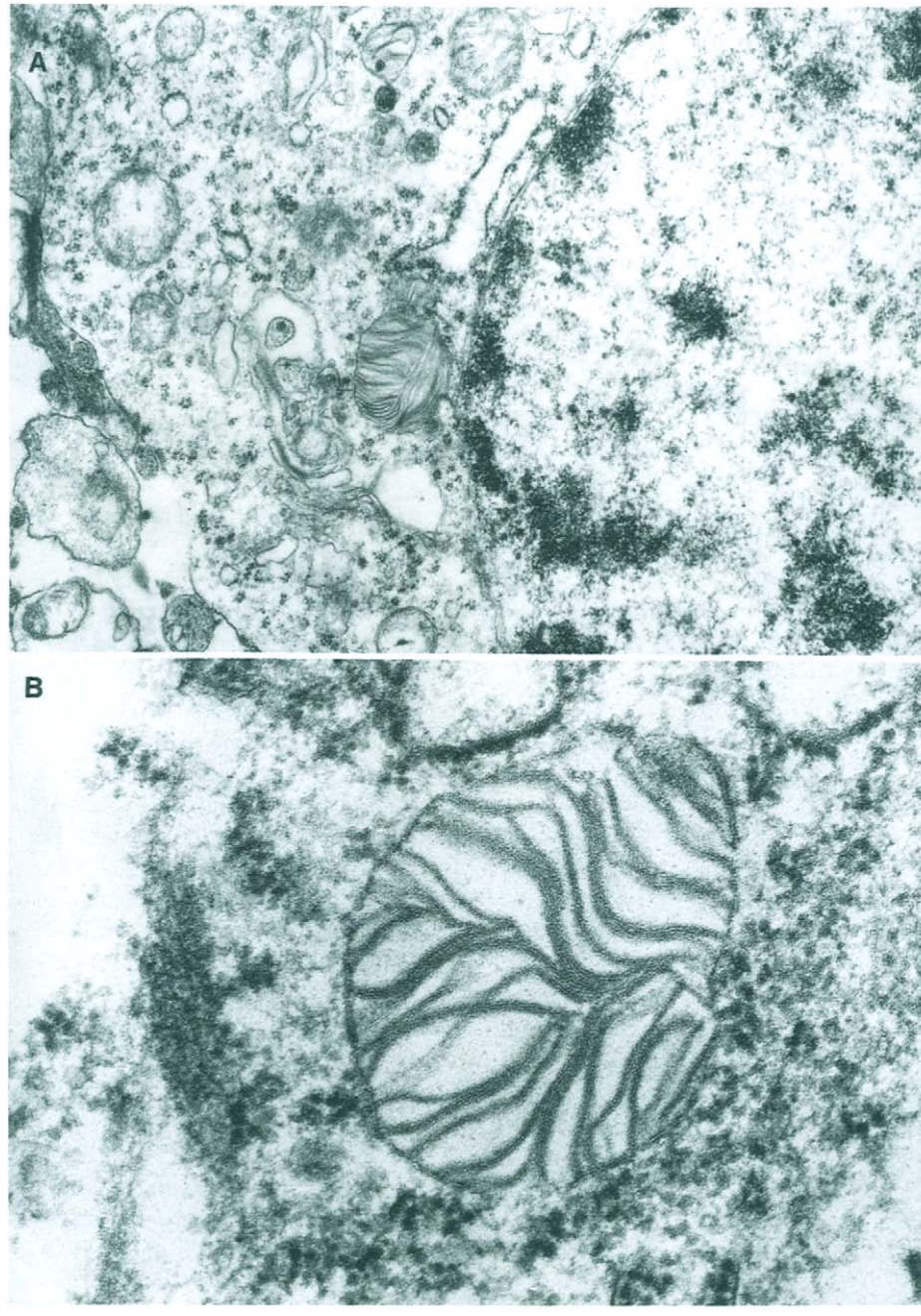


Fig. 110 Congenital form of GM_2 gangliosidosis. A cortical neuron of a 23-week fetus, showing inclusions with loosely arranged parallel membranes, (A) ×18,000 and (B) ×60,000. (Reproduced from Yamada *et al.*, 1981.)

Electron microscopy. On electron microscopy the otherwise unremarkable liver may show a few membranous cytoplasmic bodies in hepatocytes near the surface adjacent to the bile canaliculi. They consist of laminated, parallel, or concentric membranes. Lipofuscin granules with a variable arrangement of membranes may also be seen. Occasionally, they may bear a superficial resemblance to membranous cytoplasmic bodies. Adachi *et al.* (1972) found membranous inclusions in both the neuro- and adenohypophyses.

Neuropathology *Gross appearances.* In cases with a rapid clinical course, the brain shows diffuse atrophy, associated with ventricular dilatation. In some cases there is already a hint of increased volume of the brain. In cases with slower progression of the disease, the volume and weight of the brain are distinctly increased. In children surviving into their third year, the increase may reach 40–50% above normal values. The cerebral peduncles, pons, and medulla appear normal. In cases with survival of over 2 years, the cerebellum is reduced both in size and in weight. Cystic necroses are frequently seen in the white matter. The consistency of the brain tissue is tough and leathery. The leptomeninges are cloudy, edematous, and frequently thickened.

Light microscopy. Under the light microscope all neurons of the cerebral cortex are involved in the storage process, without laminar predilection. Their appearance was already described in detail by Hirsch (1898). The neurons lose their pyramidal contour and become round or pear shaped. The nuclei are displaced to the periphery and may be shrunken and pyknotic, or altogether absent. A loss of neurons is evident in long-standing cases. A prominent astrocytic proliferation leads to fibrillary gliosis, which imparts a firm consistency to the tissue. The lamination of the cortex is largely obliterated through neuronal loss, ballooning of surviving neurons, and glial proliferation. The dendrites also undergo alterations, and their proximal parts are often visible as blunt stumps. In Golgi preparations one finds meganeurites in the pyramidal cells of the cortex, from which secondary neurites, resembling filopodia, can be seen sprouting (Purpura, 1979). Sometimes the meganeurites can exceed the perikaryon in size. These changes can also be seen in silver impregnations. These torpedoes are rarely seen, however, in the early stages of the disease (Shirabe *et al.*, 1980).

The degree of myelinization or demyelination varies considerably from case to case. The loss of myelin may involve the entire white matter and may be accompanied by reactive gliosis. Presumably, the neuronal storage leads to an arrest of myelinization, while the wallerian degeneration secondary to the loss of neurons constitutes an additional factor.

As the disease progresses, microglial cells become more numerous. They are distended and rounded, and the storage material they contain shows the same histochemical reactions as that found in neurons, but stains more intensely. Simultaneously, the protoplasmic astrocytes proliferate, forming nests in places. The not uncommonly multinucleated astrocytes contain granules (Fig. 111) that are histochemically indistinguishable from the material stored in the neurons and the microglia. The cerebellar cortex is atrophic. Both the Purkinje cells and the granular layer are considerably depleted. The Purkinje cells participate in the storage process, which is particularly

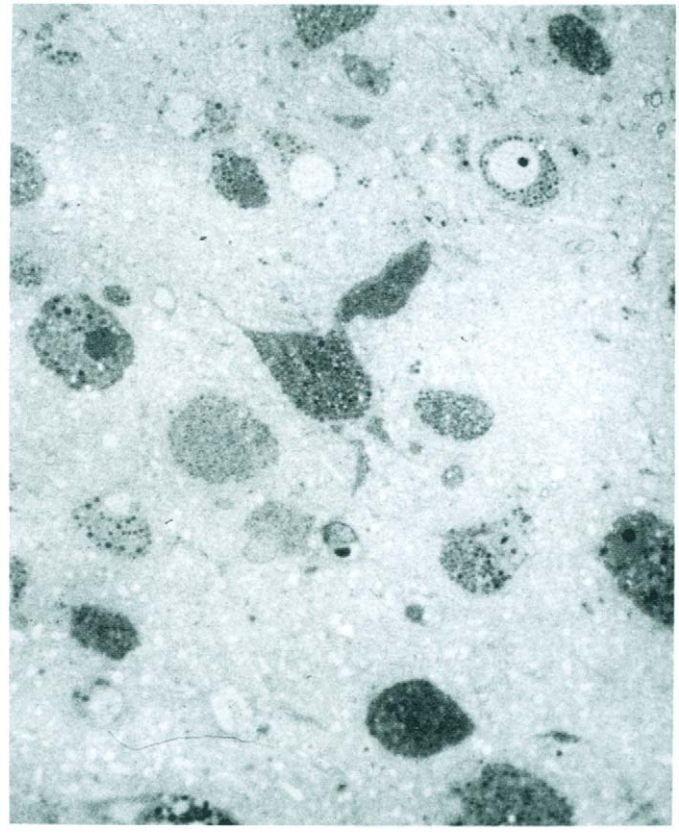


Fig. 111 Infantile form of GM_2 gangliosidosis. The cerebral cortex, showing numerous granules in the perikarya and the proximal processes of neurons, as well as in astrocytes. Nissl stain, ×400. (Reproduced from Cervós-Navarro and Goebel, 1989.)

prominent in the dendrites (Fig. 112). In later stages of the disease, the cells become pyknotic and disintegrate. In contrast with the cerebrum, the number of axis cylinders is only slightly reduced, and the astrocytic and microglial reaction is less pronounced.

In the spinal cord storage is seen in the neurons. The anterior horn cells are generally more distended than those of the posterior or lateral horns (Fig. 113). The white matter of the lateral columns (including the pyramidal tracts) is rarefied in some cases.

The cells of the autonomic nervous system, including the sympathetic ganglia, the myenteric plexus of the gut, the adrenal medulla, and the neurons in the bladder and the pancreas, are all affected by the storage process. The presence of involved neurons on rectal biopsies has been used for diagnostic purposes, but not always successfully. The histological changes in the retina were first reported by Collins (1892). In the ganglion cell layer there is a moderate loss of neurons, the remaining ones being ballooned and containing granular material similar to that in the CNS. The Nissl sub-

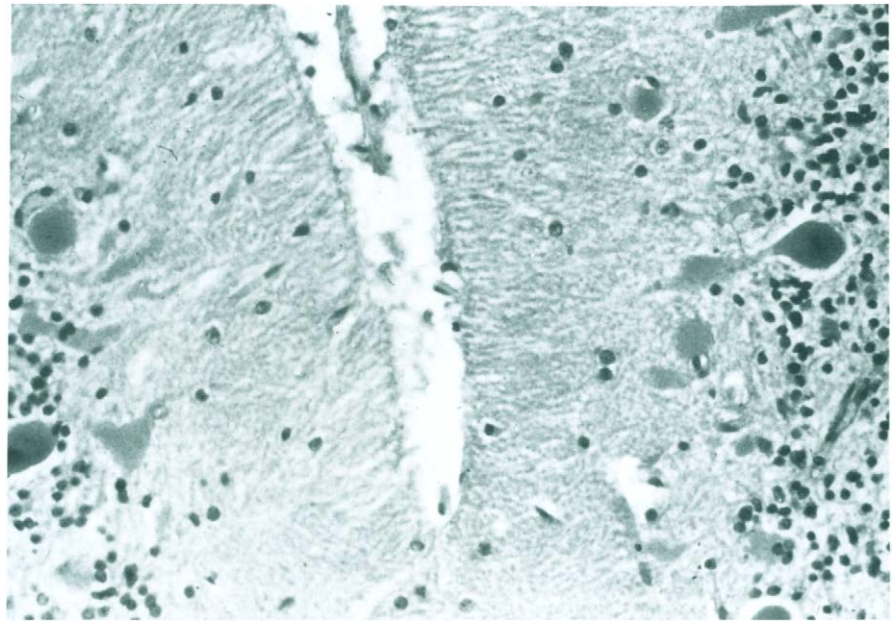


Fig. 112 Infantile form of GM_2 gangliosidosis. The cerebellum, showing prominent storage in Purkinje cell dendrites. Nissl stain, ×300.

stance is often not demonstrable, and the nucleus is displaced to the periphery. In the inner nuclear layer and the plexiform layer vacuolation and degenerative changes may be present. The rods and cones and the pigmentary epithelium are always intact.

The optic nerves are generally atrophic, the loss of axons being secondary to the destruction of ganglion cells. In the central parts of the nerve, the axons are often demyelinated.

In peripheral nerves no storage is present in the Schwann cells, but the axons, particularly the terminal ones, show spherical expansions. Lesions of peripheral nerves with severe damage to the myelin sheaths and a proliferation of Schwann cells have been recorded occasionally.

Histochemically, the material stored in neurons stains moderately well with Sudan black, but weakly or not at all with Sudan III or IV. The material reacts positively with the Smith–Dietrich and Baker methods, suggesting the presence of phospholipids, and stains a deep blue with Nile blue sulfate, indicative of phosphoglycerides and sulfatides. The PAS reaction is intense in frozen sections, but is reduced to a trace in paraffin-embedded material. The material also stains positively with the orcein–sulfuric acid reaction for pentoses and hexoses and with Okamoto's reaction for sphingolipids. The modified Bial reaction (Wolman, 1964) is generally negative in the neurons, but positive in the microglial cells. Tests for proteins are uniformly negative. Enzyme histochemistry yields an

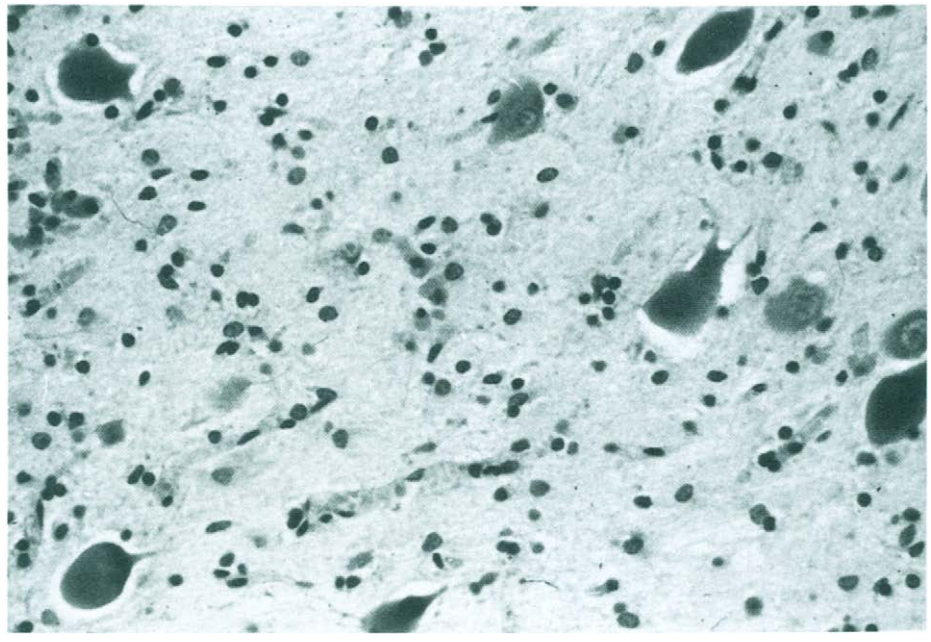


Fig. 113 Same case shown in Fig. 112. The spinal cord, showing ballooning of the anterior horn cells. Nissl stain, ×400.

enhanced reaction for acid phosphatase in the neurons and the glial cells. The reaction is localized in the same spots as the PAS and Sudan reactions.

Electron microscopy. Numerous membranous bodies are present in the cytoplasm of ballooned neurons (Goebel, 1984). They are 0.5–2 μm in diameter (Fig. 114) and consist of multilaminar electron-dense membranes, approximately 2.5 nm thick, arranged concentrically. The membranes often surround a homogeneous or finely granular center (Fig. 115). They can also be demonstrated by the freeze–fracture technique (Volk, 1986). Collections of small vesicles may be present side by side with the membranous cytoplasmic bodies. The expanded axons and dendrites also contain membranous cytoplasmic bodies. The presence of axodendritic synapses in the meganeurites can be demonstrated electron microscopically. The ganglion cells of the retina contain membranous bodies as well as amorphous lipid inclusions (Nagashima *et al.*, 1981). Membranous cytoplasmic bodies are also found in the astrocytes and the microglial cells (Yamada *et al.*, 1981).

The neurons of the spinal ganglia (Abe *et al.*, 1985) as well as the neurons and Schwann cells of the myenteric plexus may also contain membranous bodies or inclusions resembling zebra bodies. More commonly, however, they contain small granular bodies, consisting of a few membranes and small vesicles. Membranous and pleomorphic inclusions have also been described in terminal axons in the skin (Wisniewski, 1986) and in various muscles.

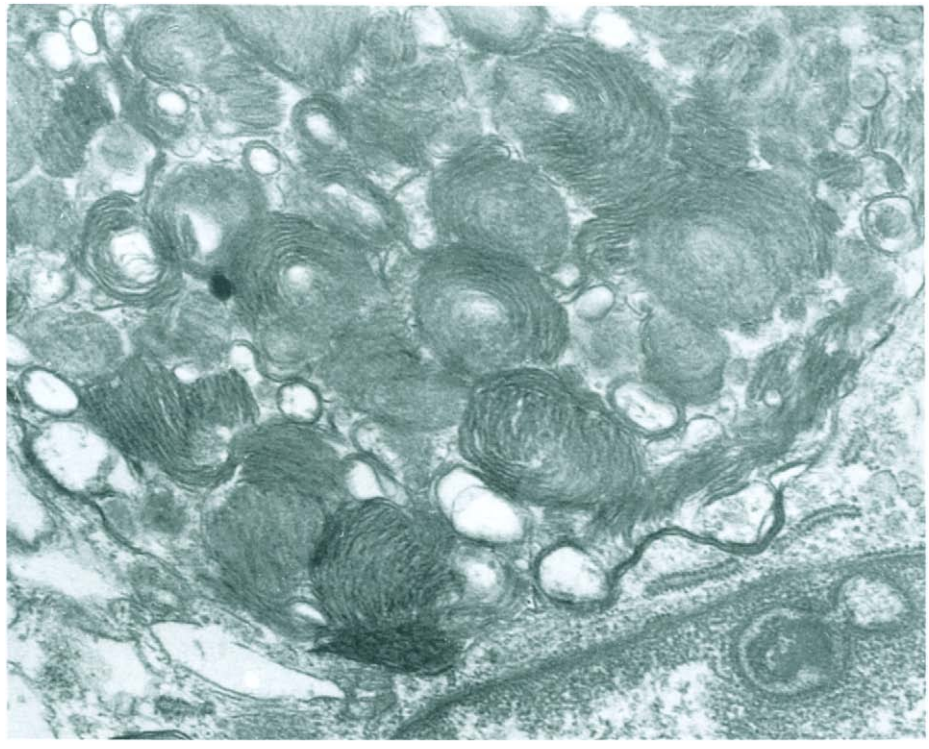


Fig. 114 Infantile form of GM_2 gangliosidosis. Concentric membranous inclusions (membranous cytoplasmic bodies) in the perikaryon of a neuron, ×32,000.

B1 Variant: The B1 variant, first described by Conzelmann *et al.* (1985), differs from Tay–Sachs disease in that it has a fairly high residual hexosaminidase A activity. This can be tested on an artificial substrate, 4-methylumbelliferyl-2 acetamino-2-deoxy-βA-D glucopyranoside (4MUG), and its sulfated form (4MUGS). Sera of patients with the B1 variant show normal activity with 4MUG, but absent or deficient activity with 4MUGS. Over 30 cases of this variant have been reported (Benninger *et al.*, 1993). These patients tend to experience a more protracted clinical course and may survive to juvenile (Maia *et al.*, 1990) or even adult age (Specola *et al.*, 1990). The morphological appearances closely resemble those of Tay–Sachs disease with ubiquitous neuronal storage, which, ultrastructurally, consists of multilamellar concentric bodies and zebra bodies (Benninger *et al.*, 1993). There does not appear to be any specific ethnic prevalence.

Type 2 (Sandhoff Disease; GM_2 Gangliosidosis Variant O; Hexosaminidase A and B Deficiency)

This variant of Tay–Sachs disease with visceral storage of renal globoside was described by Sandhoff *et al.* (1968) and Pilz *et al.* (1968). O'Brien *et al.* (1971) called

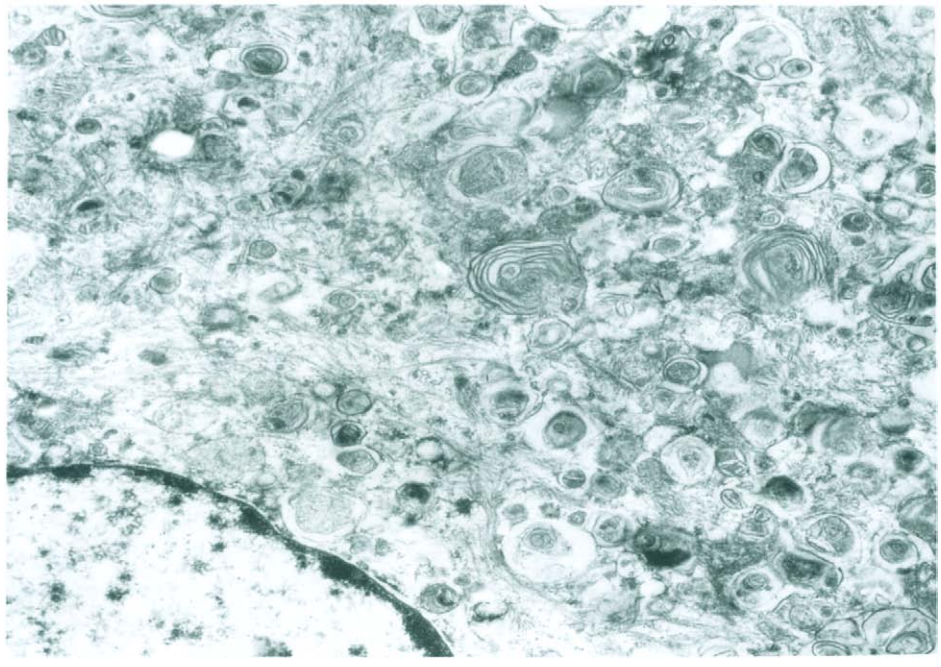


Fig. 115 Infantile form of GM_2 gangliosidosis. A neuron with membranous inclusions surrounding a homogeneous center, ×10,500. (Reproduced from Yamada *et al.*, 1981.)

it Sandhoff disease, while Sandhoff *et al.* (1971) coined the term *variant O of GM_2 gangliosidosis*. The case reported by Norman *et al.* (1964) probably belongs to this group.

Clinical Picture The infantile form appears during the first year or, rarely, at the beginning of the second. The first clinical symptoms are similar to those of GM_2 gangliosidosis type 1. After initial normal development muscular weakness and psychomotor retardation set in. These are followed by rapid physical and mental decline. The initial hypotonia changes to spasticity and ultimately to decerebrate rigidity. The juvenile form begins after the age of 2 years and runs a protracted course, sometimes into adulthood. Clinically, these cases represent a transition to type 5 (see p. 327). Both forms derive from heterogeneous mutations at various loci of the hexaminidase gene (O'Dowd *et al.*, 1986). The cherry-red spot and amaurosis do not differ from those of type 1. Tonic–clonic jerks and generalized seizures are common. The condition occurs in patients of Jewish origin, but not more commonly than in others. Further differences from type 1 include slight hepatomegaly and cardiac involvement. A cardiomyopathy involving the left ventricle and the mitral valve has been described. Repeat MRI showed a low-intensity signal in the white matter in the early stages of the disease, with involvement of the thalamus and the basal ganglia in the later stages (Koelfen *et al.*, 1994).

Pathology *Light microscopy.* All viscera, particularly the liver, kidneys, pancreas, and lymph nodes, contain lipid-laden foam cells (Dolman *et al.*, 1973). The histochemical reactions of the stored substance are the same as in the nerve cells (Pilz *et al.*, 1968). The deposits consist of globoside and a tetrahexosylceramide (Dolman *et al.*, 1973). Only sparse foam cells are seen in the bone marrow. There is conspicuous fine vacuolation of the epithelial cells of the renal tubules as well as in the loops of Henle. The coupled tetrazolium reaction produces a deep orange–brown staining of the cytoplasm of Kupffer's cells.

Electron microscopy. Pleomorphic inclusions are found in the hepatocytes, Kupffer's cells, spleen, bone marrow, and lymph nodes (Tatematsu *et al.*, 1981), and also in cells of the mitral valve in the endothelia of the blood vessels and the lymphatics, in smooth muscle cells (Fig. 116A and B), and in the cornea (Brownstein *et al.*, 1980). The inclusions are membrane bound and consist of bundles of membranes in a parallel or concentric arrangement, or merely of vesicles and granules (Dolman *et al.*, 1973). The visceral storage is quantitatively less abundant, both biochemically and ultrastructurally, than the storage of ganglioside and asialo derivatives in the CNS (Sandhoff *et al.*, 1971). Exceptionally, the storage is more pronounced in the viscera. The visceral storage material consists of globoside (Sandhoff *et al.*, 1968), hexosamine-containing glycopeptides, or oligosaccharides (Berra and Brunngraber, 1977). These substances are also detectable in the urine. Further biochemical peculiarities of type 2 are a disturbance of mucopolysaccharide catabolism detectable on tissue culture and a lack of enzyme activity against steroid hexosamines found in liver fractions (Tomasi *et al.*, 1974).

Neuropathology *Gross appearances.* The brain is considerably enlarged (Tatematsu *et al.*, 1981), but the cerebellum and the optic nerves are atrophic. The cerebral cortex is frequently thin and of a firm consistency. The subcortical white matter may be softer than normal, however, and the demarcation between the gray and white matter may thus be blurred.

Light microscopy. Practically all neurons of the cerebral cortex are ballooned. Their nuclei are displaced to the periphery, and the perikaryon is honeycombed or foamy. The Nissl substance is scanty and situated peripherally. In sections stained with luxol fast blue, the neurons contain masses of dark blue granules. The PAS reaction is only weakly positive in paraffin-embedded material, but shows numerous PAS-positive granules and clumps in frozen sections (Fig. 117). Sudan III stains the granules a pale brownish yellow; Sudan black, a bluish gray. Bright red or reddish purple metachromasia is obtained with thionin. The α-naphthol reaction for the demonstration of gangliosides is not unequivocally positive (Pilz *et al.*, 1968).

Immunohistochemically, the sections treated with an anti–GM_2 antibody show a specific fluorescence of the storage material (Schwerer *et al.*, 1982). In some cases a severe loss of neurons and gliosis can be seen in the entire cerebral cortex. Similar changes can be observed in neurons throughout the CNS. Intracytoplasmic storage is particularly prominent in various nuclei of the medulla oblongata (Fig. 118) and in the dentate nucleus of the cerebellum. The cerebellar cortex is shrunken and spongy (Tatematsu *et al.*, 1981). There is almost a total loss of Purkinje cells. The granular layer is also considerably rarefied

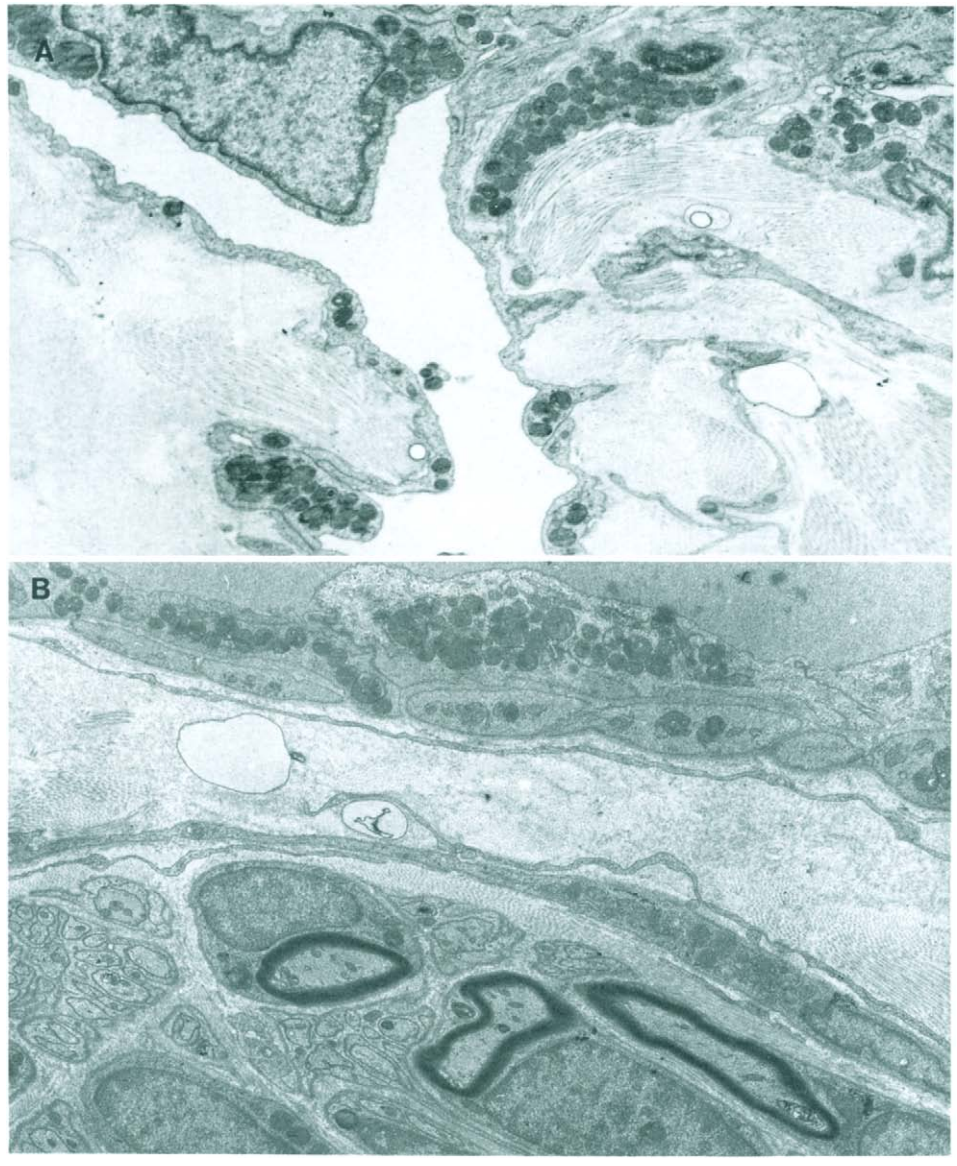


Fig. 116 GM_2 gangliosidosis type 2. The tunica propria of the conjunctiva, showing numerous inclusions in (A) endothelia of the lymphatics and (B) smooth muscle cells of a blood vessel, ×3000.

and, in places, is reduced to scanty remnants. Bergmann's glia undergoes a massive prolifera-tion. The remaining granule cells contain PAS-positive storage material. The neurons of the retina are ballooned and contain luxol fast blue-positive granules (Okuda *et al.*, 1982).

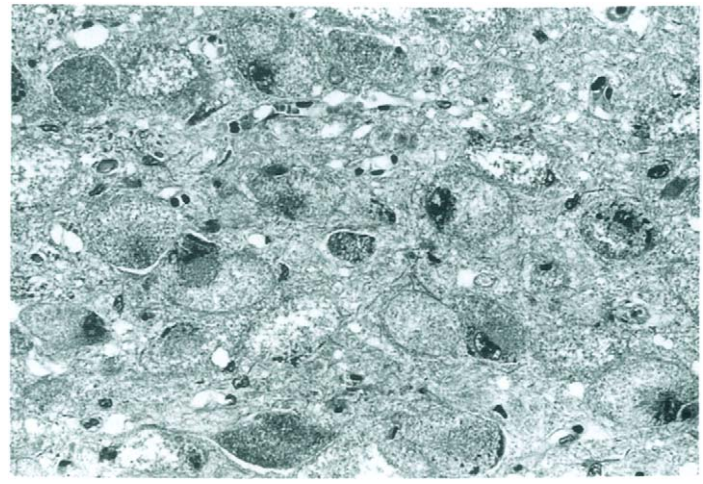


Fig. 117 GM_2 gangliosidosis type 2. Ballooned cortical neurons with large numbers of periodic acid–Schiff (PAS)-positive granules in the cytoplasm. PAS stain, ×400.

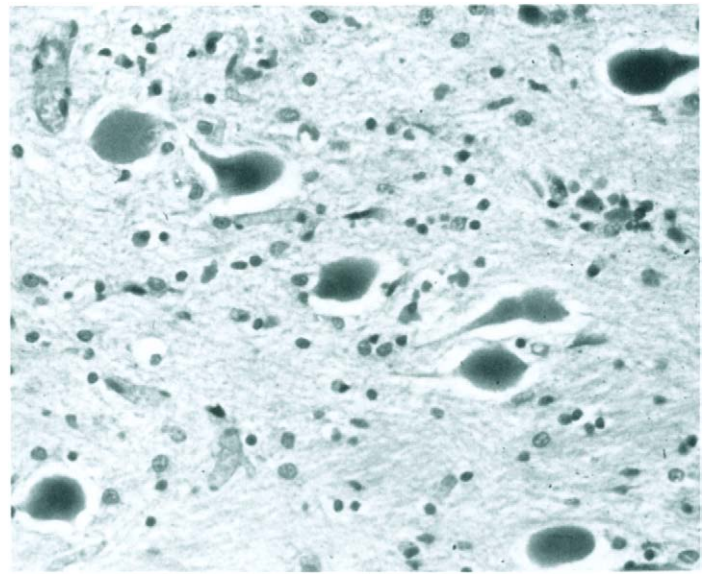


Fig. 118 GM_2 gangliosidosis type 2. Prominent storage in the neurons of the medulla oblongata. Nissl stain, ×400.

The cerebral and cerebellar white matter shows a diffuse, but not total, loss of myelin, also involving the subcortical U-fibers. A few myelin sheaths are present in the fleece of the dentate nucleus. The tracts in the pons and the medulla oblongata are pale, but not totally devoid of myelin. Fibrillary gliosis is present throughout the white matter, varying in intensity with the degree of demyelination. It is particularly dense in the dorsolateral region of the frontal and parietal lobes (Fig. 119). There is a considerable loss of axis cylinders in the white matter of the cerebrum, cerebellum, and brain stem. Biochemically, the stored substances differ from those of type 1 by a higher concentration of gangliotriosylceramides and globotetraosylceramides (Rosengren *et al.*, 1987).

Electron microscopy. The neurons contain intracytoplasmic inclusions, 1–4 μm in diameter, consisting of concentric lamellae and closely resembling the membranous cytoplasmic bodies of type 1 (Fig. 120). In addition, inclusions are present with parallel membranes, re-

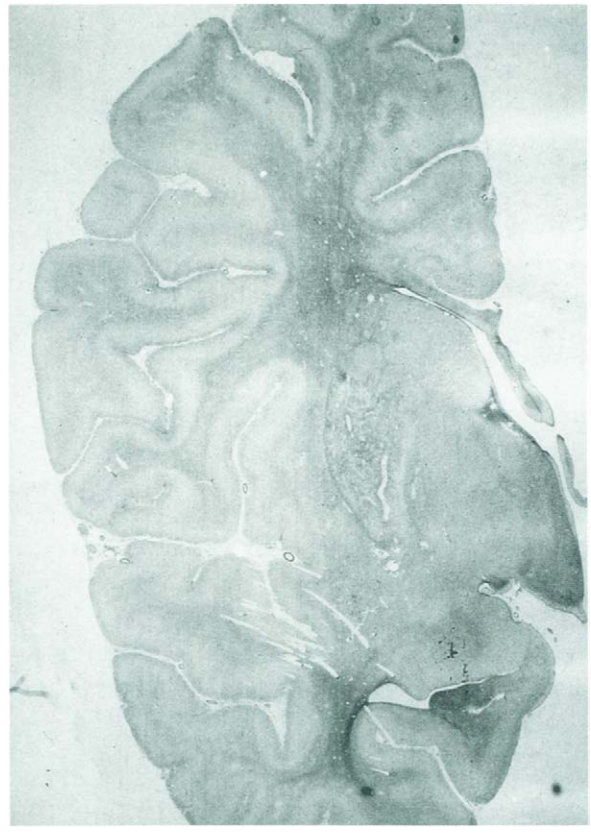


Fig. 119 GM_2 gangliosidosis type 2. Moderate to intense gliosis in various parts of the white matter. Holzer stain.

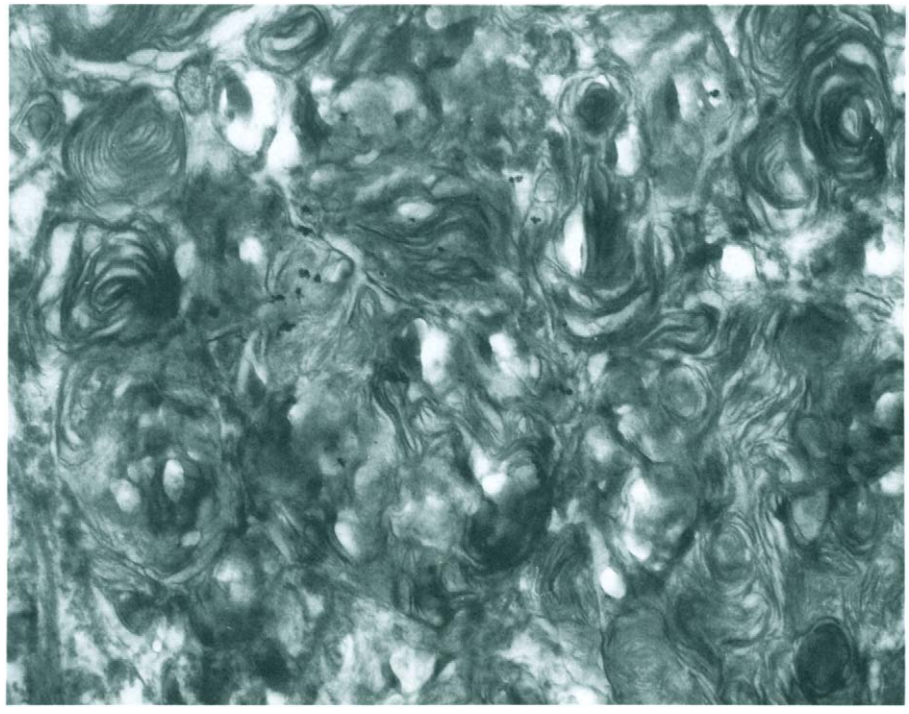


Fig. 120 GM_2 gangliosidosis type 2. A cortical neuron with lamellar intracytoplasmic inclusions, ×22,000.

sembling zebra bodies (Tatematsu *et al.*, 1981). Smaller multivesicular bodies, containing some lamellae, are seen predominantly in the astrocytes and in the endothelia of cerebral capillaries.

The neurons of the retina contain a variety of intracytoplasmic inclusions, mainly membranous cytoplasmic bodies (Okuda *et al.*, 1982). These have been seen in a 15-week fetus. In the neurons of the myenteric plexus, both membranous cytoplasmic bodies and multivesicular inclusions are present. In the axons of cutaneous nerves, numerous osmiophilic amorphous inclusions have been seen. Both in the skin and in the conjunctiva membranous cytoplasmic bodies are found in the Schwann cells (Dolman, 1984) and in the axons (Figs. 121A and B and 122).

Type 3 (Bernheimer–Seitelberger Type; Late Infantile–Juvenile Amaurotic Idiocy; Juvenile Variant)

Biochemical and ultrastructural investigations showed that the cases originally described by Jansky (1909–1910), Bielschowsky (1914), and Batten (1914) as a "late infantile form of amaurotic idiocy" form a heterogeneous group. While most of these cases belong to the ceroid lipofuscinoses (see p. 364), Jatzkewitz *et al.* (1965) mentioned an increase in GM_2 ganglioside in the brain of a patient who died at the age of 10 years with

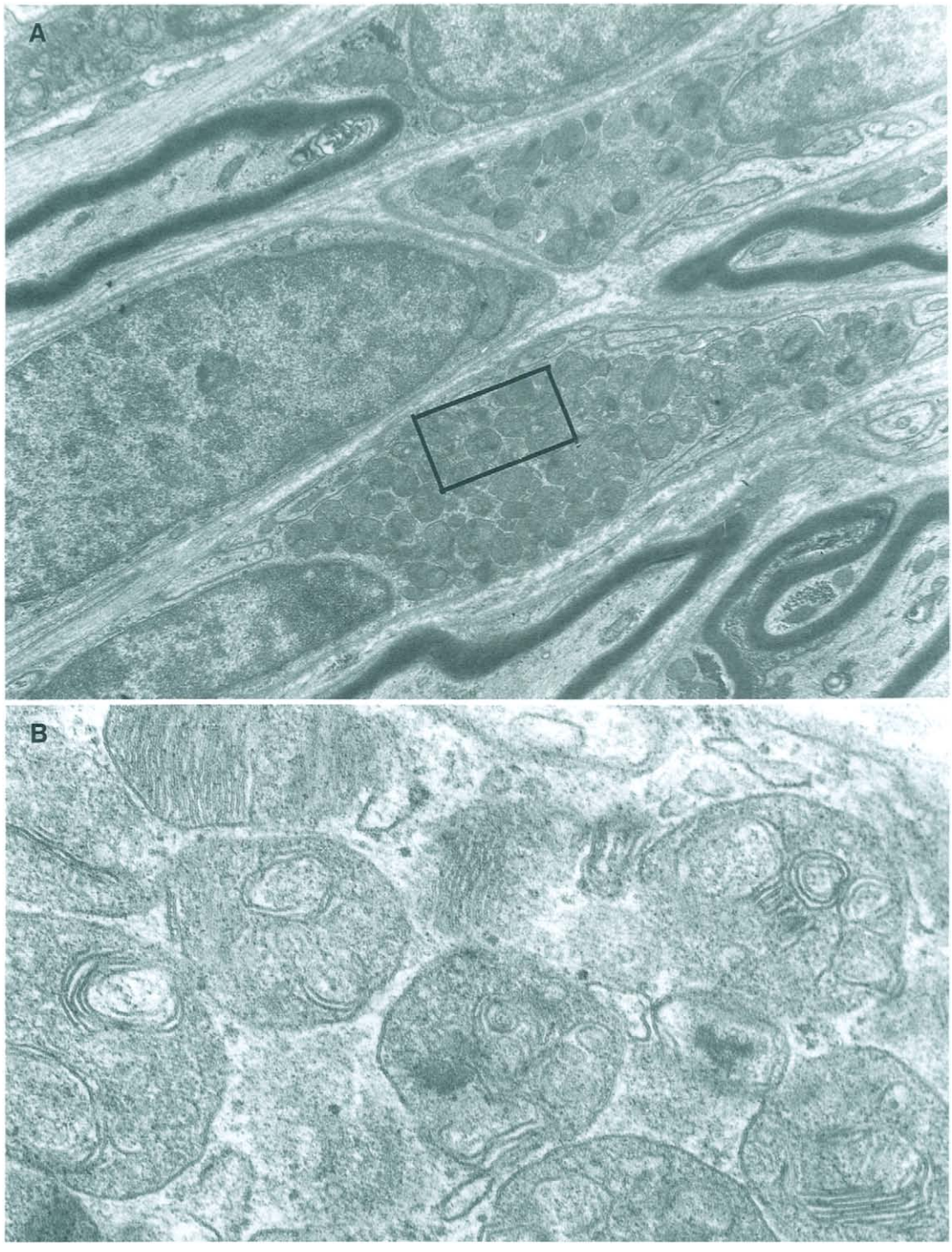


Fig. 121 GM_2 gangliosidosis type 2. The tunica propria of the conjunctiva, showing numerous inclusions in the cytoplasm of Schwann cells, consisting of irregularly arranged, partially parallel, membranes, (A) ×6000 and (B) ×40,000.

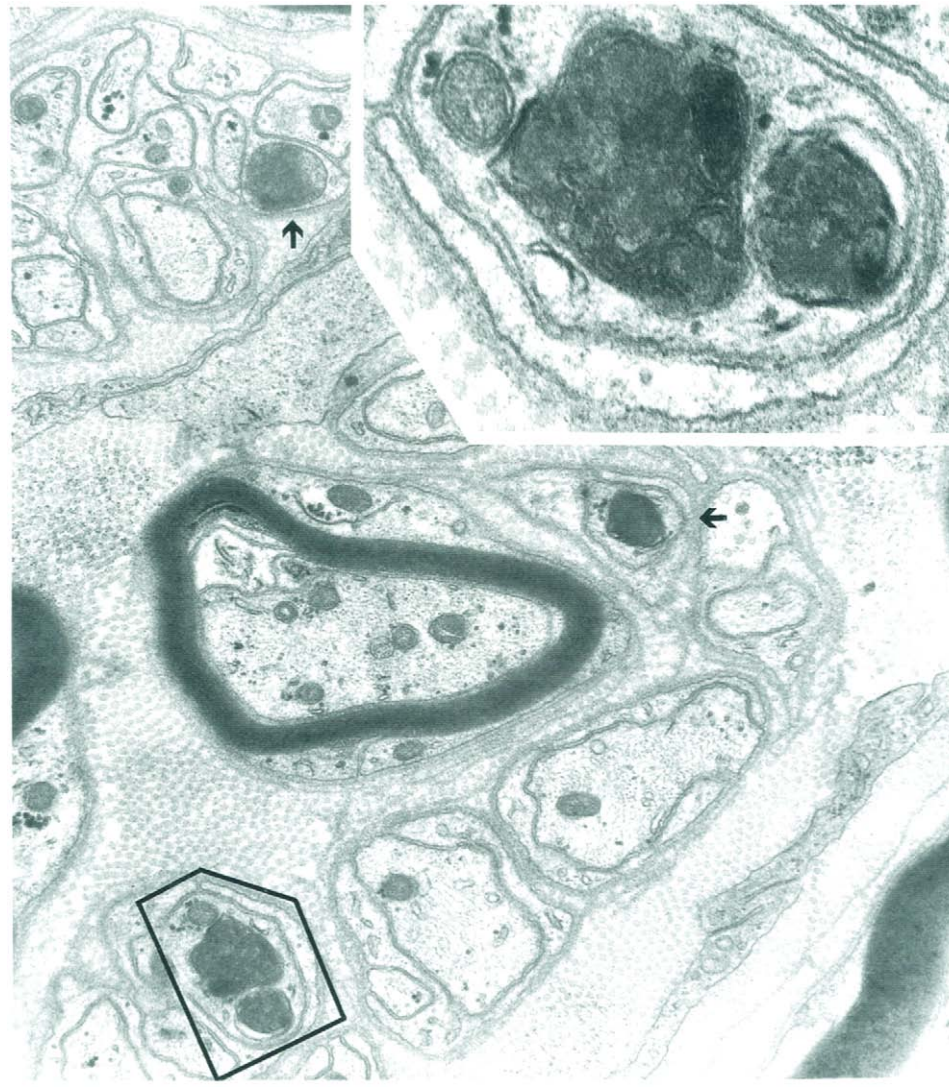


Fig. 122 Same case shown in Fig. 121. Membranous inclusions in unmyelinated axons (arrows), ×12,000 (inset ×40,000).

amaurotic idiocy. Bernheimer and Seitelberger (1968) described in detail two patients with late infantile amaurotic idiocy in whom an accumulation of GM_2 ganglioside was demonstrated by thin-layer chromatography.

Clinical Picture The disease begins toward the end of the second year or later with psychomotor disturbances, often with ataxia as the first symptom. Seizures and mental decline follow. Dystonia occurs occasionally (Nardocci *et al.*, 1992). In the first few years of the dis-

ease, gait remains preserved. In contrast with the case in types 1 and 2, which characteristically exhibit a cherry-red spot at the macula, the fundus remains normal, although in later stages optic atrophy and RP may become apparent (Brett *et al.*, 1973). Also in contrast with types 1 and 2, there is no macrencephaly in type 3 of GM_2 gangliosidosis. The final stage of the disease presents the picture of decerebrate rigidity (Brett *et al.*, 1973). The patients die between the ages of 5 and 10 years.

Pathology *Gross appearances.* The liver and the spleen may show slight atrophy. They, as well as the kidneys and the bone marrow, are histologically unremarkable.

Electron microscopy. Intracytoplasmic inclusion bodies with a concentric or irregular arrangement of lamellae may be seen in the hepatocytes (Volk *et al.*, 1969).

Neuropathology *Gross appearances.* The brain is atrophic. On coronal sections the cerebral cortex appears thin; the white matter, exceptionally firm. The atrophy affects preferentially the thalamus and the optic system. The cerebellum is not atrophic, as a rule.

Light microscopy. Almost all neurons are ballooned in the brain, spinal cord, and dorsal root ganglia, with regional differences in the intensity of the storage process. The third and fifth cortical layers are particularly affected (Borri *et al.*, 1971). The storage in the brain and the spinal cord tends to be more prominent than in other types of GM_2 gangliosidosis (Rey-Pias *et al.*, 1979). The histochemical reactions of the stored material resemble those of types 1 and 2. The astrocytes contain few PAS-positive granules, and the oligodendrocytes are unremarkable. Slight demyelination is present in the white matter of the cerebrum and the cerebellum, with apparently preserved axons. Some degeneration of the pyramidal tracts may also be present.

Electron microscopy. The neurons contain intracytoplasmic inclusions consisting of parallel or concentric membranes, pleomorphic cytosomes, and zebra bodies (Buxton *et al.*, 1972). In addition, large conglomerates of various composition may be seen, consisting of loosely or tightly packed lamellar structures, electron-dense granular material, membranovesicular bodies, and typical lipofuscin pigment. In astrocytes, perivascular histiocytes, and neurons of the rectal myenteric plexus pleomorphic cytosomes have been demonstrated.

Type 4 (Variant AB; GM_2 Gangliosidosis with Activator Protein Deficiency)

Sandhoff *et al.* (1971; Sandhoff, 1969) described a syndrome that clinically and neuropathologically resembled GM_2 gangliosidosis, in which hexosaminidases A and B were normally active against artificial substrates, but failed to catabolize natural GM_2. The variant was therefore defined as AB. A further variant was described by Inui *et al.* (1983), characterized by the inability of hexosaminidase A to bind the sufficiently available activator protein.

Clinical Picture The infants with this disease appear unremarkable during the first few months after birth, but toward the end of the first year they begin to show disturbances of motor development, increasing hypotonia, and myoclonic jerks in response to auditory stimuli. Generalized epileptic seizures have also been reported (Goldman *et al.*, 1980). The usual cherry-red spot may be seen as well as one with a black center, the so-called "black cherry-

red spot." The duration of the illness in patients with early onset is about 2 years, while those with later onset run a more protracted course (Goldman *et al.*, 1980). All children, however, die before the age of 6 years.

Pathology The viscera and the skeletal muscles show no macroscopic or microscopic abnormalities.

Neuropathology *Gross appearances.* Atrophy of both the cerebrum and the cerebellum and an increase in the total brain weight have been reported (Goldman *et al.*, 1980).

Light microscopy. Neuronal swelling has been observed in various areas, particularly the third layer of the cerebral cortex, sectors H2 and H3 of Ammon's horn, parahippocampal gyrus, thalamus, and substantia nigra and in various nuclei of the brain stem, anterior horn cells, and the intermediolateral nucleus of the spinal cord. The neurons are generally not reduced in number. In only one case was rarefaction of the neuronal population with corresponding gliosis observed in the occipital cortex (Goldman *et al.*, 1980). The stored material stains pale blue in Nissl stains and very weakly with fat stains, but is strongly PAS positive. The material often accumulates in the proximal axon near the axon hillock and shows a strong acid phosphatase activity. These swellings are often referred to as "torpedoes." In a cerebral biopsy Purpura and Suzuki (1976) demonstrated meganeurites and torpedoes in Golgi preparations. About $2\frac{1}{2}$ years later a considerable increase in the size of meganeurites and sprouting of secondary aberrant neurites could be demonstrated in autopsy material of the same case. The Purkinje cells in the cerebellum are moderately involved in storage; their number and that of the granule cells is slightly reduced. The ganglion cells of the retina are, as a rule, swollen only in the region of the macula, but not in the periphery. Neuronal swelling was also found in the autonomic nervous system (Goldman *et al.*, 1980). Astrocytes contain PAS-positive granules, which stain more intensely with toluidine blue than do those in the neurons.

Electron microscopy. The neurons contain membranous cytoplasmic bodies, 0.5–2 μm in diameter (Kotagal *et al.*, 1986). The periodicity of the lamellae is 6 nm. In the center of the membranous bodies, there is often a granular zone or a membrane-bound inclusion containing fine granular material. The membranous cytoplasmic bodies are particularly common in large pyramidal neurons. In small neurons zebra bodies are commonly seen. Pleomorphic lipid bodies and amorphous membrane-bound inclusions also occur (Goldman *et al.*, 1980). All types may coalesce to form conglomerates. Large inclusions, up to 7 μm in diameter, are conspicuous in the astrocytes. They are generally circumscribed by parallel membranes of a periodicity of 5 nm and contain aggregates of straight or curved small membranes, irregularly arranged. Sometimes they form small vesicles and may be adjacent to mitochondria or glycogen granules. The astrocytes of the white matter and the oligodendrocytes show generally smaller inclusions, 0.2–0.5 μm in diameter, but some inclusions in the oligodendrocytes may reach the size of 2 μm. They contain packed curvilinear membranes in a densely granular matrix. Endothelial cells and pericytes contain lipid inclusions, and occasionally structures resembling zebra bodies (Goldman *et al.*, 1980).

Type 5 (Adult GM_2 Gangliosidosis; Chronic GM_2 Gangliosidosis with β-Hexosaminidase Deficiency)

Type V is a genotypically and phenotypically heterogeneous group in which the common factor is a very protracted clinical course. Symptoms arise late and progress slowly with minimal deterioration so that the full clinical picture does not appear until adulthood. The inclusion of all cases in a single group is provisional. The wide variation of symptomatology in the few reported cases does not justify a detailed classification. Nevertheless, two subtypes may be recognized. The full range of clinical manifestation in both subgroups has been reviewed by Federico *et al.* (1991). Sensory neuropathy may be a prominent feature, as has been shown in a few cases (Barnes *et al.*, 1991; Sica *et al.*, 1992). Presentation with psychiatric disturbances has been reported by Hurowitz *et al.* (1993).

Subtype 5/1 (Motor Neuron Type): This subtype includes the majority of the cases of Rapin *et al.* (1976) as well as those of Navon *et al.* (1981) and Johnson (1982). Some of the patients were Ashkenazi Jews; others were of non-Jewish origin (Johnson, 1982). Other, not easily classifiable, cases may also be included in this group.

Clinical Picture Weakness of the legs becomes apparent between the ages of 15 and 20 years. In retrospect, it can be presumed that a slight weakness may have been present since childhood in some patients (Navon *et al.*, 1981; Johnson, 1982). The muscular weakness develops slowly and is followed by disturbances of speech and psychotic manifestations (Dale *et al.*, 1983). The disease may mimic amyotrophic lateral sclerosis (Siliman *et al.*, 1983) or spinal muscular atrophy (Parnes *et al.*, 1985). Occasionally, protracted acne may continue long after puberty (Navon *et al.*, 1981). The disease runs a decidedly chronic course and most patients survive for decades after the onset of symptoms and often die at ages over 60 years.

Subtype 5/2 (Spinocerebellar Ataxia Form): Some of the cases of Rapin *et al.* (1976) belong to this group, as well as those of Willner *et al.* (1981), among others. The first symptoms appear already at the age of 2–3 years. Even if they are obvious only at a later age (Willner *et al.*, 1981), they can be traced retrospectively to early childhood.

Tremor or dysarthria with dysdiadochokinesis and limb and trunk ataxia are often the first symptoms. Many patients are first diagnosed as having Friedreich's or spinocerebellar ataxia. Disturbances of cerebellar control of the eye movements have been described (Musarella *et al.*, 1982). A case with internuclear ophthalmoplegia and a peripheral sensory neuropathy was reported by Barnes *et al.* (1991). The disease is slowly progressive and most patients are at first mentally normal. Psychotic episodes or dementia are described in one third of the older patients. The only hitherto reported death was due to intercurrent hepatitis and bronchopneumonia (Rapin *et al.*, 1976). The nine patients of this phenotype belong to four families of Ashkenazi Jews.

Other patients exhibit tremor, dystonia, or choreoathetosis and other symptoms of cerebellar or extrapyramidal origin (Meek *et al.*, 1984; Oates *et al.*, 1986).

Pathology In view of the paucity of recorded autopsies, it is not possible to distinguish characteristic features of the two subtypes. The available findings are therefore presented together.

Hepatosplenomegaly was rarely reported. On light microscopy a muscle biopsy showed neurogenic atrophy with fiber type grouping (Navon *et al.*, 1981; Willner *et al.*, 1981). No storage was seen in the viscera other than in their neuronal elements.

Neuropathology *Gross appearances.* The cerebrum is generally unremarkable, while the cerebellum shows distinct atrophy in some cases (Rapin *et al.*, 1976). Occasionally, the lateral ventricles are dilated. The consistency of the cerebellar white matter is firm.

Light microscopy. The lesions are predominantly subcortical (Suzuki, 1991). More obvious ballooning is seen in subcortical centers, particularly the substantia nigra (Fig. 123), Ammon's horn, and the mesencephalic and pontine nuclei. The thalamus is not always involved. There is general agreement on the slight involvement of the striatum and the pallidum. The most severe lesions are found in the spinal cord (Rapin *et al.*, 1976). The cytoplasm of the ballooned cells is granular in appearance. The granules stain with Sudan black, luxol fast blue, and PAS. There is a diffuse loss of myelin in both the cerebral and cerebellar white matter with mild gliosis. The number of Purkinje cells is reduced. The remaining cells show conspicuous storage in the perikarya and the dendrites. The neurons in rectal biopsies show swollen cytoplasm, which stains with Sudan black.

Electron microscopy. Pleomorphic inclusions are seen in the neuronal cytoplasm of the entire CNS. Some of these inclusions contain concentric membranous bodies (Fig.

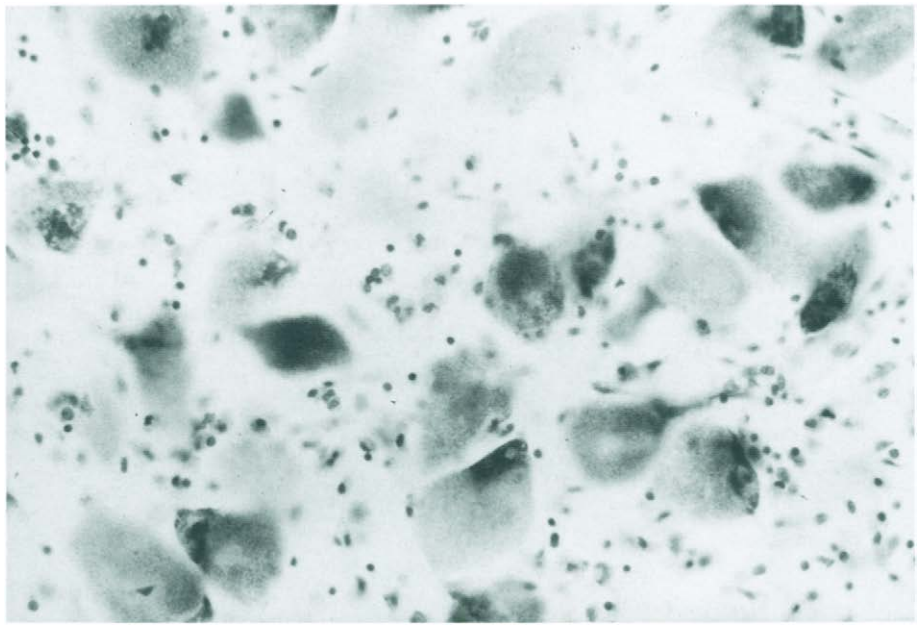


Fig. 123 GM_2 gangliosidosis type 5. Swollen neurons in the substantia nigra. Nissl stain, ×250.

124A–D), but the majority show a parallel or irregular arrangement of membranes. In addition to membranous bodies, large amounts of lipopigments form pleomorphic inclusions (Fig. 125A and B). Occasionally, fingerprint profiles are seen, as in juvenile neuronal ceroid lipofuscinosis. Most inclusions range from 0.5 to 1 μm in diameter, but some may reach 2 μm. Conglomerates of adjacent inclusions may reach the size of 6 μm. Inclusions are also present in the astrocytes and the oligodendrocytes, generally in the form of fingerprint bodies (Fig. 126), and less commonly in the pericytes of intracerebral blood vessels. In the neurons of the peripheral ganglia, in various organs, and in the intestinal plexuses, membranous bodies are the most common inclusions (Oates *et al.*, 1986). In the peripheral nerves one finds axonal degeneration and disintegration of the myelin sheaths. Both in the axons and in Schwann cells one finds laminated membranous bodies, occasional zebra bodies, and dense osmiophilic inclusions (Cashman *et al.*, 1986). The membranous inclusions resemble those of the nerve cells, but they have a more irregular structure.

Pathogenesis The enzymopathy of GM_2 gangliosidosis concerns the hexosaminidases, which split off the terminal β-*N*-acetylglucosamine and β-*N*-acetylgalactosamine. One can distinguish three isoenzymes of hexosaminidase: A, B, and S. In normal circumstances only hexosaminidase A is relevant to the catabolism of GM_2 ganglioside (Sandhoff *et al.*, 1971). All other natural hexosaminidase substrates can be broken down by both isoenzymes A and B. Mucopolysaccharides and steroid hexosamines are natural substrates of the hexosaminidases.

Gilbert *et al.* (1975) established that the genes responsible for the three isoenzymes are located on different chromosomes. Furthermore, it has been shown that the deficiency of hexosaminidase A in types 1 and 2 is caused by different gene defects, as hybridization of cells from the two types corrects the deficiency. During immunological investigation of GM_2 gangliosidosis type 2, practically no hexosaminidase A antigen was detected, while the B antigen was present, although in this type both enzymes are inactive. These findings supported the view that the hexosaminidases consist of two subunits, one of which is shared by hexosaminidases A and B.

As mentioned above, there are three isoenzymes of hexosaminidase. Each consists of an α- and β-subunit. The gene locus that codes for the α-subunit is located on chromosome 15; that which codes for the β-subunit can be found on chromosome 5. Both subunits combine to form the complete hexosaminidases: A, B, and S. Hexosaminidase B consists of β-subunits of a structure $(\beta/\beta)_n$, hexosaminidase A consists of an α- and a β-subunit (α/β), and hexosaminidase S consists of two α-subunits $(\alpha/\alpha)_n$ (Johnson, 1981).

Patients with hexosaminidase A deficiency but with normal B activity (type 1) have a defect at the α-locus. Patients with hexosaminidase A and B deficiency (type 2) have, in addition, a defect at the β-locus. Patients with type 5 have, as a rule, a defect at the α-locus, and possibly also at the β-locus.

As both the α- and β-subunits consist of numerous amino acids that can be substituted in a variety of ways, the possibilities of mutations affecting both subunits are immense (Akli *et al.*, 1993). Most of the hitherto identified mutations affect the α-subunit, the gene of which has been coded and located on chromosome 15q22–25. As a general principle, mutations that produce highly unstable mRNA, or none at all, cause the most severe infantile forms of the disease, while late-onset forms are due to point mutations (Suzuki, 1994a). In Tay–Sachs disease of Ashkenazi Jews, the mutation consists of a

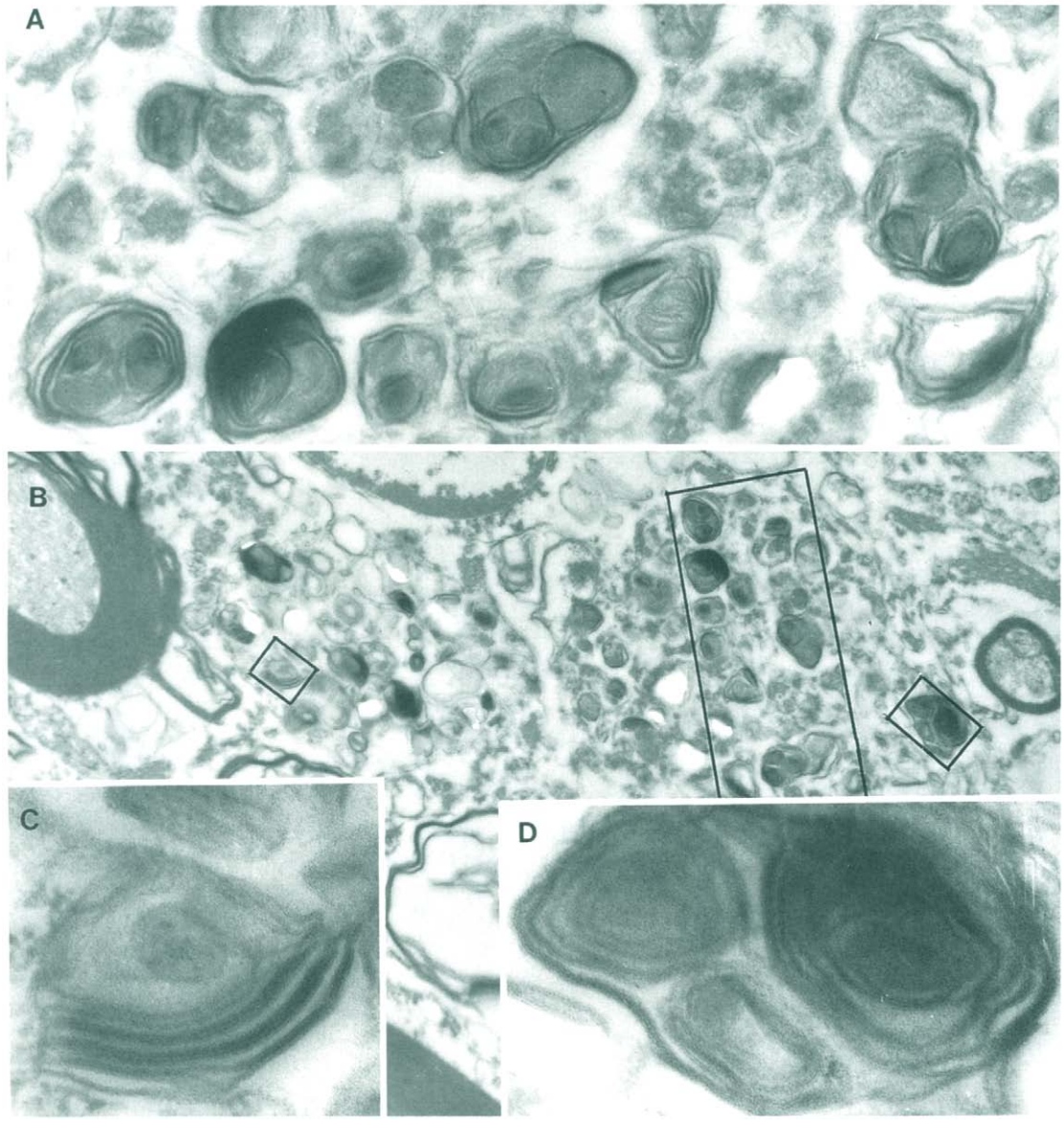


Fig. 124 Same case shown in Fig. 123. A neuron in the substantia nigra, showing pleomorphic inclusions with laminated membranes, partly parallel and partly concentric, (A) ×20,400, (B) ×6300 and (C and D) ×50,000.

G-to-C transversion at the 5′ splice site of intron 12 (Paw *et al.*, 1990) and a 4-bp insertion in exon 11 (Myerowitz and Costigan, 1988). In the French Canadian population the disease is due to a major deletion at the 5′ end of the gene (Hechtmann *et al.*, 1992). A high frequency of an intron 9 mutation was found in patients from the British Isles (Lan-

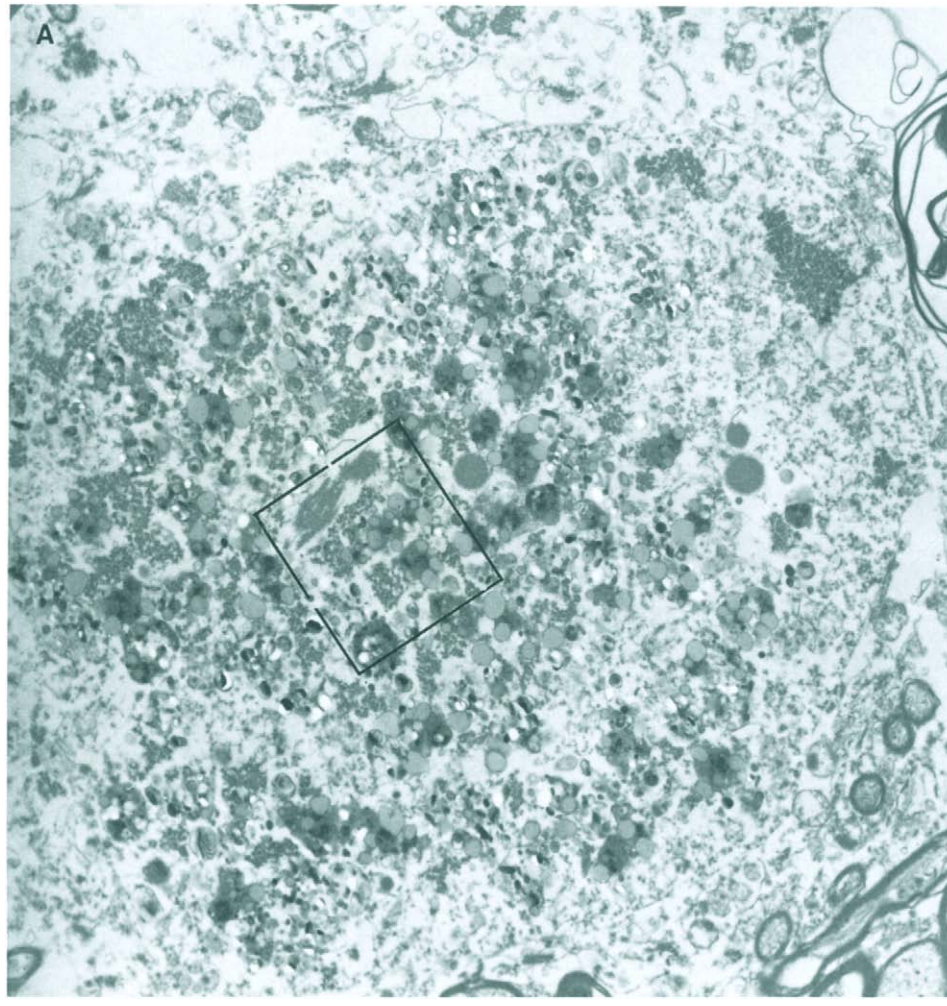


Fig. 125 Same case shown in Fig. 123. A neuron in the parietal cortex, showing abundant lipopigment and formation of pleomorphic inclusions, (A) ×3960 and (B) ×20,000.

dels *et al.*, 1993). The most common mutation in the B1 variant (the so-called "*DN* allele") is a G-to-A transition at nucleotide 533 causing an R-to-C substitution at position 178 (Tanaka *et al.*, 1990). Most adult patients are either homozygotes or compound heterozygotes for a point mutation causing an S-to-G substitution at position 269 (Navon, 1991).

In GM_2 gangliosidoses the deficiency of hexosaminidase (*N*-acetyl-D-galactosamine) (Sandhoff, 1969) renders the splitting off of the terminal hexosamine (*N*-acetyl-β-D-galactosaminidase) impossible. The gangliosides and their asialo derivatives accumulate in variously structured inclusions, the high acid phosphatase activity of which indicates their lyso-

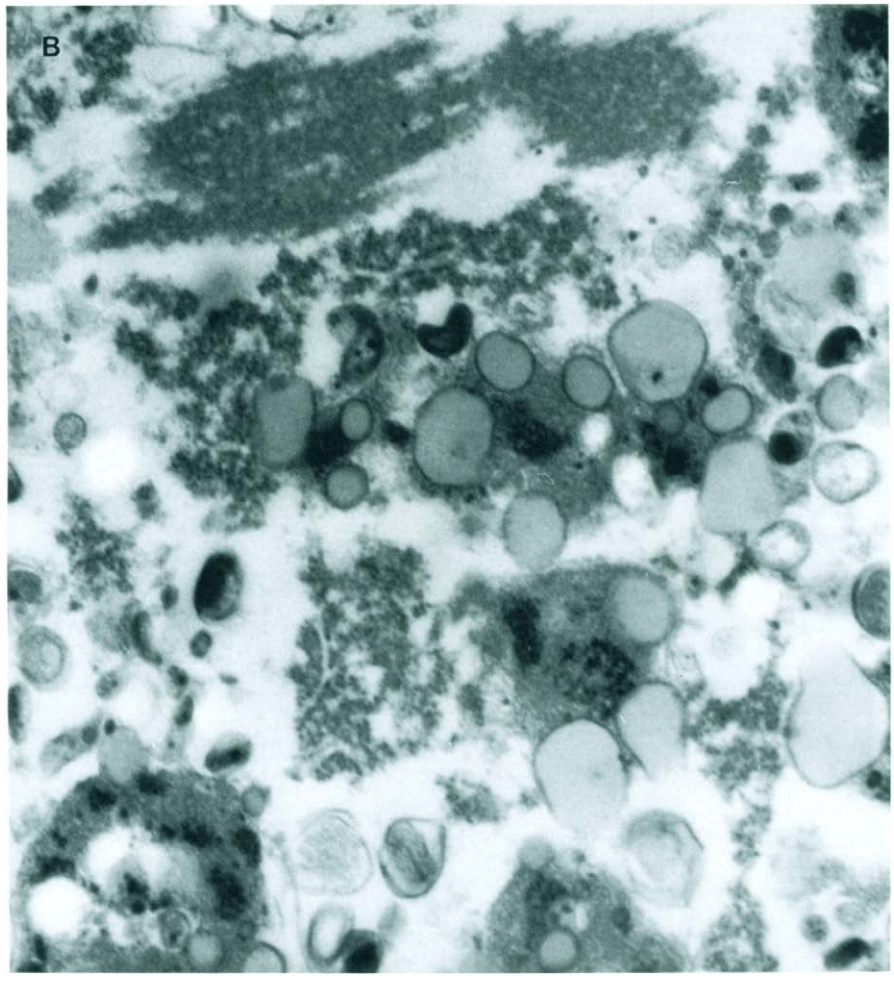


Fig. 125 Continued.

somal origin. As gangliosides are characteristic components of the nervous tissues, the storage affects primarily the brain.

The cherry-red spot found at the macula in GM_2 gangliosidosis types 1 and 2, as well as in some other neurolipidoses, is due to an increased opacity of the ganglion cell layer, caused by neuronal storage and aggravated by interstitial edema. The ganglion cells, being particularly numerous in the zone surrounding the macula, form a dense white ring and throw into relief the normal macula, which, being devoid of ganglion cells, retains its translucency. The disappearance of the cherry-red spot, observed in some cases in the advanced stages of the disease, is due to the progressive degeneration and loss of the affected ganglion cells.

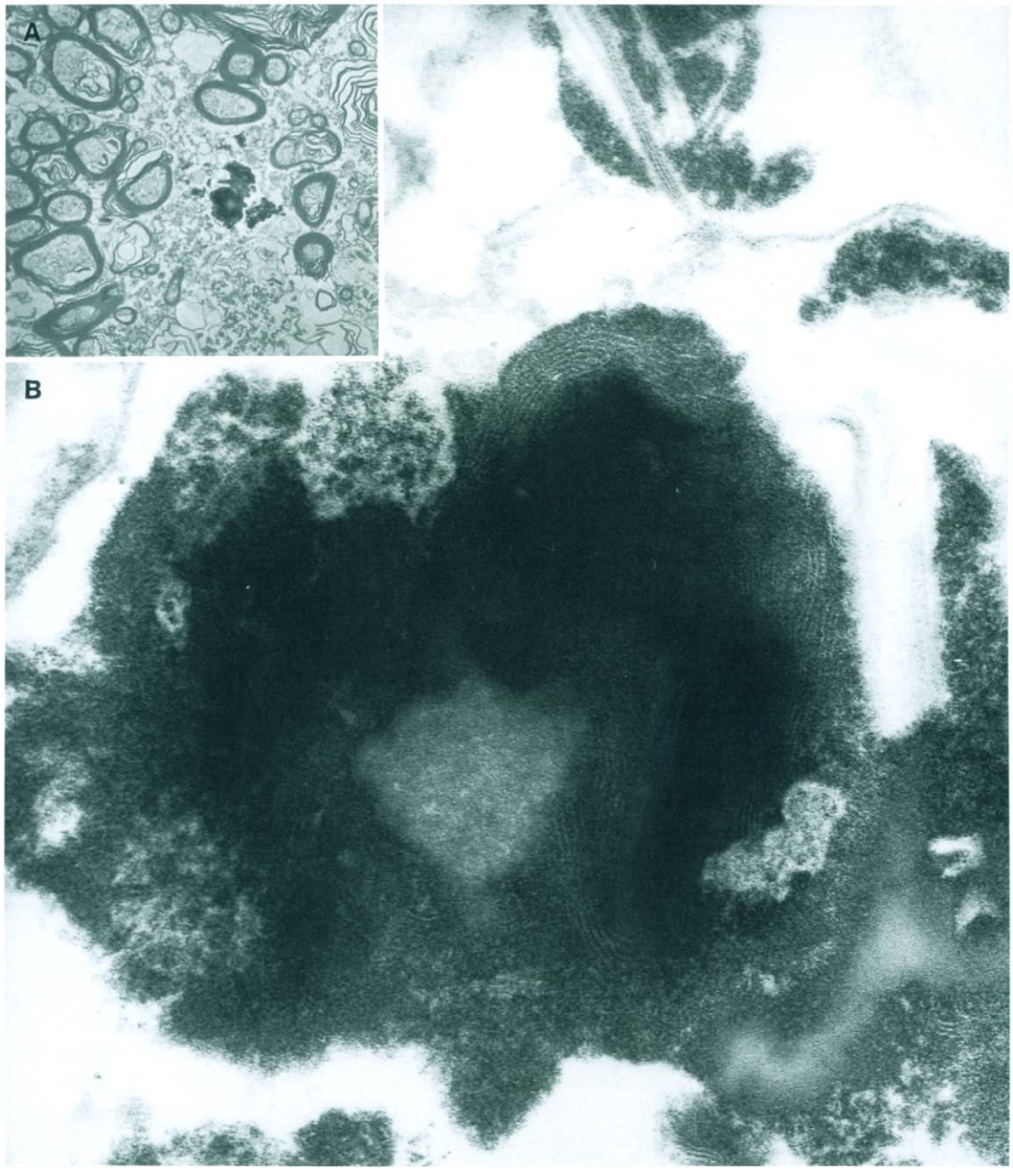


Fig. 126 Same case shown in Fig. 123. The white matter, showing an inclusion in an oligodendrocyte with a fingerprint pattern, ×60,000 (inset ×1800).

In GM_2 gangliosidosis types 1 and 2 the visceral organs are also involved in storage. Few gangliosides accumulate in the organs, as, with the exception of GM_3 and some GM_1, they are not normal components of visceral lipids. On the other hand, oligosaccharides and globosides (proteoglycans) accumulate, as they share with cerebral gangliosides the terminal sugar residue that cannot be split off because of the enzyme deficiency.

The deficiency of only one part of the system (hexosaminidase A) results in a different pattern in the quantity and distribution of storage from the effect of deficiency of the entire system (hexosaminidases A and B) (Sandhoff *et al.*, 1971). The latter deficiency in type 2 causes an accumulation of more substances, both qualitatively and quantitatively, than in type 1 (Sandhoff *et al.*, 1971). This is due to both the loss of the partially compensatory function of hexosaminidase B for the missing hexosaminidase A and the loss of its specific function. The heterogeneity of the cases in type 2 has been repeatedly demonstrated (Gautron *et al.*, 1983). The enzyme deficiencies responsible for the storage processes are rarely complete, and some residual activity is found in most cases. The correlation of this residual activity with the amount of stored material is clearly seen in type 3, in which considerable residual activity of hexosaminidase A remains. This results in a relatively low-grade storage and a protracted clinical course. Some symptoms, such as the cherry-red spot, may be entirely absent. There are, however, exceptions to this rule. The residual activity of hexosaminidase A may be no higher in type 3 than in type 1 and yet the other criteria of type 3 may be satisfied.

The absence of a natural activator protein was demonstrated in extracts of human kidneys, in patients of type 4. This activator protein is necessary for the hydrolytic activity of the hexosaminidases, as it forms a water-soluble complex with GM_2 and renders it accessible to the enzyme. The full cDNA for the activator protein has been characterized by Klima *et al.* (1991). A mutation in this gene, with a T-to-C transition at nucleotide 412, causing a C-to-R substitution at position 107, was discovered in a case of GM_2 gangliosidosis variant AB (Schröder *et al.*, 1991). Another type of the AB variant may possibly be caused by a structural change in hexosaminidase A. Clinically and biochemically, the two variants are indistinguishable. A further biochemical finding in the gangliosidoses is the decrease in the myelin lipids, cerebroside, sulfatide, C_{24} sphingomyelin, and others. This is largely due to the neuronal loss with a breakdown of myelin, followed by stagnant myelin formation (Sandhoff *et al.*, 1971).

In GM_2 gangliosidosis type 5 all patients show a reduction of hexosaminidase A activity in the plasma, leukocytes, and tear fluid. Some of these patients are heterozygotes in families of type 1. It may be assumed that the coexistence of heterozygosity with different alleles leads to the chronic variant (Johnson, 1982). The available residual activity of the enzyme ensures that storage occurs exclusively in the neurons. In other patients a reduced activity of hexosaminidase B is also detected. In some patients an increased activity of both hexosaminidases is present, with a simultaneous accumulation of GM_2 ganglioside in all tissues. It was therefore concluded that the patients belonged to type 4. The variations in the clinical course in the early forms of the disease depend on the stage of development at which the disturbances of cellular function develop. In the late forms one must assume regional differences in the storage mechanism (Schulte, 1984).

GM_2 Gangliosidosis in Animals GM_2 gangliosidosis has been found in dogs (Ishikawa *et al.*, 1987) and in Yorkshire pigs (Pierce *et al.*, 1976). A hereditary autosomal

disease was observed in cats, presenting with head tremor and ataxia. A severe deficiency of hexosaminidases A and B was found in the brain and the liver, with a massive accumulation of GM_2 gangliosides (Neuwelt *et al.*, 1985).

GM_3 Gangliosidosis

There are only a few adequately documented cases of GM_3 gangliosidosis in the literature (Max *et al.*, 1974; Mitra *et al.*, 1978). Whether other cases belong to this group is debatable. The confirmed cases differ considerably in their morphology and in their probable pathogenesis. They are therefore considered separately here.

Case of Max et al. (1974)

Clinical Picture The patient was a male infant of Jewish descent who, soon after birth, presented with poor psychomotor development; coarse facies; macroglossia; gingival hypertrophy; squat hands and feet; flexor contractures of the fingers; thickened, loose, hirsute skin; bilateral inguinal hernias; an enlarged liver and spleen; and normal fundi. His parents were healthy and unrelated. The child's condition deteriorated rapidly, he became limp and unresponsive, and he died at the age of $3\frac{1}{2}$ months. Mitra *et al.* (1978) described a female who died at the age of $4\frac{1}{2}$ years, having suffered from psychomotor retardation, hypotonia, myoclonus, and seizures. This case probably represented a pathogenetically different form of GM_3 gangliosidosis (see below).

Pathology Morphological studies have been reported by Tanaka *et al.* (1975). In spite of the clinical hepatosplenomegaly, the liver was histologically normal but contained an increased amount of GM_3 ganglioside.

Neuropathology *Gross appearances.* The brain weight was 20% above normal. The cerebral cortex was unremarkable, but the subcortical and deep white matter of the hemispheres was soft and gray. The corpus callosum was thin. The internal capsule and the white matter of the pons and the medulla were chalky white and sharply demarcated from the surrounding tissue.

Light microscopy. No neuronal storage was found. Vacuolation and status spongiosus were seen in the white matter of the hemispheres, brain stem, cerebellum, optic nerve, and spinal cord. There was an increased number of astrocytes, which resemble Alzheimer's type II cells.

Electron microscopy. The vacuolation of the white matter was seen to be due to separation of the myelin lamellae. The astrocytic cytoplasm and processes were swollen. Cytoplasmic membranes continuous with dilated cisternae of the endoplasmic reticulum were seen in the astrocytes. The mitochondria contain a granulofilamentous matrix and distorted cristae. Cytoplasmic granulofilamentous bodies were found adjacent to the mitochondria.

Pathogenesis The amount of GM_3 ganglioside was increased to several times the normal values in the brain and the liver, while the higher gangliosides, GM_2 and GM_1,

were totally absent. There was a deficiency of GM_3 UDP-*N*-acetylgalactosamyltransferase. This enzyme is required for the synthesis of GM_2 from GM_3 (Fishman, 1974). Both the morphological and biochemical findings suggest a defective anabolic mechanism, not a deficiency of GM_3 catabolism.

Case of Mitra et al. (1978)

Clinical Picture This patient was a $4\frac{1}{2}$-year-old girl with a history of progressive psychomotor retardation, hypotonia, seizures, and myoclonic jerks. No abnormalities were found in the leukocyte enzymes. A brain biopsy showed lipid storage in the neurons.

Neuropathology Autopsy confirmed generalized neuronal storage of lipid material. Electron microscopy revealed membranous cytoplasmic bodies, zebra bodies, and granular cytoplasmic inclusions.

Pathogenesis Analysis of the cerebral gray matter revealed a 20–30% increase in total gangliosides. Thin-layer chromatography demonstrated a 15-fold increase in GM_3 ganglioside with a lesser increase in the GM_2 type. The authors postulated a deficiency of a catabolic enzyme that breaks down GM_3 ganglioside to lactosylceramide and ruled out the possibility of a defect in ganglioside biosynthesis.

Disorders of Long-Chain Fatty Acid Metabolism (Peroxisomal Diseases)

The fact that both in the cerebrohepatorenal syndrome and in adrenoleukodystrophy there is defective oxidation of very long-chain saturation and unbranched fatty acids has led to the conclusion that both diseases may share a common pathogenetic mechanism. This has been shown to be due to defective function of the peroxisomes (Wanders *et al.*, 1988).

These bodies, described by Rhodin (1954) and stained with diaminobenzidine, are respiratory organelles that contain oxidases and catalases. They are ubiquitous in mammalian cells and have a round or irregularly oval profile and a diameter between 80 and 200 nm. They are surrounded by a single membrane, have a dense coarsely fibrillary structure, and exhibit a strong catalase activity. Their principal enzyme is catalase, which splits hydrogen peroxide into water and oxygen, but oxidases that form H_2O_2 are also present. In addition, they have the following functions: the synthesis of plasmalogens, the synthesis of bile acids, the catabolism of very long-chain fatty acids, the catabolism of pipecolic acid, and the catabolism of phytanic acid. The appropriate enzymes are synthesized in free polysomes and transported through the cytosol into the peroxisomes (Powers, 1994). Over 40 peroxisomal enzymes have been identified (Moser *et al.*, 1991). Many of these can be identified in section by immunohistochemistry (Kamei *et al.*, 1993). Small peroxisomes (microperoxisomes), frequently associated with the endoplasmic reticulum, have been seen in some disease with absent peroxisomes and are also seen normally in cells with low peroxisomal activity.

Classification of Peroxisomal Diseases

The diseases associated with defective function of the peroxisomes fall into three main groups (Powers, 1994).

1. Diseases in which peroxisomes are, for practical purposes, absent or severely deficient in all their functions: Zellweger, or cerebrohepatorenal, syndrome; neonatal adrenoleukodystrophy; infantile Refsum disease; and hyperpipecolic acidemia
2. Diseases in which peroxisomes are present but lack several enzymes: rhizomelic chondrodysplagia punctata and the Zellweger-like syndrome of Suzuki
3. Diseases with a single deficient enzyme: adrenoleukodystrophy and adrenomyeloneuropathy, pseudo-Zellweger syndrome, and pseudo-neonatal adrenoleukodystrophy.

To these may be added disorders with circumstantial evidence of a peroxisomal disease, but with an unknown defect, and Refsum disease, which shares some features with these disorders, but is probably caused by deficiency of a mitochondrial enzyme.

Cerebrohepatorenal Syndrome (Zellweger Syndrome)

Cerebrohepatorenal syndrome was described by Bowen *et al.* (1964). It is an autosomal-recessive disorder characterized by multiple developmental defects in organs of mesodermal and ectodermal origin. A transitional form between the Zellweger and Lowe syndromes without disturbances in iron metabolism was described by Vuia *et al.* (1973).

Clinical Picture The disease is apparent at birth. The infants are weak and hypotonic with brisk reflexes. The dysmorphic features consist of a high forehead, a flat occiput, deformed ears, a high arched palate, and a protruding tongue. Chondrodysplasia calcificans congenita, equinovarus pes, and camptodactyly are also present. Hepatomegaly and splenomegaly are frequently found. Fatal gastrointestinal disturbances may occur. Almost all infants find drinking and swallowing difficult. Epileptic seizures occur in about one half of the patients. Hittner *et al.* (1981) drew attention to opacities in the lens as an additional diagnostic sign. The blood level of iron and the iron binding capacity are considerably increased. The CT scan reveal widespread demyelination and abnormally deep sulci suggestive of a cortical malformation (Aubourg *et al.*, 1985).

Seventy percent of these patients die within weeks or months of birth (Zellweger, 1982). Patients suffering from a variant with muscular hypertonia and without dysmorphic facial features may survive over 1 year (Vermold *et al.*, 1977). Another, milder, variant was reported by Barth *et al.* (1985).

Pathology *Gross appearances.* The kidneys are atrophic in all cases and exhibit multiple superficial cortical cysts (Lindhard, 1993). In 50% of the patients, particularly those who survive longer than 6 months, one finds cirrhosis of the liver with hepatomegaly.

Light microscopy. Iron deposits are seen in the liver, kidneys, and bone marrow. Abundant hemosiderin pigment is present in the reticuloendothelial cells, spleen, and pulmonary alveoli, among other organs. Partial agenesis of the thymus and hyperplasia of the pancreatic islets have been reported. Kerckaert *et al.* (1988) found two types of bire-

fringent inclusions in kidney and brown adipose tissue. The first was transparent on a bright field; the second appeared as brown granules or rods, similar to lipofuscins. Electron microscopic investigation of these cells showed trilaminar structures within membrane-bound organelles. Lipid-laden cells with striated cytoplasm are found in the adrenals. The diagnosis of Zellweger syndrome can be made based on the absence of histochemical staining for catalase in the liver biopsy (Raafat *et al.*, 1991).

Electron microscopy. An absence of peroxisomes and smooth endoplasmic reticulum, as well as abnormal mitochondria, has been observed by Goldfischer *et al.* (1973) in the liver and the kidneys. Vermold *et al.* (1977) confirmed the absence of peroxisomes, but found a normally developed smooth endoplasmic reticulum. Abnormally small peroxisomes were seen in the hepatocytes by Pfeifer (1979). Lamellar structures similar to those found in adrenoleukodystrophy are seen in the adrenals. A mitochondrial myopathy (Mueller-Hoecker *et al.*, 1984) was reported, as well as inclusions in the fibers of the lens (Hittner *et al.*, 1981).

Neuropathology *Gross appearances.* Both polymicrogyria and macrogyria are apparent in the cerebral cortex, particularly in the supralimbic regions (Lindhard *et al.*, 1993). The corpus callosum is very thin and may be partially or totally absent (Bowen *et al.*, 1964). Agenesis of the vermis may be present in the cerebellum (Fig. 127). Paraventricular cysts have been observed (Zellweger, 1982).

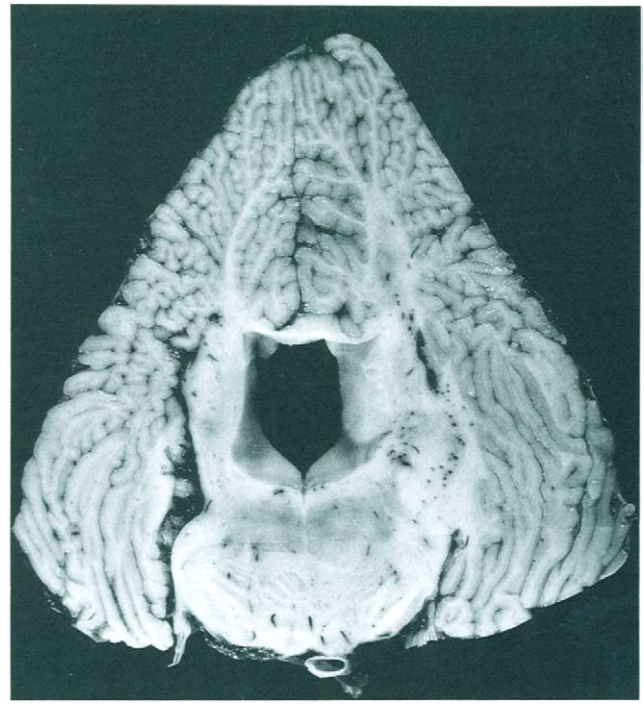


Fig. 127 Zellweger syndrome. Agenesis of the vermis.

Light microscopy. Multiple symmetrical subcortical heterotopias are apparent, consisting of various types of pyramidal cells. Golgi impregnations revealed irregular neuronal arrangement, immature neurons, poor dendritic arborization, and poor spine development (Takashima *et al.*, 1991b). The thalamic and hypothalamic nuclei as well as the dentate nuclei may show an abnormal structure (Fig. 128A and B). Neuroblasts are found scattered throughout the white matter. Heterotopias of large cells, resembling Purkinje cells, are seen in the cerebellar white matter. Reductions in the number of large pyramidal neurons in the third and fifth cortical layers, of Purkinje cells, of olivary neurons, and of neurons of the anterior and posterior horns of the spinal cord have been repeatedly reported. The astrocytes proliferate with the formation of numerous Alzheimer's type II cells. Numerous foam cells in the cortex form well-defined clusters and can be visualized by a variety of stains. A patchy demyelination with gliosis and isolated fat granule cells was seen in a few cases. A selective neuronal lipidosis and axonal dystrophy were found in the nucleus dorsalis of Clarke (Fig. 129B) and in the lateral cuneate nucleus. Immunohistochemical study of the peroxisomal enzymes, catalase, and β-oxidation enzymes can be performed on the brain by conventional paraffin-embedded autopsy material (Kamei *et al.*, 1993). Changes in the retina and the optic nerves suggestive of tapetoretinal degeneration or congenital optic atrophy are present. In contrast with other organs, no iron pigment is deposited in the brain.

Electron microscopy. Prominent glycogen accumulation is seen in the neurons and the glial cells. Homogeneous lipid droplets are present in the glial cells; lamellar and complex residual bodies are seen in the histiocytes. In addition, elongated, slightly curved, prismatic rods, resembling those seen in adrenoleukodystrophy, and cholesterol crystals may be seen. Similar inclusions have been found in retinal ganglion cells. Abnormal mitochondria and peroxisomes have been observed in the astrocytes. Axonal swellings filled with neurofilaments are seen in the peripheral nerves.

Pathogenesis Goldfischer *et al.* (1973) drew attention to the absence of peroxisomes in the liver and the kidneys. The pathogenetic significance of an abnormal excretion of pipecolic acid found in patients from different families remains unclear. Björkhem and Falk (1983) observed abnormalities in the bile acids, which are a reflection of the disorder of oxidation of long-chain fatty acids. Datta *et al.* (1984) found reduced activity of the peroxisomal enzyme dihydroxyacetone phosphate acetyltransferase, and Heymans *et al.* (1984) noted a deficiency of plasmalogens in the liver, kidneys, and brain. The disease is ascribed to the lack of a protein component necessary for the formation of peroxisomes or a defect in the import of peroxisomal components (Björkhem *et al.*, 1985). Peroxisomes are present in cultured fibroblasts from patients with Zellweger syndrome, but are less numerous than in controls. The sudanophil leukodystrophy or leukoencephalomyelopathy is considered to be the result of ischemic lesions caused by seizures or repeated food aspirations.

Neonatal Adrenoleukodystrophy

This condition was first described by Ulrich *et al.* (1978), followed by several other reports. It is inherited as an autosomal-recessive trait, and both boys and girls are affected.

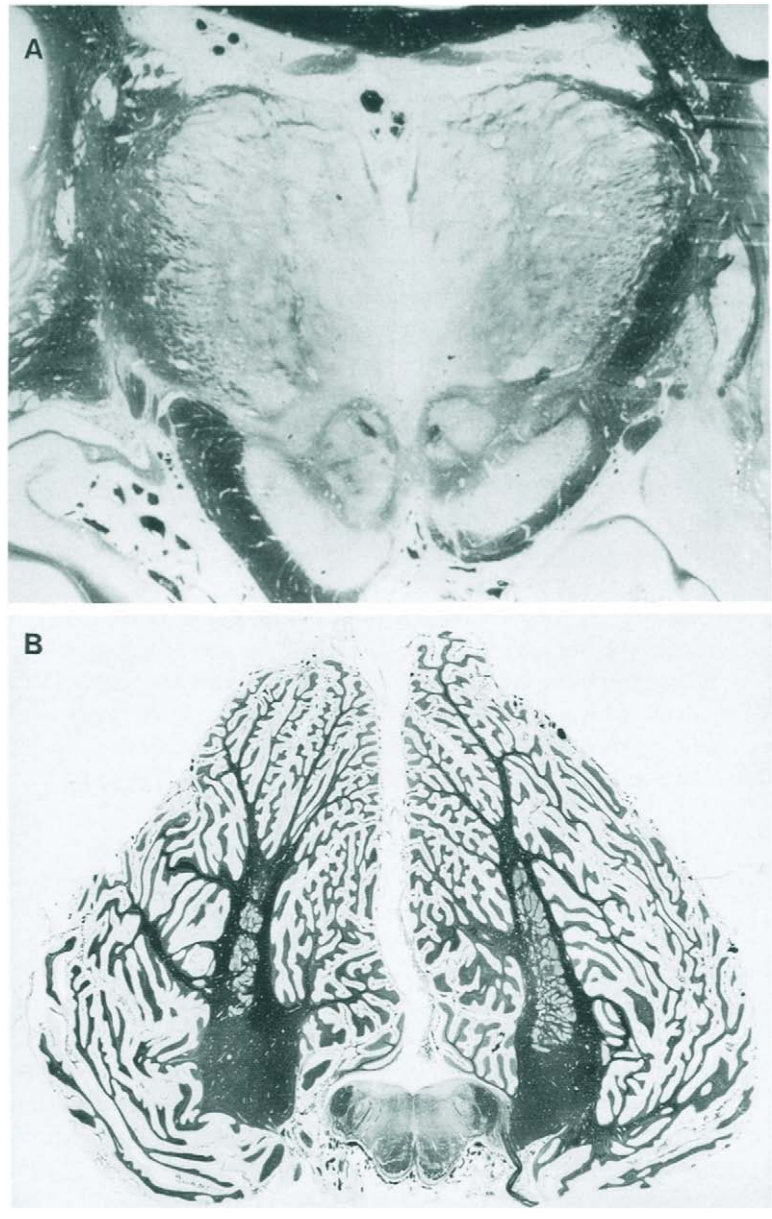


Fig. 128 Same case shown in Fig. 127. (A) A disorganized pattern of thalamic nuclei. The red nucleus is separated into several layers. (B) Heterotopias in the dentate nuclei.

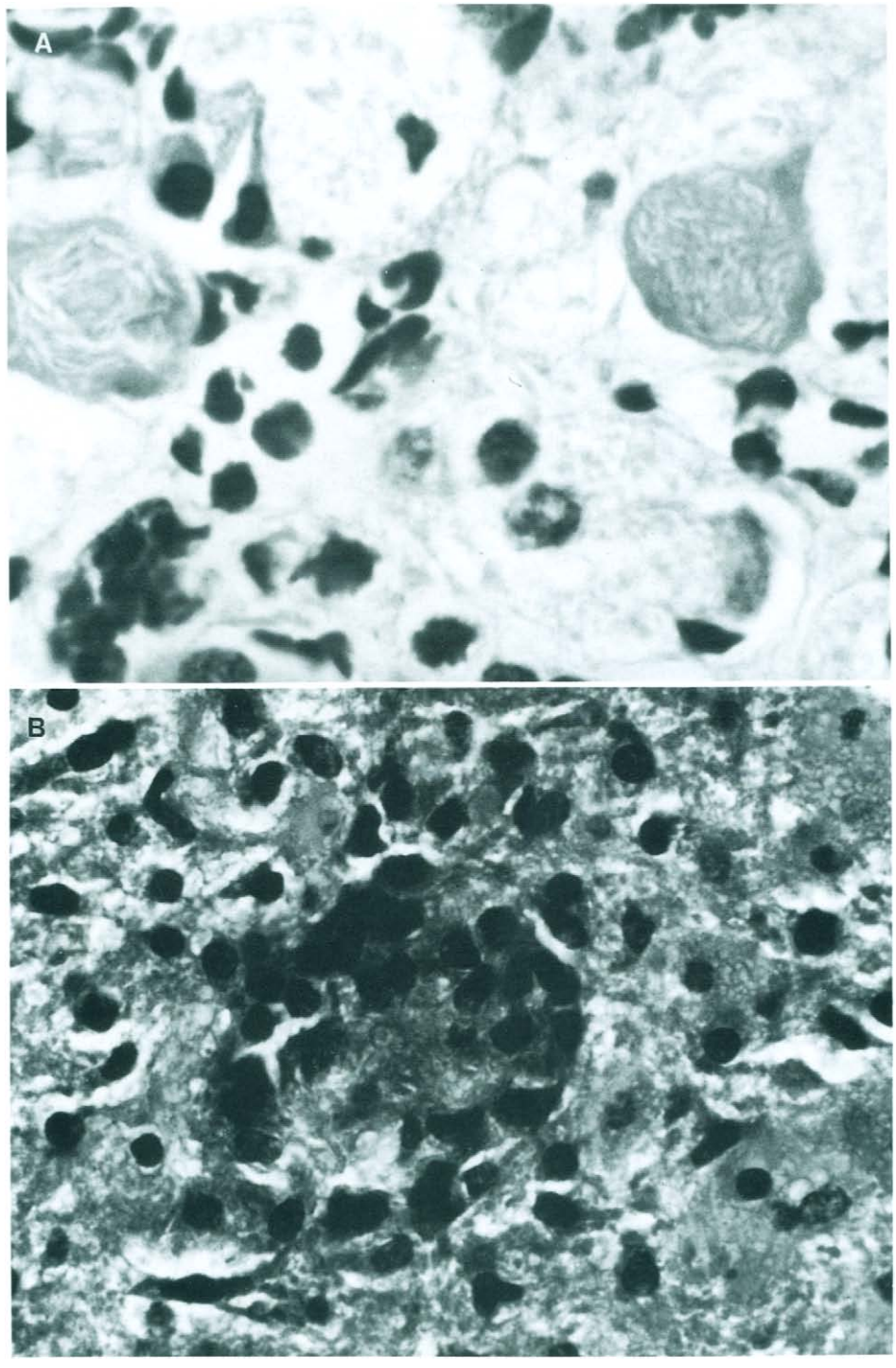


Fig. 129 Zellweger syndrome. (A) An adrenal gland containing cells with striated cytoplasm, ×500. (B) Neuronophagia in the nucleus dorsalis of Clarke, ×1000.

Clinical Picture Even a few days after birth, severe psychomotor retardation is obvious. Epileptic seizures may occur. The adrenocortical insufficiency was subclinical in some cases (Ulrich *et al.*, 1978); in others it was as prominent as the neurological symptoms. Most children die before the age of 2 years (Ulrich *et al.*, 1978). Some patients with a protracted course may survive until the age of 7 years (Noetzel *et al.*, 1983). These patients develop profound dementia, blindness (Cohen *et al.*, 1983), and quadriplegia.

Pathology *Gross appearances.* The adrenal cortex is atrophic, even in cases without adrenocortical symptoms.

Light microscopy. Accumulations of lipopigment are seen in the adrenal cortex, thymus, liver, Leydig's cells, and reticuloendothelial system. Ocular changes resembling those of congenital RP have been described in two cases (Cohen *et al.*, 1983).

Electron microscopy. Parallel paired lamellae were seen in the cells of the adrenal cortex and in Leydig's cells. Needlelike membranous inclusions were described in macrophages in various organs. An absence or considerable reduction in the number of peroxisomes was repeatedly observed on liver biopsies (Goldfischer *et al.*, 1985; Farrell *et al.*, 1983).

Neuropathology *Gross appearances.* The cerebral cortex shows a conspicuous polymicrogyria (Ulrich *et al.*, 1978). Upon sectioning the brain, extensive demyelination is apparent in the cerebrum, cerebellum, and midbrain, with sparing of various areas in individual cases. The ventricles are always dilated, and occasionally gross hydrocephalus may be present.

Light microscopy. The boundaries of the demyelinated areas are usually, but not always, sharply demarcated (Ulrich *et al.*, 1978). Dense gliosis is present in areas of demyelination with hypertrophic astrocytes. A glial wall may form at the edges of sharply demarcated lesions. Perivascular inflammatory infiltrates and an accumulation of fat granule cells vary from case to case. Changes in the gray matter are less pronounced, aside from polymicrogyria and heterotopia. Neuronal loss has been reported in the thalamus, inferior olives, and dentate nucleus and occasionally also in the Purkinje cell layer. An excessive accumulation of neuronal lipopigment has been noted. Axonal swellings (torpedoes) may be present in the Purkinje cell axons. Myelin basic protein and myelin-associated glycoprotein undergo the same changes as in wallerian degeneration (Ulrich *et al.*, 1983).

Electron microscopy. Various inclusions are found in the neurons and in macrophages. Some of them contain splinter-shaped arrangements of membranes, while others consist of irregular stacks of membranous material (Ulrich *et al.*, 1978). Bilaminar inclusions were seen in the ganglion cells and in pigmented and unpigmented macrophages in the retina (Brown *et al.*, 1983).

Pathogenesis This disease belongs to the group of peroxisomal disorders with a total absence or very severe reduction of peroxisomes. It occupies an intermediate position between the more severe Zellweger syndrome and the milder infantile Refsum disease. The absence of all peroxisomal enzymes leads to an accumulation of very long-chain fatty acids, pipecolic acid, and, to a lesser degree, phytanic acid. This last component, being of dietary origin, tends to accumulate only in long-term survivors.

Infantile Refsum Disease

This condition, which has little in common with classical Refsum disease other than an accumulation of phytanic acid, was first described by Scotto *et al.* (1982). Further accounts include those of Poll-Thé *et al.* (1987) and Torvik *et al.* (1988).

Clinical Picture The disease is slowly progressive. The children appear normal at birth, but by the age of 6 months they develop dysmorphic features, hepatomegaly, diarrhea, and vomiting. Neurological symptoms develop between the ages of 6 and 36 months (Poll-Thé *et al.*, 1987) and consist of seizures, psychomotor retardation, and progressive hearing loss. Torvik *et al.* (1988) reported on a patient who died at the age of 12 years, and in whom blindness and spasticity developed in the later stages. The biochemical profile resembled that of Zellweger syndrome and neonatal adrenoleukodystrophy, but with a disproportionate increase in phytanic acid (Poll-Thé *et al.*, 1987). Liver biopsies revealed an absence of peroxisomes.

Pathology The only autopsy reported to date is that of the patient of Torvik *et al.* (1988). The adrenals were hypoplastic, but showed no inclusions. Micronodular cirrhosis was present in the liver, which contained scattered clear cells. Similar clear cells were present in the spleen and the lymph nodes. All of these cells were PAS and oil red O positive. Large birefringent inclusions, transparent on a bright field, in nonparenchymal, PAS-positive, macrophage-like cells in the liver were described (Roels *et al.*, 1986). Under the electron microscope the polarizing inclusions correspond to lysosomes containing trilaminar structures (Poulos *et al.*, 1984).

Neuropathology *Gross appearances.* No malformations were seen in the cerebral hemispheres. The subcortical white matter was grayish; the corpus callosum, thin. The cerebellum was atrophic.

Light microscopy. There was a reduced density of myelin and axons, but no evidence of active demyelination. Severe atrophy of the granular layer was present in the cerebellum; several Purkinje cells were dislocated into the molecular layer. The retina was atrophic, as was the organ of Corti, with preservation of the spiral ganglion.

Pathogenesis This condition is one of those associated with an absence of peroxisomes, and as such is related to the Zellweger syndrome and neonatal adrenoleukodystrophy, being the least severe form of the three. It is not clear why a similar defect should produce three syndromes with different degrees of severity. The greater accumulation of phytanic acid is due to longer survival on a mixed diet, phytanic acid being exclusively dietary in origin.

Hyperpipecolinemia

The first case of hyperpipecolinemia, reported by Gatfield *et al.* (1968), was followed by many others (Challa *et al.*, 1983). Pipecolic acid is a degradation product of lysine.

Clinical Picture The disease manifests itself in early infancy with hypotonia, psychomotor retardation, hepatomegaly, and a variety of malformations, including dolichocephaly, multiple hemangiomas on the face, head, and trunk, and micrognathia.

Pathology *Light microscopy.* Light microscopy reveals micronodular cirrhosis of the liver. The hepatocytes contain small and large vacuoles.

Electron microscopy. On electron microscopy the vacuoles have a round or polygonal profile. They are membrane bound and contain granular material of medium electron density with isolated strongly osmiophilic granules (Challa *et al.*, 1983).

Neuropathology *Gross appearances.* There are signs of cerebral edema. A striking pallor, particularly of the putamen, is apparent in coronal slices, as well as moderate atrophy of the white matter.

Light microscopy. Ballooning and fine granularity of the astrocytic cytoplasm are seen in the cerebral cortex and the basal ganglia (Fig. 130A). The affected astrocytes are widely dispersed, but are more numerous in the deeper cortical layers. The cytoplasmic granules are PAS positive. A reactive gliosis is present in the basal ganglia. A few astrocytes with scanty PAS-positive granules can be seen in the brain stem (Challa *et al.*, 1983).

Electron microscopy. The astrocytes contain irregularly shaped vesicles with clear contents.

Pathogenesis The clinical picture and the changes in the brain and the liver resemble those found in Zellweger syndrome (see p. 337). A generalized loss of peroxisomal functions due to a deficiency of peroxisomes was found in the fibroblasts (Wanders *et al.*, 1988). Not all patients with deficiency of all peroxisomal enzymes are severely handicapped. MacCollin *et al.* (1990) reported on a patient with minimal neurological disability, consisting of ataxia and peripheral neuropathy. Very long-chain fatty acids were considerably increased in the plasma and the fibroblasts, and all peroxisomal enzymes were present but showed markedly reduced activity.

Rhizomelic Chondrodysplasia Punctata

This is one of a heterogeneous group of bone dysplasias, inherited as an autosomal-recessive trait. It is clinically characterized by an abnormally short stature, dysmorphic facial features, contractures, ocular involvement resembling that of Zellweger syndrome, and severe mental retardation. Radiological studies reveal shortening, metaphyseal cupping, and disturbed ossification of the humerus and the femur, together with epiphyseal and extraepiphyseal calcifications. Studies on skin fibroblasts have shown deficiencies of dehydroxyacetone phosphate acyltransferase, alkylglycerone-phosphate synthase, and phytanic acid oxidase (Hoefler *et al.*, 1988; Schutgens *et al.*, 1988). An increased number of irregularly shaped peroxisomes was found in some hepatocytes, while in others they were undetectable.

Zellweger-like Syndrome

A syndrome indistinguishable from Zellweger syndrome, but showing abundant peroxisomes in the liver cells, was described by Suzuki *et al.* (1988). Three peroxisomal β-oxida-

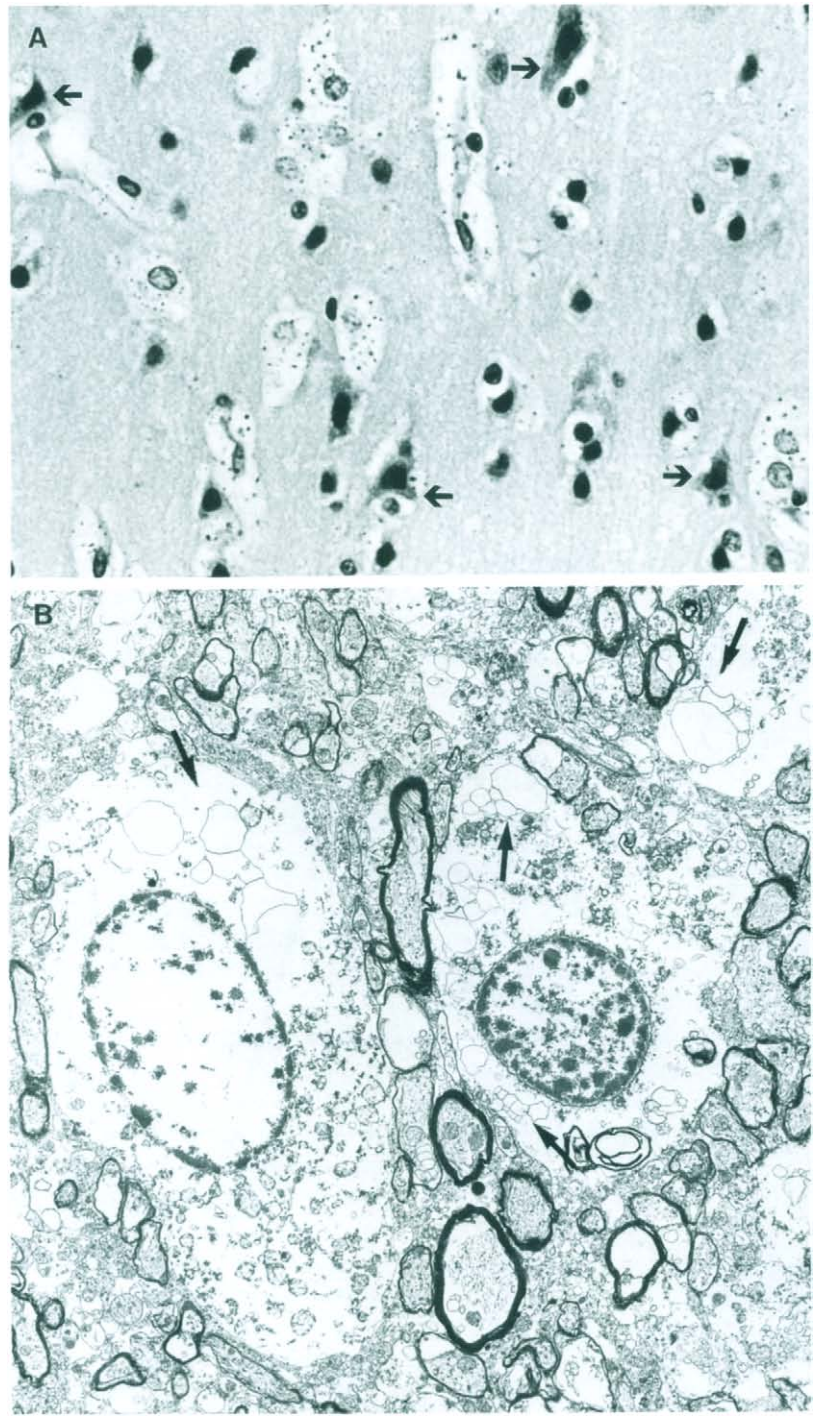


Fig. 130 Hyperpipecolinemia. (A) The cerebral cortex with periodic acid–Schiff (PAS)-positive granules in astrocytes and shrunken neurons with storage (arrows). PAS–alcian blue stain, ×340. (B) Irregular membrane-bound vesicles in the cytoplasm of astrocytes, ×2500. (Reproduced from Challa *et al.*, 1983.)

tion enzymes (oxidase, bifunctional protein, and thiolase) were absent, while other peroxisomal enzymes were found to be normal.

Adrenoleukomyeloneuropathy (Infantile and Juvenile Forms)

X-linked adrenoleukomyeloneuropathy is a comprehensive term for a group of phenotypically different diseases. Within this group of X-linked disorders, differences in clinical features and morphological appearances form the basis of their subdivision into several types. They all depend on similar pathogenetic mechanisms, particularly an identical disturbance of fatty acid metabolism. It has been shown that different variants may occur even in the same family (Martin *et al.*, 1982). Therefore, the term *adrenoleukomyeloneuropathy*, introduced by Marmion *et al.* (1979), seems appropriate, and includes both adrenoleukodystrophy, which affects predominantly the brain, and adrenomyeloneuropathy, in which the brunt of the disease falls on the spinal cord and the peripheral nerves.

The association of adrenal and cerebral involvement was already observed by earlier authors. The first case of this combination was published by Siemerling and Creutzfeldt (1923), but it was not until the 1960s that it was recognized that the involvement of both organs was part of a single process inherited as an X-linked recessive trait (Hoefnagel *et al.*, 1962). It was recognized that almost all male patients previously diagnosed as having Schilder's disease or sudanophilic leukodystrophy (see p. 487) were, in fact, suffering from adrenoleukodystrophy. A few female patients with this condition have also been identified (Molzer *et al.*, 1981).

The independent identity of this disease and its separation from diffuse forms of multiple sclerosis were established on genetic and biochemical grounds. The term *adrenoleukodystrophy* was coined by Blaw (1970). In many cases of adrenoleukodystrophy, adrenal failure may not be clinically apparent. The disease was finally identified as a lipid storage disease by Schaumburg *et al.* (1972) and Powers *et al.* (1982), who identified the storage material in the adrenal cortex, testes, CNS, and peripheral nervous system and demonstrated the identical ultrastructure of the storage material in all affected organs.

Clinical Picture The majority of these patients present only with cerebral symptoms, which appear usually around the beginning of school age, sometimes earlier, or as late as the second decade. The adrenocortical component manifests itself usually in the form of skin pigmentation (the melanodermic type) and, rarely, in that of addisonian crises. An electrolyte imbalance does not occur, as the zone glomerulosa is not affected. In the neurological syndrome disorders of behavior are the first to appear and are sometimes diagnosed as schizophrenia. The further course is characterized by visual disturbances of occipital origin, impairment of hearing, and optic atrophy. A hyperkinetic syndrome with choreiform movements may develop simultaneously. Spastic paralysis and dementia supervene in the terminal stage. Epileptic seizures and ataxia of cerebellar origin are not uncommon. The CSF albumin level is raised and may exceed the globulin fraction by a factor of 3. The CT scan reveals the low density of the demyelinated areas (Greenberg *et al.*, 1977). Increased density at the periphery of the lesions is characteristic, but not pathognomonic. Death occurs usually in the second decade. An acute course of the disease is rare. Juvenile cases run a more protracted course than infantile ones. Patients whose

course was punctuated by periodic exacerbations and remissions as well as cases with a prolonged clinical course and very slow disease progression have been reported (Cavaletti *et al.*, 1990).

Pathology *Gross appearances.* The severely atrophic adrenals may be difficult to find at autopsy.

Light microscopy. Nests of adrenocortical cells may be found in the capsule and the surrounding fat, accompanied in about 20% of the cases by lymphocytic, histiocytic, and, to a lesser degree, plasmacytic infiltrates. Only a thin rim of cortex remains, consisting of nests of cells in an alveolar grouping. Clusters of eosinophilic storage cells with distended cytoplasm contained striated hyaline inclusions. In frozen sections the crystalline structure of the inclusions is recognized under polarized light. The crystals are resistant to extraction with acetone, ethanol, and methanol, but lose their birefringence when exposed to chloroform, xylene, or propylene oxide. The anterior pituitary shows a proliferation of large basophilic cells and a reduction of eosinophilic ones, typical of adrenal insufficiency. The testes show interstitial fibrosis and thickening of the basement membranes. They contain clusters of large intestinal cells, 30 μm or more in diameter, with finely granular cytoplasm.

Electron microscopy. The lamellae of storage material lie loosely in the cytoplasm of the adrenocortical cells. They fill the cytoplasm, have a needlelike or tangled shape, are 1–6 μm in length, and are formed by pairs of electron-dense lamellae, 3–6 nm in thickness, framing an electron-lucent space, 5–20 nm wide. Similar structures are found in the testes. In the eccrine glands of the skin, Martin *et al.* (1977) found the cytoplasm studded with clear vacuoles. A normal number of peroxisomes was seen on liver biopsies (Goldfischer *et al.*, 1985).

Neuropathology *Gross appearances.* Symmetrical—and, in places, discontinuance—demyelination is evident in the central and subcortical white matter, the internal capsule, the cerebral peduncles, and the region of the pyramidal tracts of the pons and the medulla oblongata. The foci of demyelination have a peculiar glassy grayish green appearance and a firm consistency. The preferential sites are the parietal lobes (81%) and, less so, the occipital (18%) and frontal (15%) lobes. Occasionally, a rim of softening appears in the periphery of a demyelinated area. The corpus callosum and the fornix are usually involved. Demyelination of the cerebellar white matter can often be recognized macroscopically. A grayish discoloration is sometimes present in the lateral and posterior columns of the spinal cord (Probst *et al.*, 1980).

Light microscopy. Patchy or diffuse demyelination can be seen in the cerebral white matter, generally sparing the U-fibers (Fig. 131). In some cases the geniculocalcarine optic radiation appears to be selectively affected. At the periphery of the lesions, the number of oligodendroglial cells and axons appears slightly reduced. The latter frequently contain spheroids. Significant inflammatory infiltrates are seen in the perivascular spaces (Fig. 132), consisting of macrophages and B and T lymphocytes, the latter being mainly T4 helper cells (Griffin *et al.*, 1985). The degradation of myelin is orthochromatic. Occasionally, no sudanophilic lipid is found in the perivascular histiocytes. There is marked proliferation of the astroglia, particularly at the periphery of the lesions. The oldest lesions are

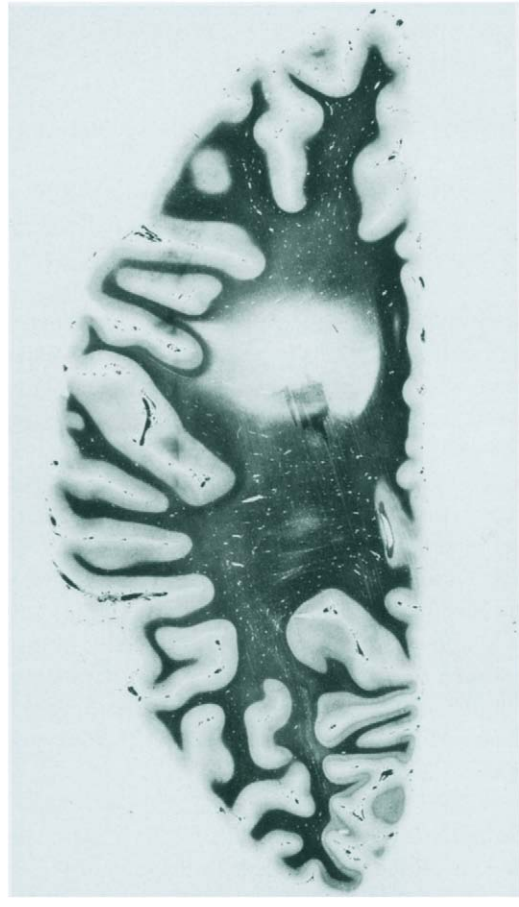


Fig. 131 Juvenile adrenoleukodystrophy. Patchy demyelination in the centrum ovale.

usually found in the deeper parts of the parieto-occipital white matter. Recent lesions with active myelin breakdown and inflammatory infiltrates are usually localized in the subcortical white matter. Dense gliosis is present in older lesions (Fig. 133A and B), well demonstrated immunohistochemically with antibodies against glial fibrillary acidic protein. Indications of remyelination in older foci were obtained immunohistochemically with antibodies against myelin basic protein.

The cerebral cortex is generally normal. Neuronal losses observed in various localization in some cases are considered to be a secondary phenomenon. Only the loss of retinal ganglion cells is thought to be a primary lesion. Losses of axons and myelin, of variable degree, without perivascular infiltrates, have been found in the peripheral nerves.

Electron microscopy. The macrophages in areas of demyelination contain numerous lamellar structures, consisting of pairs of membranes 3–6 nm thick, of variable length

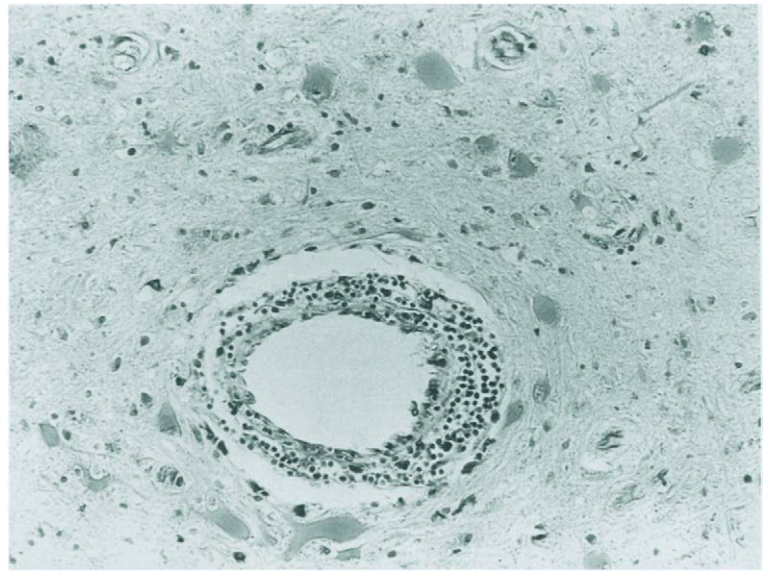


Fig. 132 Same case shown in Fig. 131. A perivascular infiltrate and hyperplastic astrocytes. Nissl stain, ×150.

and shape (Probst *et al.*, 1980). They are frequently needle shaped and arranged in groups. They are generally surrounded by a membrane separating them from the cytosol. They are also seen in astrocytes together with laminar degradation products. In some cells, presumably oligodendrocytes, the storage material lies free in the cytoplasm, as in adrenals and Leydig's cells. Electron-dense filamentous inclusions often appear in the nuclei of macrophages. Membrane-bound collections of parallel lamellae are found in the peripheral nerves. Bilaminar structures are present in the cytoplasm of Schwann cells (Powers *et al.*, 1982).

Adrenoleukomyeloneuropathy in Adults

Neusser and Wiesel (1910) described the first patient with Addison's disease and spastic paraplegia. The familial cases were not subjected to postmortem examination. Budka *et al.* (1976) provided morphological evidence that the disease was a variant of adrenoleukodystrophy. This was confirmed by subsequent authors, and the name *adrenoleukomyeloneuropathy* was introduced.

Clinical Picture The adrenocortical insufficiency manifests itself in childhood with hyperpigmentation and hypogonadism, but may remain asymptomatic, in which case it can be diagnosed only by stress tests and by the high plasma level of corticotropin. The appearance of neurological symptoms in adulthood may be preceded by Addison's disease in childhood (Sadeghi-Nejad and Senior, 1990). Neurological symptoms in the form

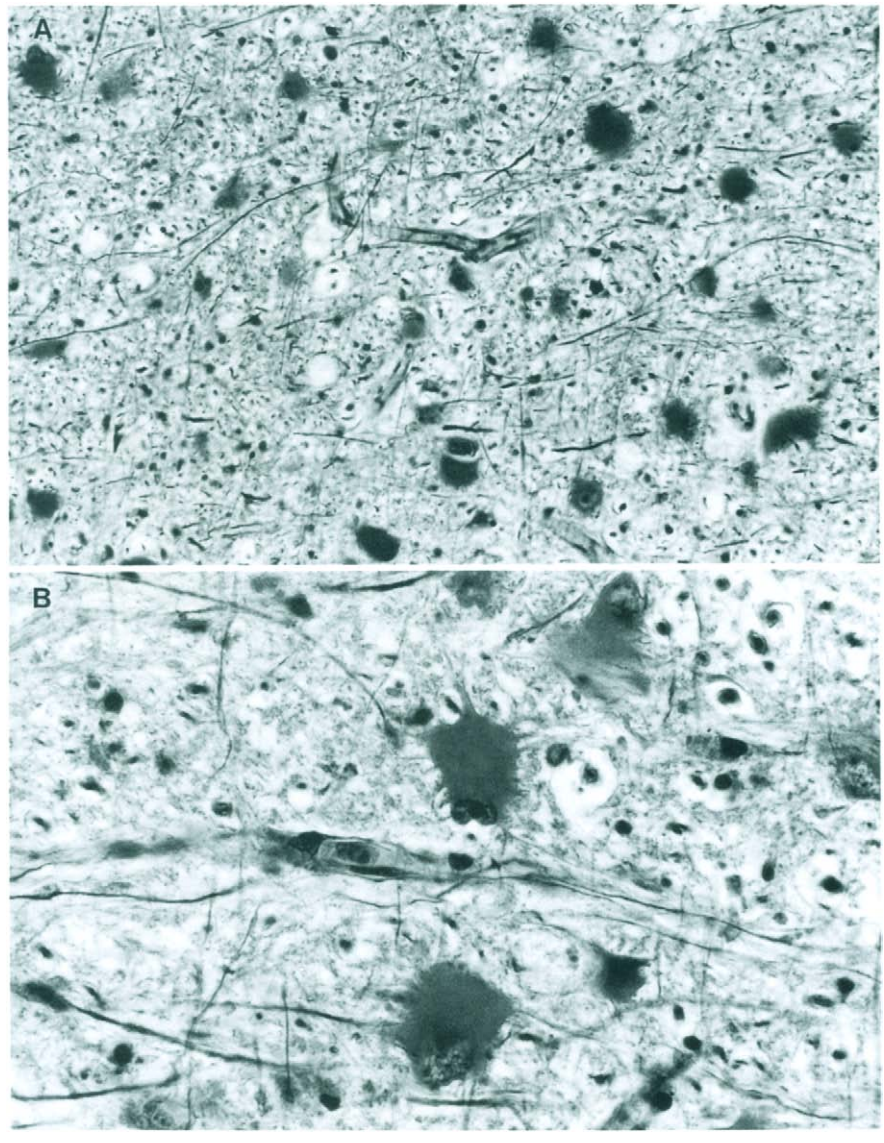


Fig. 133 Same case shown in Fig. 131. Marked gliosis and a loss of axons in an area of demyelination. Bielschowsky stain, (A) ×250 and (B) ×700.

of a paraparesis do not appear, as a rule, before the age of 20 years, although occasionally an earlier onset has been recorded. Paresthesias, disturbances of sphincter control, and signs of peripheral neuropathy appear in addition to the slowly progressive spastic paraplegia. At this stage familial spastic paraplegia must be considered in the differential diagnosis (see p. 648). Cerebellar ataxia and dementia may supervene later. Rarely, the clin-

ical picture resembles that of spinocerebellar degeneration (Marsden *et al.*, 1982) or olivopontocerebellar atrophy (Ohno *et al.*, 1984) from the beginning. Death occurs usually 20 years after the onset of symptoms or later. Adult cases combining the features of adrenoleukodystrophy and adrenomyeloneuropathy have been recorded (Josien *et al.*, 1993).

A rare form of the syndrome, first described by Urechia *et al.* (1924), presents with adrenocortical insufficiency toward the end of the third or beginning of the fourth decade. The neurological symptoms are relatively mild, and in many cases are confined to a cerebellar ataxia. In some cases psychotic symptoms that may have led to a diagnosis of schizophrenia were the first manifestation of the disease (Esiri *et al.*, 1984). Alzheimer's disease was diagnosed in a 55-year-old patient, in whom adrenoleukodystrophy was recognized only postmortem. The patients die an average of 6 years after the onset of symptoms, but cases with a more rapid course are known to occur.

Pathology *Gross appearances.* The atrophy of the adrenal cortex may be so severe that one or the other adrenal gland may not be recognized macroscopically. The testes are also atrophic and the thymus is often enlarged (Probst *et al.*, 1980). In one of the cases reported by Esiri *et al.* (1984), the adrenals were paradoxically hyperplastic.

Light microscopy. The atrophic adrenal cortex consists of nodular aggregates of ballooned cells with striated cytoplasm (Budka *et al.*, 1976). The thymus shows a lymphoepithelial hyperplasia and the skin exhibits an excess of melanin in the basal layer of the epidermis.

Electron microscopy. Bilaminar inclusions, irregularly arranged in needles or whorls, are seen in the cells of the adrenals and the testes (Probst *et al.*, 1980).

Neuropathology *Gross appearances.* A firm consistency of the otherwise unremarkable cerebral and cerebellar white matter may be observed. In paraplegic cases the white columns of the spinal cord are gray.

Light microscopy. The long tracts in the brain stem are depleted of myelin (Fig. 134A and B), with a reduction in the number of axons. These tract degenerations vary from case to case, even between siblings (Esiri *et al.*, 1984). In cases with cerebellar symptomatology, the loss of myelin is particularly striking in the cerebellar white matter. Perivascular aggregations of PAS-positive, but Sudan-negative, histiocytes may be present. Focal or diffuse demyelination with moderate gliosis and perivascular PAS-positive macrophages may also been seen in the cerebral white matter. In some cases the sudanophilic breakdown is more pronounced in sharply demarcated foci (Urechia *et al.*, 1924). Selective parenchymal necroses were seen in some cases in various areas of the cerebral cortex.

In the spinal cord the loss of myelin is irregularly distributed. The crossed and uncrossed cerebrospinal tracts are most frequently and most severely affected. The funiculus gracilis shows marked pallor in the cervical segments. The spinocerebellar tracts may be affected to a variable degree. In all of the involved tracts, PAS-positive macrophages may be present, with a negligible sudanophilic component.

A progressive retrograde ("dying-back") axonopathy is present in the peripheral nerves, with a loss of axons and myelin sheaths and a thickened perineurium (Budka *et al.*, 1976).

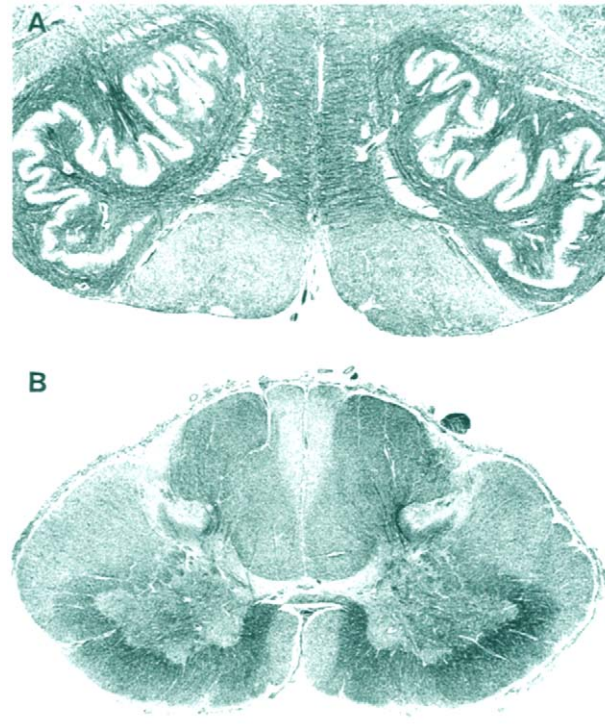


Fig. 134 Adult form of adrenomyeloneuropathy. (A) Symmetrical pallor of the myelin in the medullary pyramids. (B) A loss of myelin in the pyramidal tracts, posterior columns, and spinocerebellar tracts in the cervical cord. Wölcke's stain. (Reproduced from Probst *et al.*, 1980.)

Electron microscopy. Paired laminar inclusions (Fig. 135) are found lying free in the cytoplasm of perivascular macrophages in the demyelinated areas of the cerebrum, brain stem, and spinal cord. In peripheral nerves, including the small branches in the skin and the conjunctiva, the characteristic osmiophilic paired lamellae are seen in Schwann cells and endoneurial macrophages. Splitting of myelin was described along the interperiod lines and a helical twist of the dense lines.

Adrenoleukomyeloneuropathy in Females

In spite of the overwhelmingly male disease preponderance, adrenoleukomyeloneuropathy can also occur in females of all age groups (Anzil and Jirasek, 1981; Holmberg *et al.*, 1991).

Clinical Picture The clinical picture corresponds in most details to that of male patients in the same age group. In infants and young girls the disease presents with psychomotor retardation and seizures, followed by quadriparesis. In adult women Addison's

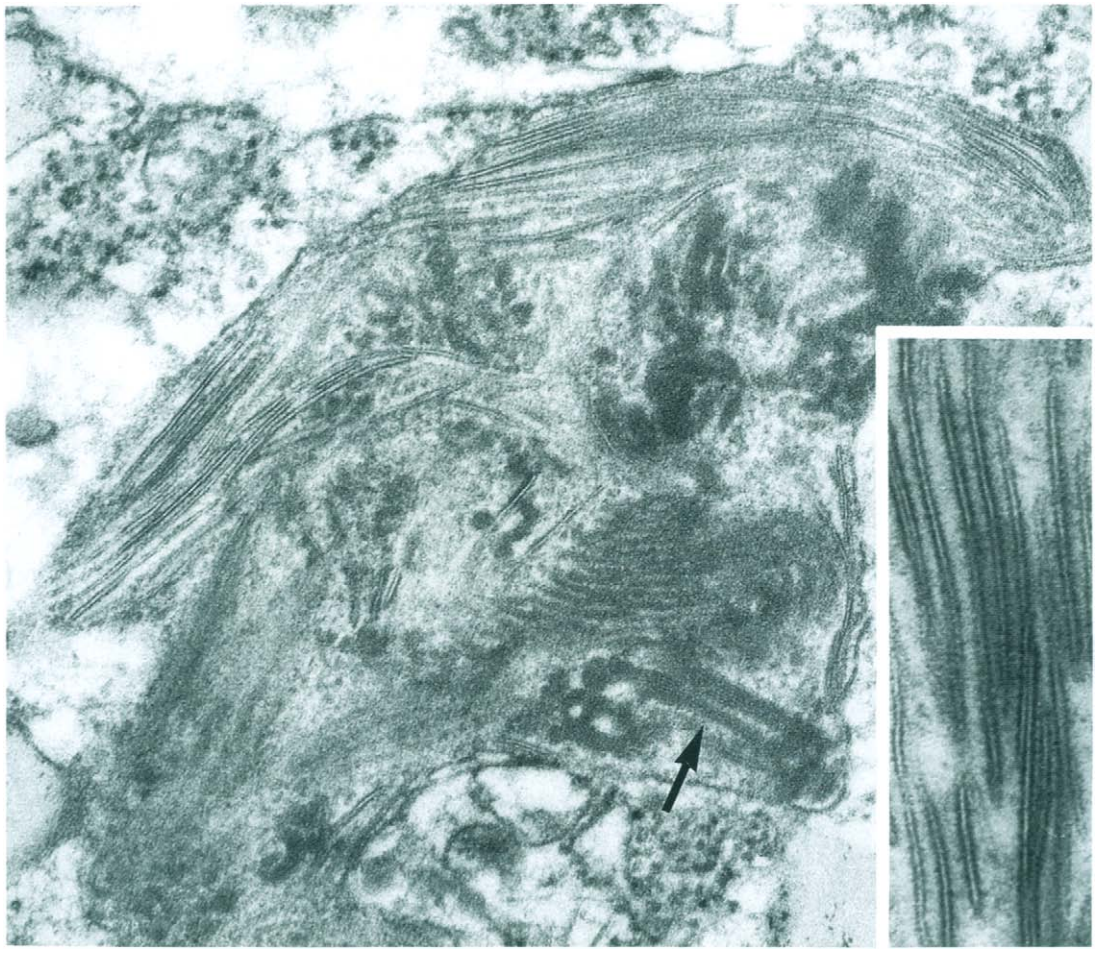


Fig. 135 Same case shown in Fig. 134. A perivascular histiocyte containing bilaminar and membranous (arrow) inclusions, × 20,000 (inset × 173,000).

disease, or only hyperpigmentation of the skin, dominates the early picture (Schlote *et al.*, 1987). Hypoesthesias and spastic pareses appear a few years later. These are followed by seizures and mental deterioration. In some cases, however, neurological symptoms predominate from the onset.

Pathology Aside from lipid storage in the atrophic adrenals, the liver, and the reticuloendothelial system, thymic hyperplasia is seen in the majority of the patients. In electron microscopy bilaminar inclusions are seen in the macrophages of all organs affected by lipid storage.

Neuropathology *Gross appearances.* Large grayish parieto-occipital areas of demyelination join each other through the splenium of the corpus callosum. A diffuse asymmetrical lesion has been observed affecting only one hemisphere.

Light microscopy. The affected areas show a loss of myelin sheaths, a considerable reduction in the number of axons, and dense fibrillary gliosis. A perivascular accumulation of macrophages containing both sudanophilic and PAS-positive material is associated with a variable degree of lymphocytic cuffing. At the edges of the demyelinated areas and in other parts of the cerebral white matter, signs of a recent florid demyelination may be present with a dense infiltration by fat granule cells and massive lymphocytic and plasmacytic perivascular cuffs (Schlote *et al.*, 1987). The demyelination spares most U-fibers, but can encroach on deeper cortical layers, or even on the entire thickness of the cortex in the occipital lobes. In the congenital cases the demyelination was diffuse: slight to moderate in the cerebral hemispheres and less marked in the cerebellum.

Electron microscopy. Bilaminar inclusions are present in the macrophages and the astrocytes (Molzer *et al.*, 1981). The macrophages also contain numerous lipid droplets. Disorganized membranous material may be seen in the congenital form.

Pathogenesis The bilaminar structures forming the substance stored in all types of adrenoleukomyeloneuropathy were thought to be related to cholesterol compounds, particularly the 3β-hydroxysterol of the adrenal cortex. Biochemically, there are increases in the total cholesterol esters and the long-chain (C_{22}–C_{26}) fatty acid fraction, not normally present to this extent, in particular the penteicosanic (C_{25}) and hexeicosanic (C_{26}) acids (Menkes and Corbo, 1977). These findings were confirmed in various forms of the disease (Molzer *et al.*, 1981). The hypothesis that the disease was a disorder of cholesterol metabolism could not be confirmed, however. It was Singh *et al.* (1984) who established the fact that faulty oxidation of the long-chain fatty acids was the metabolic defect in adrenoleukomyeloneuropathy. No structural abnormalities in the liver peroxisomes have been found in adrenoleukodystrophy or adrenomyeloneuropathy. The missing enzyme is very long-chain-fatty-acid CoA ligase, essential in the first stage of the very long-chain fatty acid catabolism (Wanders, 1988; Lake, 1992). A gene was localized on the X chromosome responsible for the faulty oxidation of long-chain fatty acids with ultrastructurally normal-appearing peroxisomes (Goldfischer *et al.*, 1985). In contrast with Zellweger syndrome, plasmalogen is not reduced in erythrocyte membranes (Antoku *et al.*, 1985).

The assumption seems plausible that the long-chain fatty acids exert a toxic effect on the cells of the adrenal cortex, Leydig's cells, and Schwann cells. The accumulation of long-chain fatty acids may cause changes in the molecular structure of myelin in the sense of an abnormal protrusion of these lipids from the surface of the membrane. It may also change the antigenic properties of the membrane. The thereby provoked autoimmune reaction may have a cytolytic effect on the myelin sheaths. Bernheimer *et al.* (1983) found an accumulation of immunoglobulins IgG, IgA, and IgM in the brain. The neuropathological findings support the immunological hypothesis; the lymphocytic infiltration led, in the past, to the inclusion of this disease in the group of inflammatory diffuse sclerosis. The data of Powers *et al.* (1992) support a natural im-

mune response in the demyelinative lesion consisting predominantly of reactive astrocytes, macrophages, T cells, and cytokines. The changes in the oligodendroglia are not fully explained, however.

The clinical course of infantile and juvenile adrenoleukodystrophy reflects the spread of the demyelinating process from the occipital through the parietal to the frontal lobes. Probst *et al.* (1980) considered segmental demyelination to be the primary event, with axonal degeneration following when a certain number of internodes have been affected. The inflammatory changes in the CSF are considerable for a metabolic disorder. The large number of T cells suggests an immunopathological component of the process. It could, however, be a response to the acute and extensive breakdown of myelin. The modest cellular infiltration observed in the majority of the cases and the occasional absence of sudanophilic breakdown products suggest a slowly progressive process in which the inflammatory reaction plays a secondary role.

To explain the occasional appearance of an X-linked recessive disease in women, the so-called lyonization theory has been advocated. This postulates the inactivation of the other X chromosome in the early stages of development. Under these circumstances an X-linked recessive disorder may manifest itself in a heterozygote. The defective gene has been localized on Xq28 in the neighborhood of the glucose-6-phosphate dehydrogenase locus (Willems *et al.*, 1990). Adrenoleukodystrophy and adrenomyeloneuropathy share the same locus.

Pseudo-Zellweger Syndrome

This syndrome was described by Goldfischer *et al.* (1986) in an 11-month-old female infant whose parents were first cousins. The child was hypotonic with absent reflexes, mild dysmorphism, frequent seizures, and psychomotor retardation. Adrenal atrophy and renal cortical cysts were found at autopsy. Neuronal heterotopia, most pronounced in the cerebellum, and extensive demyelination were seen in the brain. Abundant enlarged peroxisomes were present in the liver (Hughes *et al.*, 1990). The authors found deficiencies in several peroxisomal oxidative enzymes. The principal deficient enzyme is 3-ketoacyl-CoA thiolase (Lake, 1992).

Pseudo-Neonatal Adrenoleukodystrophy

This syndrome was described by Poll-Thé *et al.* (1988), who reported a condition closely resembling neonatal adrenoleukodystrophy in two children of a consanguineous marriage. The patients presented soon after birth with stridor, apneic spells, and seizures, followed by hearing defects, optic atrophy, and spasticity. A vegetative state was reached by the age of 4 years. The CT scan revealed large areas of lucency with contrast enhancement in the centrum ovale, suggestive of demyelination. MRI examination showed white matter changes, a thin corpus callosum, cerebellar malformation, and dorsal displacement of the brain stem (Kyllerman *et al.*, 1990). Numerous large peroxisomes were found in the liver. The defective enzyme was identified as acyl-CoA oxidase. Naidu *et al.* (1988) described a female infant with similar clinical, morphological, and biochemical characteristics but with normal levels of acyl-CoA oxidase.

Peroxisomal Bifunctional Enzyme Deficiency

Another syndrome mimicking neonatal adrenoleukodystrophy was reported by Watkins *et al.* (1989) in a male infant $5\frac{1}{2}$ months old at the time of death. He was macrocephalous, but not dysmorphic, severely retarded, and hypotonic, with intractable seizures. There was no hepatosplenomegaly and his fundi were normal. A brain biopsy at 6 weeks showed polymicrogyria and ectopic neurons in the unmyelinated white matter. Autopsy confirmed the polymicrogyria and showed extensive demyelination with cystic degeneration of the periventricular zones. There was a loss of all layers of the adrenal cortex, which was replaced by scattered ballooned cells. Microscopic glomerular cysts were present in the kidneys. The liver appeared normal. The missing enzyme was the peroxisomal bifunctional enzyme with the activity of enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase. A recent case of bifunctional enzyme deficiency was reported by Nakada *et al.* (1993).

Orthochromatic Leukodystrophy with Epithelioid Cells (Norman–Gullota Type; Orthochromatic Leukodystrophy with a Predilection for the Cerebellum and the Brain Stem)

Gullotta *et al.* (1970) described a disease in three sisters that was reminiscent of Krabbe's disease. This diagnosis could be ruled out, however, by the age of the patients and the absence of cerebroside storage. The disease was comparable to that reported by Norman *et al.* (1963), but the latter's patients were affected from birth. Kaga *et al.* (1984) also reported a case of a girl, hypotonic from birth, who subsequently developed spasticity, dysphagia and disorders of respiration and died at the age of 2 years, 10 months.

The three patients reported on by Gullotta *et al.* (1970) developed symptoms between the ages of 4 and 8 years. These consisted of ataxic gait, bilateral peroneal palsies, disturbances of speech, and personality changes. Later, they developed spastic or flaccid quadripareses, difficulty in swallowing, and increasing dementia. There were no symptoms suggestive of adrenal involvement. The duration of the illness ranged from 9 to 15 months.

Neuropathology Histological examination revealed an orthochromatic leukodystrophy with numerous perivascular PAS-positive epithelioid cells and a massive astroglial proliferation (Figs. 136 and 137A and B). The lesions were particularly prominent in the cerebellum, corpus callosum, anterior commissure, and internal, external and extreme capsules. PAS-positive histiocytes were also found in the internal organs. In the cases of Norman *et al.* (1963) and Kaga *et al.* (1984), the lesions were localized predominantly in the cerebellum, brain stem, and spinal cord and consisted of an orthochromatic leukodystrophy with perivascular infiltrates of PAS-positive epithelioid cells. Ultrastructurally, lamellar inclusions were found (Molzer *et al.*, 1993).

Pathogenesis Molzer *et al.* (1993) found very long-chain fatty acids to be markedly increased and phytanic acid at the borderline to be above normal in a formalin-fixed brain white matter. This demonstrates that the patient had suffered from a peroxisomal disease. The ultrastructural findings in the brain showing typical lamellar inclusions corroborated

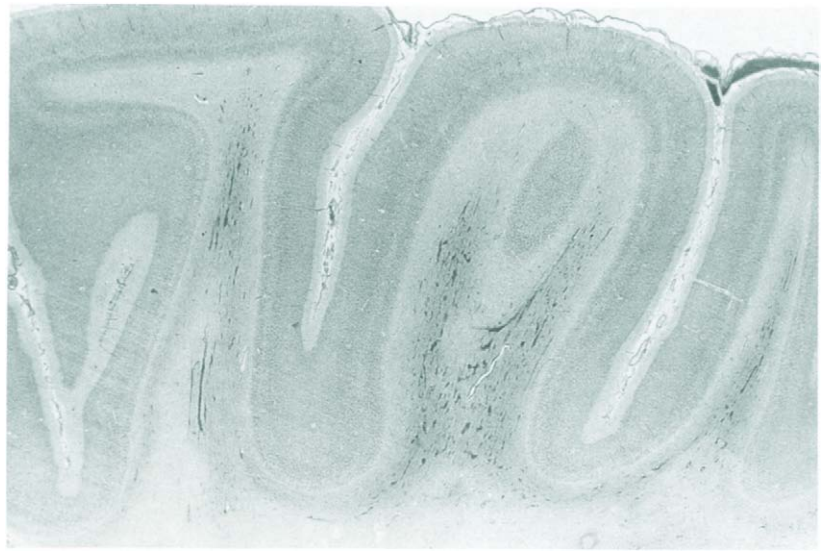


Fig. 136 Orthochromatic leukodystrophy with epithelioid cells. Prominent delineation of blood vessels in the white matter due to a perivascular accumulation of epithelioid cells. Nissl stain, ×18. (Reproduced from Gullotta *et al.*, 1970.)

the peroxisomal pathogenesis. A particular type of peroxisomal disorder, heterozygote of X-linked adrenoleukodystrophy, was suggested.

Refsum Disease (Heredopathia Atactica Polyneuritiformis)

Refsum (1945) reported this clinical syndrome in two Norwegian families. The symptoms resembled those previously reported by Thiébaut (1939) as a congenital disorder. Refsum (1945) gave the condition the name *heredopathia atactica polyneuritiformis*.

Clinical Picture In the classical form the disease manifests itself toward the end of the first, mostly during the second, and sometimes in the third decade. Within the wide range of variation, even in the same family, the main symptoms include peripheral neuropathy, RP, progressive sensory disturbances, ataxia, atrophy of the skeletal muscles, and blindness. The onset of RP usually precedes the biochemical diagnosis by several years (Claridge *et al.*, 1992). In addition, bony deformities with epiphyseal dysplasia and ichthyosis may be present. The levels of albumin and globulin in the CSF are raised. Both sexes are equally affected, suggesting an autosomal mode of inheritance. The disease is slowly progressive, but may be held in check by dietary measures. These patients can survive for several decades. The raised concentration of phytanic acid in the plasma confirms the diagnosis. A family with elevated pipecolic as well as phytanic acid was reported on by Tranchant *et al.* (1993).

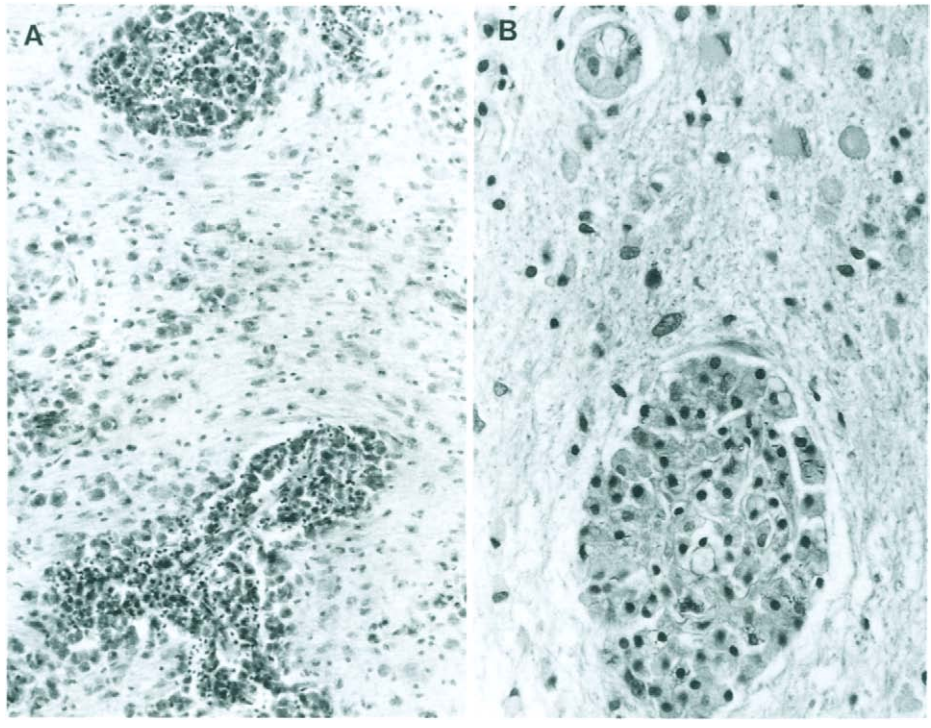


Fig. 137 Same case shown in Fig. 136. Dense aggregates of epithelioid cells around blood vessels and hyperplasia of the astroglia in the white matter. Nissl stain, (A) ×100 and (B) ×250.

Pathology *Light microscopy.* The hepatocytes, Kupffer's cells, cardiac muscle, and renal tubules contain abundant inclusions of neutral fat. An atrophy of the seminiferous tubules was described in the testes. The skeletal muscles are severely atrophic (Fig. 138A and B). The retina is also atrophic and shows discontinuous pigmentation (Fig. 139A).

Electron microscopy. An accumulation of secondary lysosomal and pleomorphic residual bodies was described in the hepatocytes (Boltshauser *et al.*, 1982).

Neuropathology *Gross appearances.* The meninges are thickened, and the cerebral cortex and the cerebellar vermis are moderately atrophic. The nerve roots are hypertrophied and grayish brown. The peripheral nerves show a similar hypertrophy, particularly in their proximal parts.

Light microscopy. The leptomeninges contain numerous macrophages with inclusions of neutral fat (Fig. 139B). The neurons in the cerebral cortex and the basal ganglia, particularly the globus pallidus, are enlarged without being grossly ballooned. The stored material is PAS positive and weakly sudanophilic. The swollen dendrites contain similar material, as do the cortical and subependymal astrocytes. A few macrophages containing sudanophilic lipid surround the blood vessels. The changes in the cerebellum are slight and

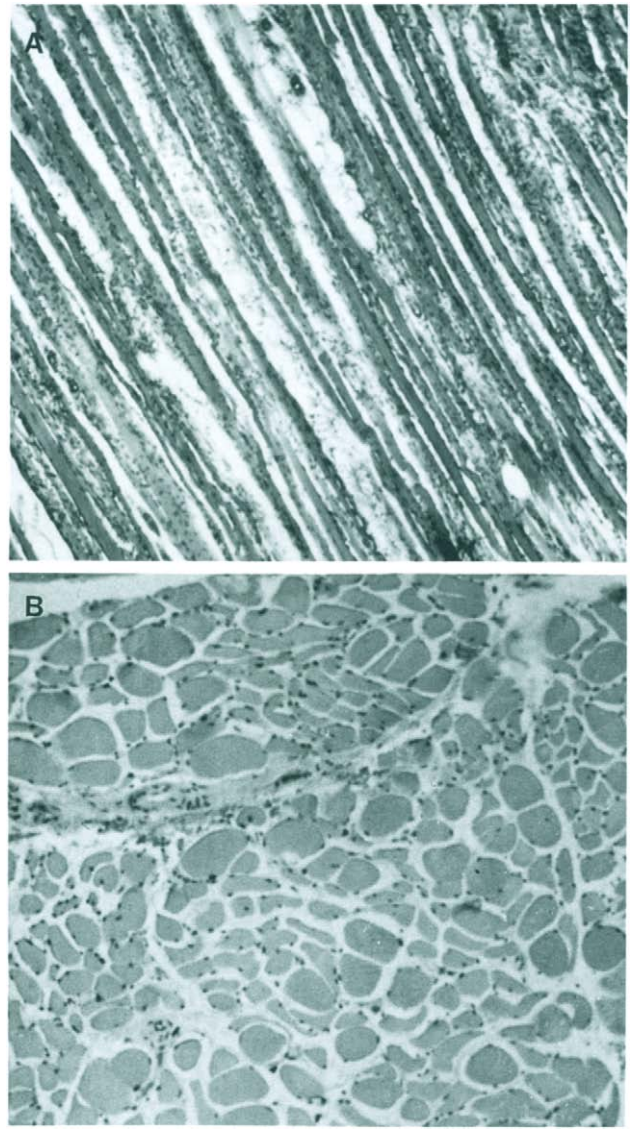


Fig. 138 Refsum disease. Quadriceps muscle, showing severe neurogenic atrophy. (A) Longitudinal section, ×100. (B) Transverse section, ×140.

very variable. A slight loss of Purkinje cells, myelin pallor of the olivocerebellar fibers, and a loss of myelin in the fleece of the dentate nucleus was observed in some cases. Cervós-Navarro (1990) found a patchy loss of neurons in the dentate nucleus and the inferior olive. In most cases, however, no significant lesions were found in the cerebellum.

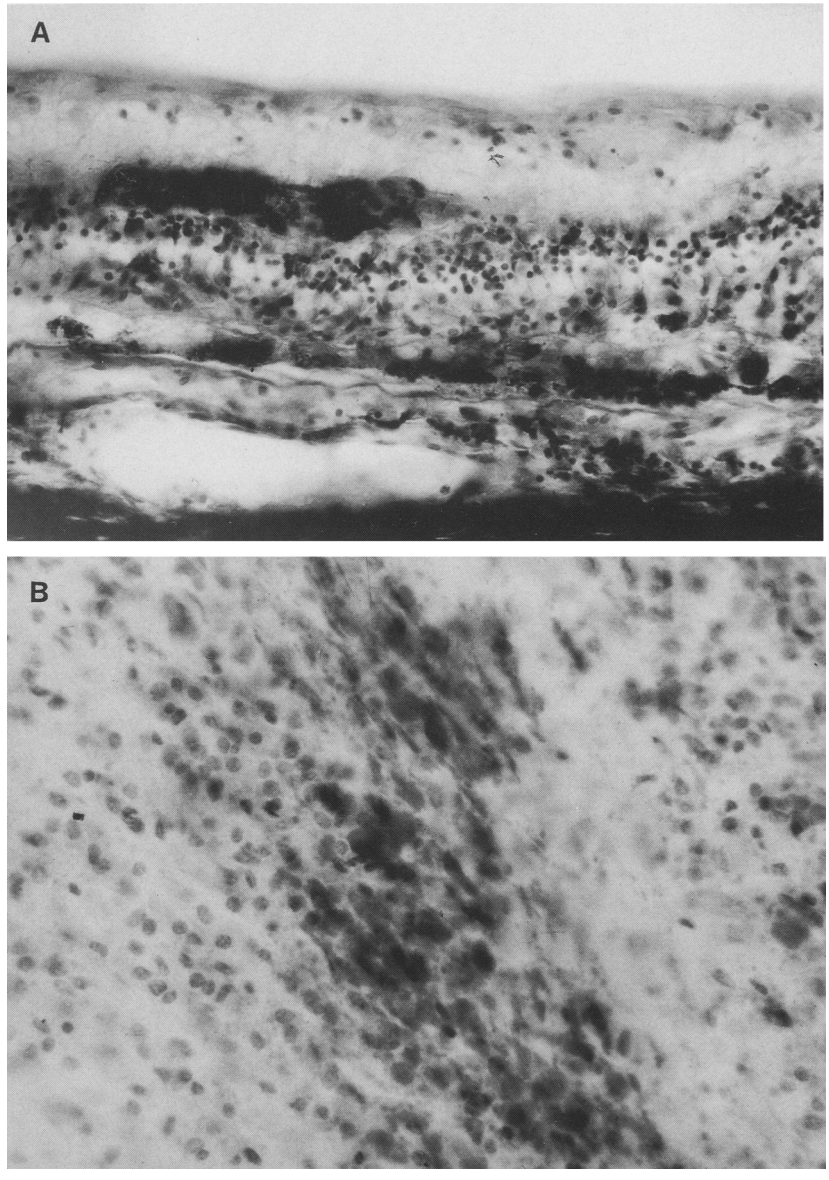


Fig. 139 Same case shown in Fig. 138. (A) Retina with atrophy of all layers and discontinuous pigmentation. Hematoxylin–eosin stain, ×180. (B) Leptomeninges with an accumulation of fat-laden macrophages. Sudan IV stain, ×250.

In the fasciculus gracilis and its nucleus a neuroaxonal dystrophy and distinct demyelination have been observed. The neurons in the spinal cord are swollen and contain abundant strongly sudanophilic lipid granules (Fig. 140). A retrograde axonal reaction may also be present in the anterior horn cells. The nerve roots and, to a lesser extent, the peripheral nerves show onion bulb formations (Fig. 141). The retina shows a loss of the normal architecture with severe atrophy and marked rarefaction of the rods and cones. The pigment epithelium is fragmented and absent in places.

Electron microscopy. Abundant lipofuscin granules and secondary lysosomes fill the neuronal cytoplasm (Fig. 142). Fragments of membranes may form lamellar spheroids. Similar membranous structures may lie free in the cytoplasm in the neighborhood of the residual bodies (Fig. 143). Proximal dendrites contain lipofuscin granules and electron-lucent secondary lysosomes. Autophagosomes may be seen in the axons, containing loosely arranged membranes and lamellar bodies. Where the contents of the lysosomes are less dense, tubular structures, 10 nm in diameter, become visible in both longitudinal and transverse sections. Astrocytes contain lipofuscin granules and pleomorphic inclusions remarkable by their size and density (Fig. 144). Here and there one can discern membranous structures (Fig. 145). The material stored in the oligodendrocytes is characterized by its electron density and areas that exhibit a fingerprint pattern, with loosely arranged tubules and granules in between. These inclusions cover a circumscribed area, 2 μm or more in diameter. In the peripheral nerves and particularly in the nerve roots (Cervós-Navarro, 1989) the most striking feature is the formation of concentric onion bulbs. In cases with a long clinical course, there is evidence of nerve regeneration with bundles of unmyelinated or thinly myelinated axons. The peripheral myelin sheaths show signs of vesicular disintegration (Fig. 146).

In the majority of Schwann cells, one is struck by the great number of residual bodies and secondary lysosomes, and also of membranes arranged in layers. Lipid droplets lie free in the cytoplasm without surrounding membranes.

Pathogenesis Klenk and Kahlke (1963) demonstrated a high concentration of phytanic acid (3,7,11,15-tetramethylhexadecanoate) in tissues obtained at autopsy. This normally appears only in very small amounts. It is a degradation product of chlorophyll and normally undergoes an oxidative breakdown.

Until recently, Refsum disease was included among the peroxisomal disorders. Watkins *et al.* (1990), however, demonstrated that in the normal liver oxidative activity for phytanic acid is present in the mitochondrial, not the peroxisomal, fraction. Poll-Thé *et al.* (1989) carried out complementation studies by culturing fibroblasts from Refsum disease with those of various types of peroxisomal disorders. On all cocultures the defect in phytanic acid metabolism was corrected, proving that the deficiency of phytanic acid α-oxidase was not in the peroxisomes. As a result of these studies, the authors concluded that four genes are essential for phytanic acid catabolism: (1) a gene for mitochondrial phytanic acid α-oxidase, (2) a gene for a regulating factor for the expression of phytanic acid α-hydroxylase and enzymes of plasmalogen synthesis, and (3) two genes for the assembly of functional peroxisomes and for protein import into the peroxisomes.

The pathogenetic mechanisms leading to changes in the CNS remain hypothetical. On the other hand, the pathogenesis of the peripheral neuropathy is well documented. The blood–nerve barrier is permeable to phytanic acid, which floods the endoneurial space of

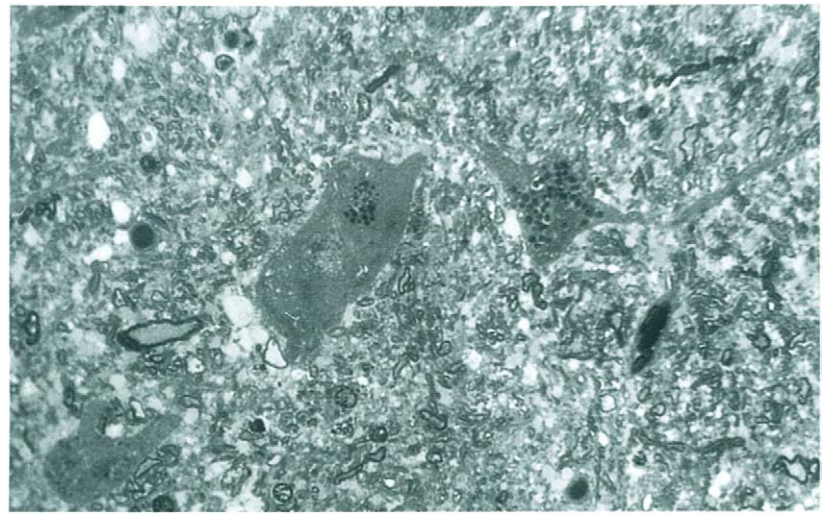


Fig. 140 Same case shown in Fig. 138. Anterior horn cells in the spinal cord with storage of pigment as signs of axonal reaction. Semithin section. Nissl stain, ×250.

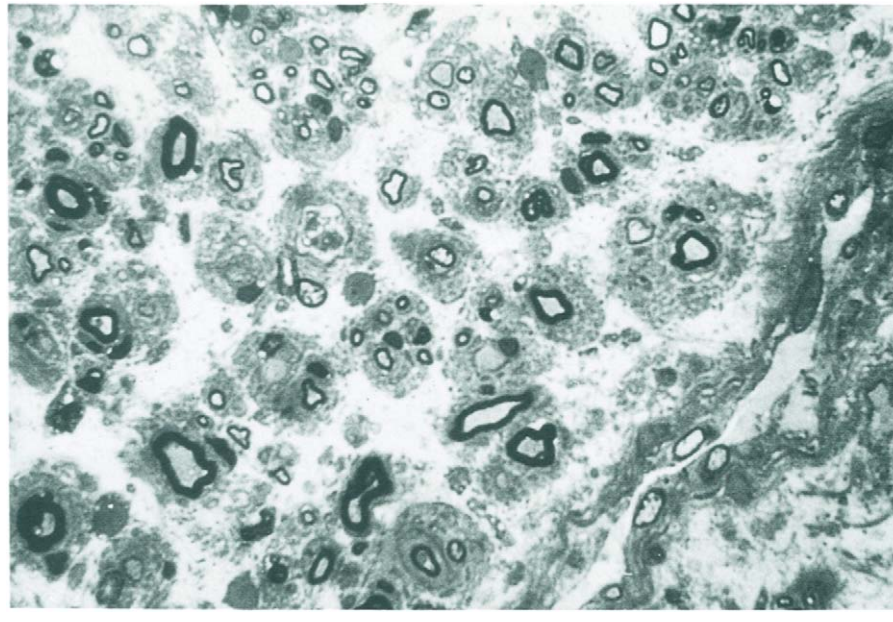


Fig. 141 Same case shown in Fig. 138. The anterior root of the cervical cord, showing numerous "onion bulb" formations. Semithin section. Giemsa stain, ×500.

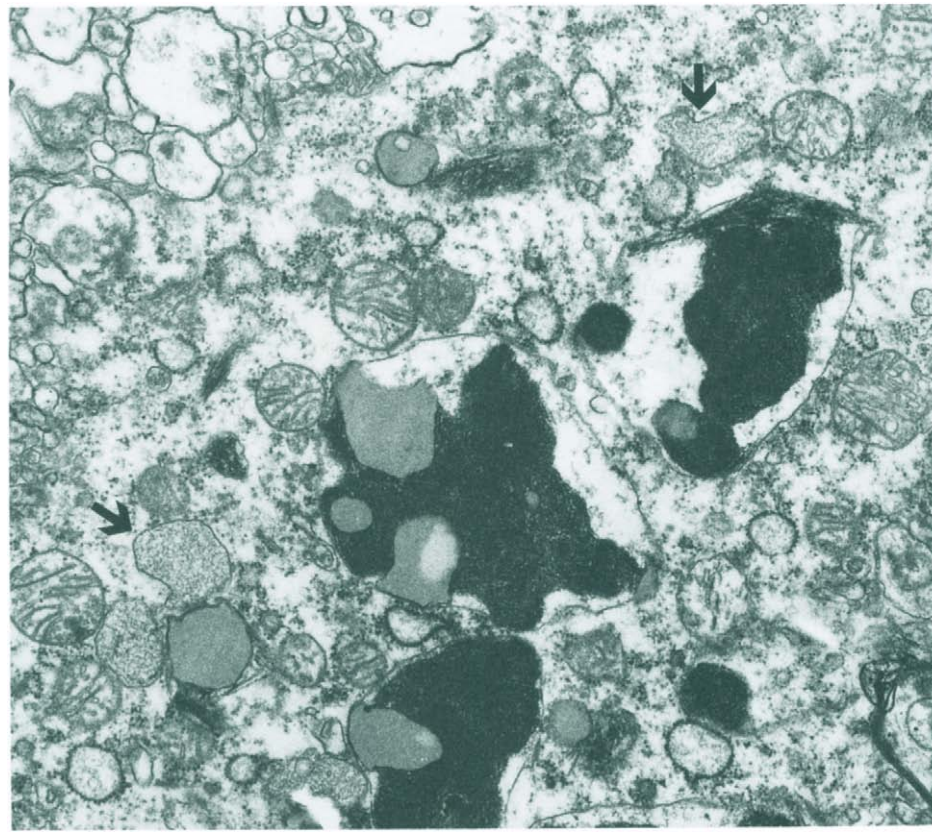


Fig. 142 Same case shown in Fig. 138. A neuron in the frontal cortex, showing secondary lysosomes (arrows) and lipofuscin-like inclusions, ×20,000.

the nerve (Cervós-Navarro, 1989), as demonstrated by the high concentration of this substance. Phytanic acid is ingested in heterophagosomes of the Schwann cells, where it remains in residual bodies in the absence of lysosomal enzymes capable of catabolizing this fatty acid. Part of the phytanic acid is incorporated into the myelin sheath, as already surmised by Kark *et al.* (1969). The increasing disproportion between phytanic acid and the normal myelin constituents leads to the disintegration of the myelin sheaths and subsequently also of axons. The repeated destruction of Schwann cells with the extrusion of the stored material results in the maximal degree of storage in the macrophages.

Lysosomal Diseases of Unknown Pathogenesis

There are several diseases characterized by the presence of abnormal lysosomes or residual bodies in which the nature of the enzyme defect is unknown.

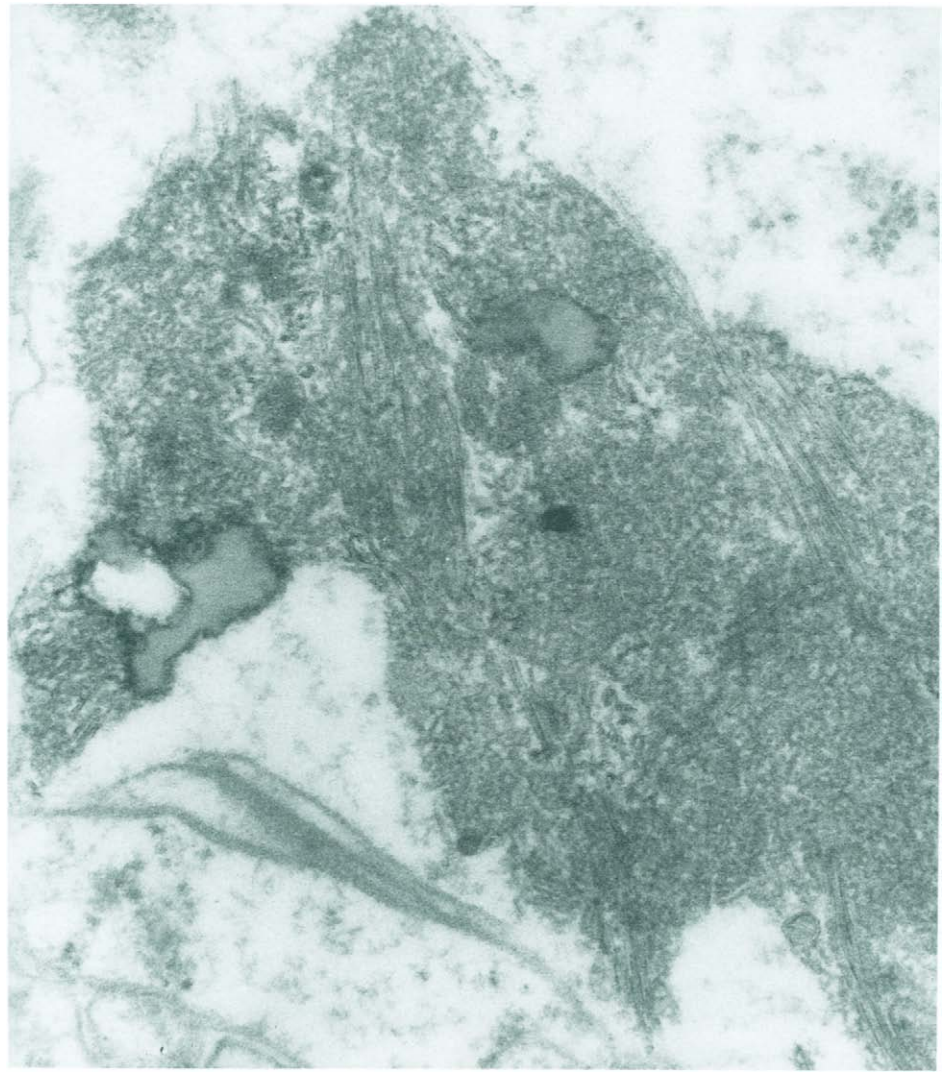


Fig. 143 Same case shown in Fig. 138. A lipofuscin-like inclusion with bilaminar structures, ×120,000.

Ceroid Lipofuscinoses

After the identification of the gangliosidoses and their separation from the "amaurotic idiocies," a large group of cases remained with neuronal storage of an unidentified material. While it appeared to be a lipid, as it took up lipid stains, albeit weakly, it differed from other lipids by being insoluble in lipid stains. It bore a certain resemblance to lipofuscin, the normal pigment present in aging neurons, as well as to ceroid, found in other

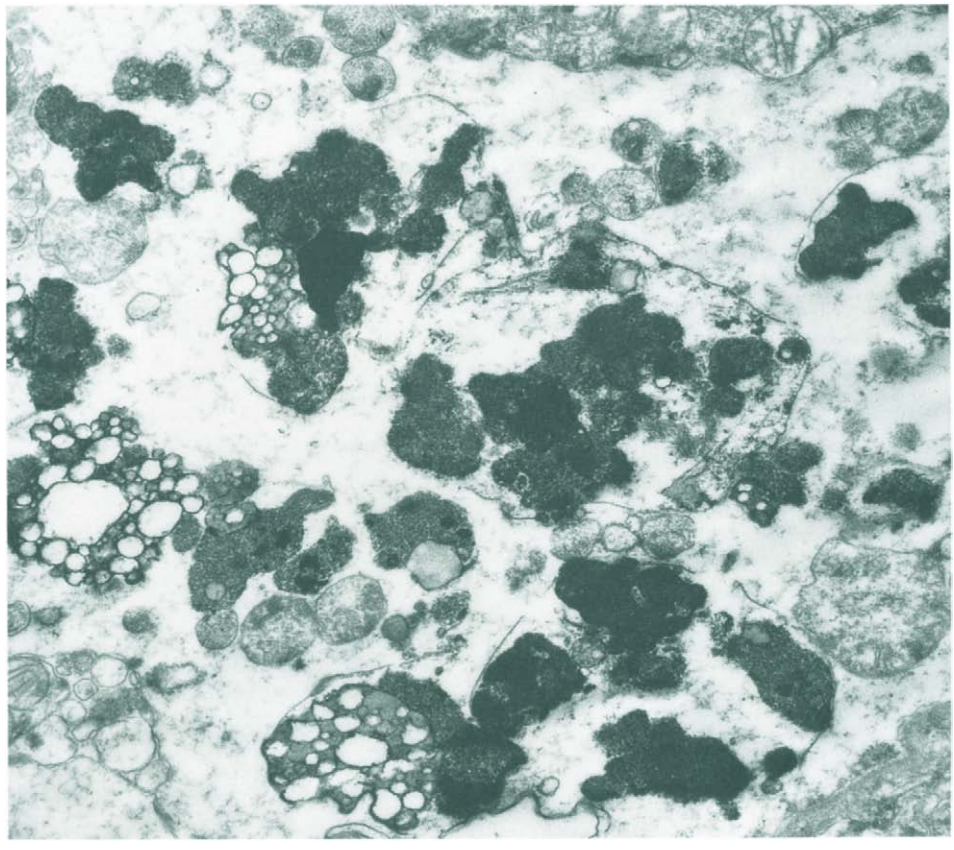


Fig. 144 Same case shown in Fig. 138. An astrocyte in the frontal cortex, showing cytoplasm studded with pleomorphic lysosomal inclusions, ×20,000.

organs. Zeman *et al.* (1970) therefore called the whole group the *ceroid lipofuscinoses*, and this term has been widely accepted.

Classification

The generally accepted classification is based on the patient's age at disease onset. The vast majority of the cases fall into four main groups: infantile, late infantile, juvenile, and adult. A small number of atypical cases are considered variants of the above groups. A classification based on age groups may appear arbitrary, yet there are important clinical and morphological differences between the groups. Their nosological identity has finally been confirmed by genetic studies. The whole subject has been recently reviewed by Goebel (1992), who also contributed an important study on the prenatal diagnosis of these conditions (Goebel, 1994).

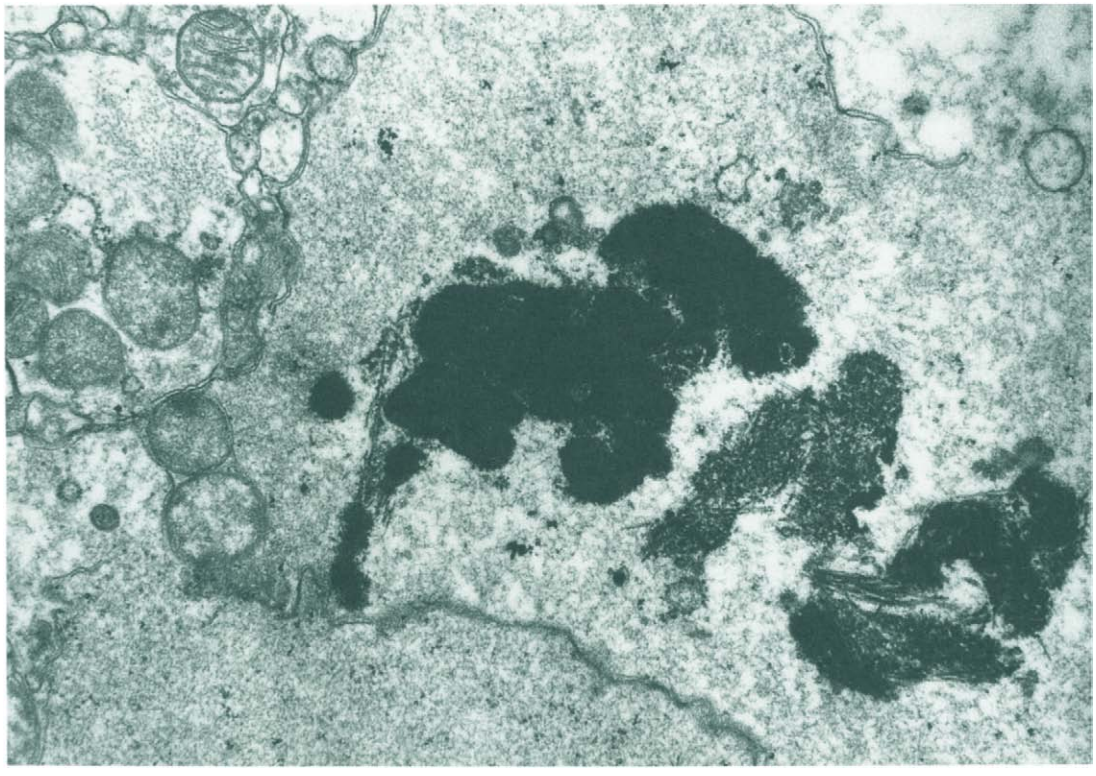


Fig. 145 Same case shown in Fig. 138. An astrocyte in the frontal cortex, showing electron-dense inclusions with bilaminar structures, ×18,000.

Congenital Form

Only a few cases of this disease have been described (Garborg *et al.*, 1987). These children died hours or days after birth. Barohn *et al.* (1992) reported a case of a full-term infant who, immediately after birth, went into status epilepticus and died 36 hours later. A microcephalic and markedly atrophic brain has been reported in most cases. The cerebral and cerebellar cortices show extensive nerve cell loss. Granular material with histochemical characteristics of ceroid lipofuscin is deposited in the neurons, macrophages, and glial cells throughout the brain (Garbourg *et al.*, 1987). Similar material was found in the macrophages in the lymphoid system and in certain other organs. Ultrastructurally, the material was identical to that described in the infantile type of ceroid lipofuscinosis.

Infantile Form (Santavuori–Haltia–Hagberg Type)

Santavuori *et al.* (1973) and Haltia *et al.* (1973) reported on a thoroughly investigated group of 15 patients whom they identified as having the infantile form of ceroid lipofuscinosis.

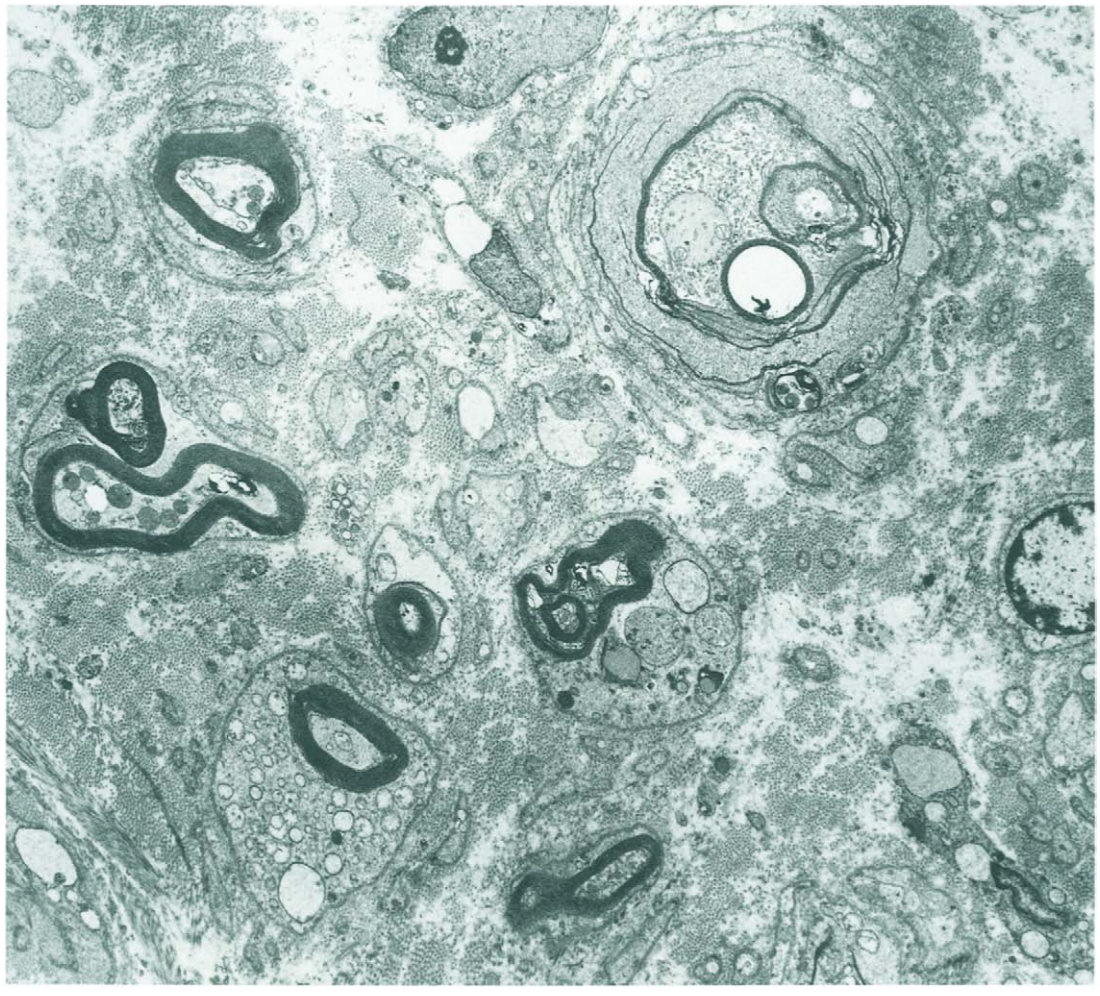


Fig. 146 Same case shown in Fig. 138. The sciatic nerve, showing vesicular degeneration of the myelin sheath and collections of vesicles and residual bodies in Schwann cells, ×6000.

Clinical Picture The disease begins between the ages of 8 and 18 months with rapidly progressive psychomotor decline, ataxia, and hypotonia, later followed by spasticity. Microcephaly and myoclonus are further characteristic features, while epileptic seizures are uncommon. Blindness is an early symptom, and the appearances of the fundus include hypopigmentation, retinal dystrophy, particularly at the macula, optic atrophy, and narrowing of the blood vessels. These appearances, together with a flat electroretinogram, may lead to a diagnosis of Leber's amaurosis congenita (Herrick *et al.*, 1983). Death occurs usually before the end of the first decade.

Pathology *Light microscopy.* Storage of granular material is found in the epithelial cells of various organs, particularly the thyroid gland, pancreas, kidneys, and testes (Martin *et al.*, 1976), as well as in skeletal, cardiac, and smooth muscle. The hepatocytes, however, are free from storage. Large macrophages laden with sudanophilic lipid are seen in the lymphoid organs, bone marrow, and lungs.

Electron microscopy. All intracytoplasmic deposits form rounded membrane-bound inclusions with osmiophilic granular contents. Additional lamellar inclusions have been seen in the epithelia of renal glomeruli and occasionally in the skeletal and cardiac muscle.

Neuropathology *Gross appearances.* Both the dura mater and the leptomeninges are thickened. The cerebral hemispheres and the cerebellum are severely atrophic. The brain stem and the spinal cord are better preserved. Upon sectioning the brain, one notices its firm consistency. The cortex is reduced to a thin, yellowish, gelatinous rim, 1–2 mm in thickness. The white matter is gray and atrophic. The globus pallidus, dentate nucleus, inferior olives, and gray matter of the spinal cord are brownish or reddish orange. The ventricles are dilated.

Light microscopy. The cerebral cortex is almost totally destroyed and devoid of neurons. Only Betz's cells of the motor cortex and the cells of Sommer's sector in Ammon's horn remain. The cellular structure of the cortex consists of numerous, often binucleate, macrophages and unusual hypertrophic astrocytes. The white matter is extensively destroyed. The surviving neurons are swollen and contain large quantities of autofluorescent granules with tinctorial properties of lipofuscin and strong acid phosphatase activity. In the cerebellum either the granule cells or the Purkinje cells (Haltia *et al.*, 1973) or both (Herrick *et al.*, 1983) have totally disappeared. The basal ganglia and the brain stem are variably affected. The neurons of the amygdaloid nucleus, hypothalamus, red nucleus, and motor nuclei in the brain stem and the spinal cord are generally preserved, while the thalamus, striatum, and substantia nigra suffer almost a total loss of neurons (Haltia *et al.*, 1973). The neuronal cytoplasm of the spinal and autonomic ganglia is packed with sudanophilic granules. The Schwann cells of the peripheral nerves contain occasional sudanophilic inclusions. The retina is severely atrophic with a total loss of neurons in all layers and a proliferation of glial cells. The white matter of the cerebrum and the cerebellum is totally devoid of axons and myelin sheaths, with the exception of the myelinated axons of Betz's cells. The astrocytes are hypertrophic and hyperplastic. Macrophages appear only occasionally in the white matter. Metachromatic breakdown products are absent. The cytoplasm of astrocytes, macrophages, ependymal cells, and cells of the choroid plexus contain sudanophilic granules. The endothelial cells of the blood vessels may be involved in the storage process.

Electron microscopy. There is considerable variation in the size of the inclusions (Martin *et al.*, 1976). The deposits may take the form of small spheroids with finely granular contents or larger membrane-bound conglomerates, which may contain some lamellar elements. Lamellar inclusions have also been found in the cells of the blood vessels.

Inclusions are also found in the neurons of the myenteric plexus and in the smooth muscle cells of the appendix. They have also been seen on skin biopsies. The inclusions of the infantile form differ from those of the other forms, not only ultrastructurally, but also in their sedimentation characteristics on ultracentrifugation.

Late Infantile Form (Jansky–Bielschowsky Type of Amaurotic Idiocy; Late Infantile Form of Batten Disease)

The early descriptions of "late infantile amaurotic idiocy" (Jansky, 1909–1910; Bielschowsky, 1914; Batten and Mayou, 1915) may be included in this group. The late infantile and juvenile types are often referred to collectively as *Batten disease* in the English literature.

Clinical Picture This disease is inherited as an autosomal-recessive trait. The symptoms appear between the second and fourth years and, after a rapid progression, lead to death within a few years. Seizures are usually the first symptom (Towfighi *et al.*, 1973). Cerebellar and extrapyramidal symptoms follow, accompanied by mental decline leading to idiocy. Myoclonus is present in some cases, particularly in the end stages of the disease. Visual disturbances are usually late in appearance, in contrast with juvenile cases, in which they often form the initial symptom. On MRI early patterns were observed, characterized by absent or mild atrophy on the T_2-weighted sequences, or diffuse hyperintensity of the supra- and infratentorial white matter. The late pattern is characterized by marked atrophy with predominant involvement of the infratentorial region (Gallucci *et al.*, 1994b).

Changes in the fundus consist of pigmentary degeneration of the retina and optic atrophy, and also narrowing of the blood vessels, all of which may occasionally be absent (Zeman *et al.*, 1970; Nevalainen *et al.*, 1973). The cherry-red spot is usually absent.

Late infantile ceroid lipofuscinosis is not a homogeneous entity. Several atypical variants have been described (Santavuori *et al.*, 1991; Wisniewski *et al.*, 1993b; Williams *et al.*, 1994). They differ from the classical type in some clinical, electrophysiological, microscopic, and ultrastructural details, and may be genetically different as well (Savukoski *et al.*, 1994). About 10% of all childhood ceroid lipofuscinoses are atypical, and most of them represent variants of the late infantile type (Williams *et al.*, 1994).

Pathology *Light microscopy.* Visceral involvement with deposition of a lipofuscin-like pigment is apparent particularly in the liver and the spleen, but also in the myocardium, kidneys, and bone marrow (Zeman *et al.*, 1970; Nevalainen *et al.*, 1973). Splenic granulomas have also been described.

Electron microscopy. The shape and distribution of curvilinear cytosomes are very irregular in the hepatocytes. In some cells they are abundant, up to 9 μm in length, and irregularly branched. In some places they contain isolated, homogeneous, round lipid droplets of low electron density. In other places densely osmiophilic substances may be interposed between the curvilinear structures. The bone marrow contains pleomorphic curvilinear cytosomes in the reticuloendothelial cells. Similar structures are found on biopsies of muscle (Fig. 147A), skin, and sweat glands.

The variation in the form of the curvilinear bodies in different tissues of children in the same family can make the diagnosis difficult based on liver or bone marrow biopsies. All lymphocytes contain, in some patients, curvilinear inclusions; fingerprint profiles are also present. On a muscle biopsy crystalloid formations were found in smooth muscle cells of the blood vessels (Fig. 147B).

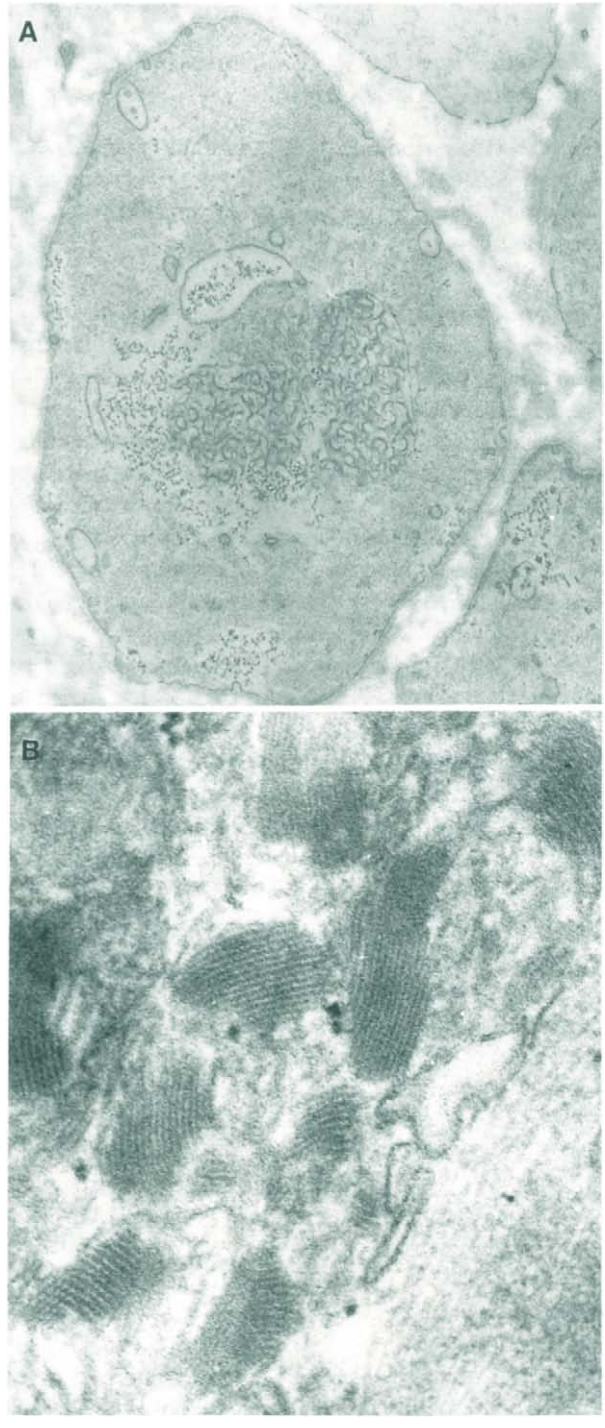


Fig. 147 Late infantile form of ceroid lipofuscinosis. (A) A smooth muscle cell in an arteriole in the skin with a curvilinear cytosome, ×16,000. (B) The gastrocnemius muscle, showing a crystalloid formation in a smooth muscle cell of an arteriole, ×30,000.

Neuropathology *Gross appearances.* The brain is diffusely atrophic, with thinning of the cortex and shrinkage of the white matter. The cortex often shows a yellowish discoloration and pseudolaminar necrosis. In most cases the cerebellum is particularly affected by atrophy (Fig. 148).

Light microscopy. There is, in places, a substantial loss of cortical neurons with gliosis (Zeman *et al.*, 1970), and sometimes status spongiosus (Fig. 149). The surviving nerve cells are swollen, but not as ballooned as in the gangliosidoses. They display ubiquitous storage of finely granular material. The granules stain dark blue with luxol fast blue and brownish orange with Sudan III or IV. They show a yellowish green autofluorescence under ultraviolet light. In the neurons of the thalamus, hypothalamus, substantia nigra, dentate nucleus, and inferior olives, some inclusions form clumps rather than granules. These have been described as "myoclonus bodies of [a] proteinaceous type."

Golgi impregnations reveal expansions of proximal axons in almost all pyramidal cells. A substantial loss of cerebellar granule cells has frequently been observed in late infantile cases (Zeman *et al.*, 1970).

The retina shows severe damage to the rods and cones and a variable degree of intraneuronal storage in the ganglion cell layer (Zeman *et al.*, 1970).

Electron microscopy. Curvilinear inclusions (Fig. 150) are found in the neurons, glial cells, endothelia, and pericytes. These have been described under a variety of names, such as *multilocular bodies*, *granular osmiophilic deposits with fragmented membranes*, *aggregates of smooth membranes*, and *multilamellated cytosomes*. The

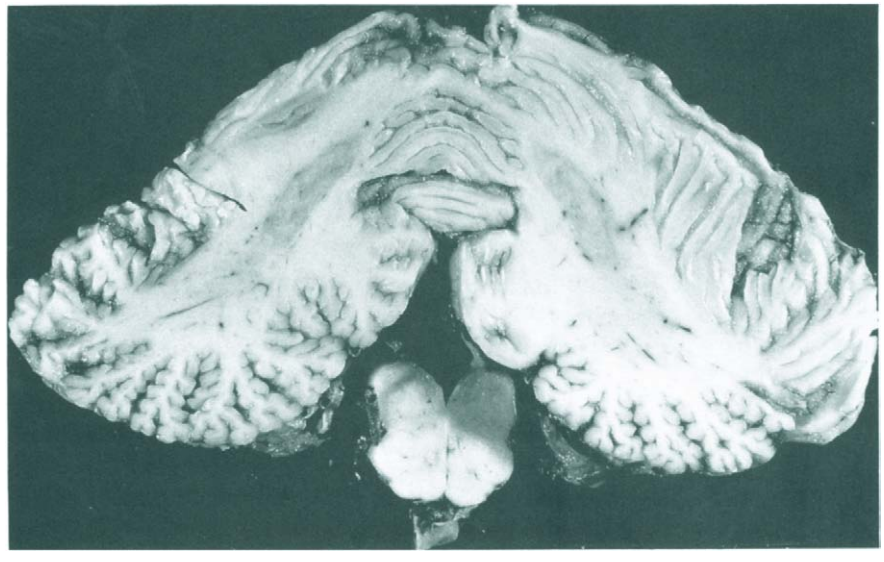


Fig. 148 Late infantile form of ceroid lipofuscinosis. Atrophy of the cerebellum.

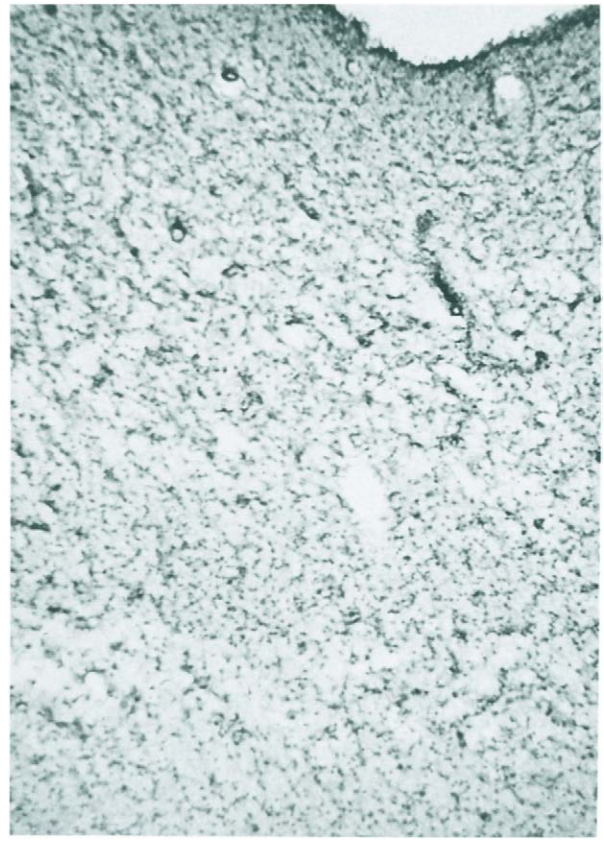


Fig. 149 Late infantile form of ceroid lipofuscinosis. Almost total loss of neurons, fibrillary gliosis, and status spongiosus of the cerebral cortex. FAN stain of the glial fibers after the method of Miquel, ×60. (Reproduced from Cervós-Navarro and Goebel, 1989.)

neuronal inclusions, which may be up to 6 μm long, consist mainly of curvilinear structures, with occasional zebra bodies (Fig. 151A). Some multicentric, curved, or concentric membrane complexes, 4–5 μm in diameter, may be seen lying in a finely granular or amorphous matrix (Fig. 151B). Lipid droplets are rarely seen within the curvilinear inclusions. Aside from curvilinear structures, typical lipofuscin complexes and fingerprint bodies can be seen in older patients. The two types of inclusions may not always be clearly distinguishable, and transitional forms may occur (Zeman *et al.*, 1970).

Ultrastructural inclusions devoid of curvilinear bodies, but consisting only of an undifferentiated matrix, are not seen, as a rule. The pattern of inclusions is remarkably constant over long periods. Curvilinear inclusions found in brain biopsies years before death were identical to those found in autopsy material (Towfighi *et al.*, 1973). At magnifications above 100,000×, a particular alternating linear pattern of the curvilinear bodies was found (Buhl *et al.*, 1994).

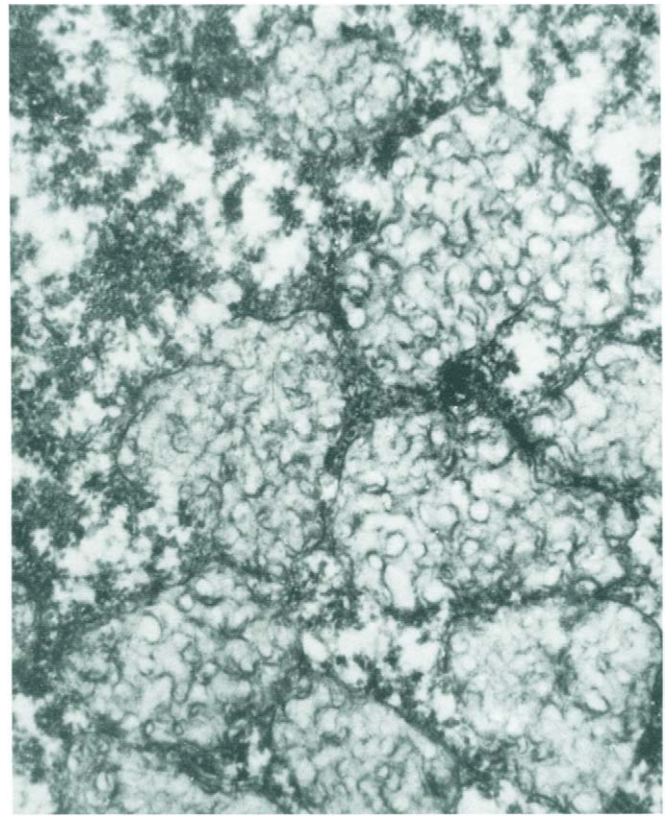


Fig. 150 Late infantile form of ceroid lipofuscinosis. Densely packed ribosomes between curvilinear inclusions, ×22,000.

Fingerprint bodies may be found in the glial cells. The clumplike inclusions in the substantia nigra consist of tightly packed electron-dense granules, often confluent, with curvilinear structures and neuromelanin granules. Curvilinear bodies are also found in the Schwann cells (Joosten *et al.*, 1973).

Juvenile Form (Ceroid Lipofuscinosis of Spielmeyer–Sjögren Type; Batten–Spielmeyer–Vogt Disease; Juvenile Amaurotic Idiocy)

This disease was first described by Stengel in 1826, when he reported on four siblings who all died around the age of 20 years. Further case reports, some with histopathological findings, followed 80 years later with the publications of Batten (1903) and Mayou (1904) in the English literature and Spielmeyer (1906) and Vogt (1907) in German. In a comprehensive study emphasizing the genetic aspects, Sjögren (1931) reported his observations on 120 patients from 53 Swedish families. This study

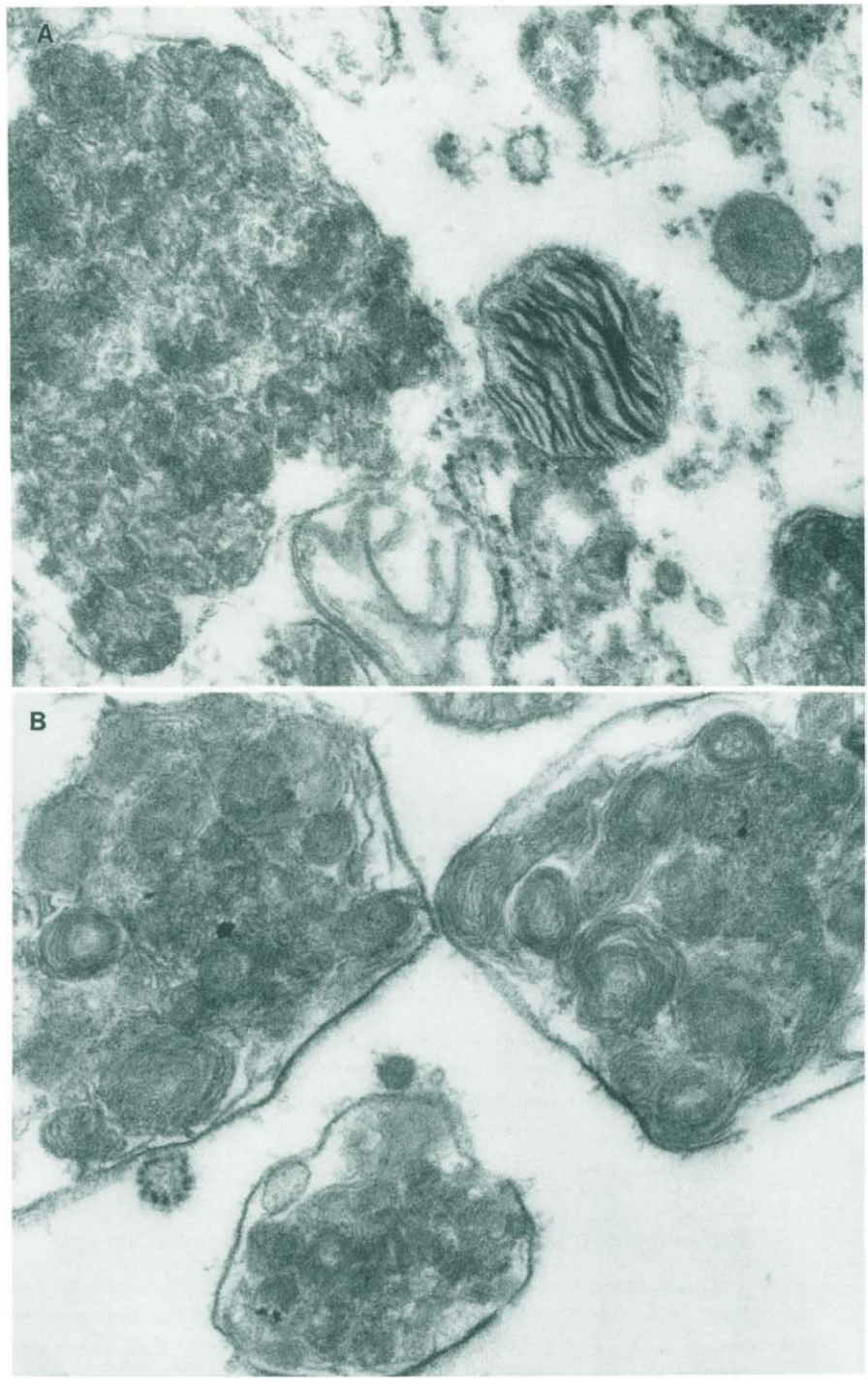


Fig. 151 Same case shown in Fig. 149. Neuronal cytoplasm in the parietal cortex. (A) A curvilinear inclusion and a zebra body. (B) A multicentric membranous inclusion, ×60,000.

established the autosomal-recessive inheritance of the disorder and differentiated it clearly from Tay–Sachs disease.

The last 20 years have added extensively to the literature describing the disease in detail and encompassing ultrastructural and biochemical findings (Goebel and Braak, 1989).

Clinical Picture The first symptom is a deterioration of vision, which sets in at about the age of 6 or 7 years and is followed by a slowly progressive mental retardation. A decline in motor function, epileptic seizures, and intermittent myoclonus appear in later stages. Extrapyramidal symptoms are common (Sjögren, 1931). The visual symptoms, terminating in blindness, may precede the neurological manifestations by some years. The appearances of tapetoretinal degeneration have been repeatedly confirmed. While the majority of the cases conform to this pattern, considerable variability in the clinical symptomatology has been observed (Wisniewski *et al.*, 1992) even in members of the same family.

The final stage is one of total decerebration. The patients die after a disease duration of 8–12 years, between the ages of 14 and 20 years, usually of intercurrent infections. In patients who survive beyond the age of 14, CT scans show enlargement of the subarachnoid space and dilatation of the ventricles. Some cases with an early onset between the ages of 5 and 6 years ("early juvenile") occupy an intermediate position between the late infantile and juvenile forms (Santavuori *et al.*, 1991). Others have disease with a later onset and a more protracted course that may extend over several decades (Ebhardt *et al.*, 1973; Goebel *et al.*, 1976). These cases are sometimes confused with Kufs' disease, from which they differ by their severe visual impairment and pigmentary retinal degeneration.

The juvenile form is inherited as an autosomal-recessive trait, and several siblings may be affected. There is no racial predilection, but a disproportionately high incidence has been reported from Sweden (Sjögren, 1931).

Pathology Involvement of the visceral organs in juvenile amaurotic idiocy was first mentioned by Böhmig and Schob (1929). The deposits in the myocardium, liver, kidneys, spleen, and lymph nodes are identical to the material stored in neurons. Both vacuolated lymphocytes and, to a lesser extent, hypergranulated neutrophils are found in the peripheral blood. As both of these abnormalities are also found in asymptomatic heterozygotes, they may help in the identification of carriers (Zeman *et al.*, 1970).

Electron microscopy. The vacuolated lymphocytes contain inclusions with fingerprint bodies (Baumann and Markesbery, 1978). In the histiocytes of the skin, both curvilinear and fingerprint bodies may be found. Occasionally, both types of structures may be seen in the same inclusion. Ebhardt *et al.* (1973) found curvilinear structures in macrophages and fibroblasts of the rectal mucosa (Fig. 152) in a "juvenile case with [a] protracted course."

Neuropathology *Gross appearances.* The brain is slightly to moderately atrophic in most cases (Fig. 153A). A moderate cortical atrophy may also be present in the cerebellum (Goebel *et al.*, 1976) (Fig. 153B).

Light microscopy. The neurons are slightly swollen, sometimes shrunken or rounded, but not substantially enlarged (Fig. 154). They contain granular inclusions that stain positively with Sudan black and PAS. Granular material in the white matter of two cases stained

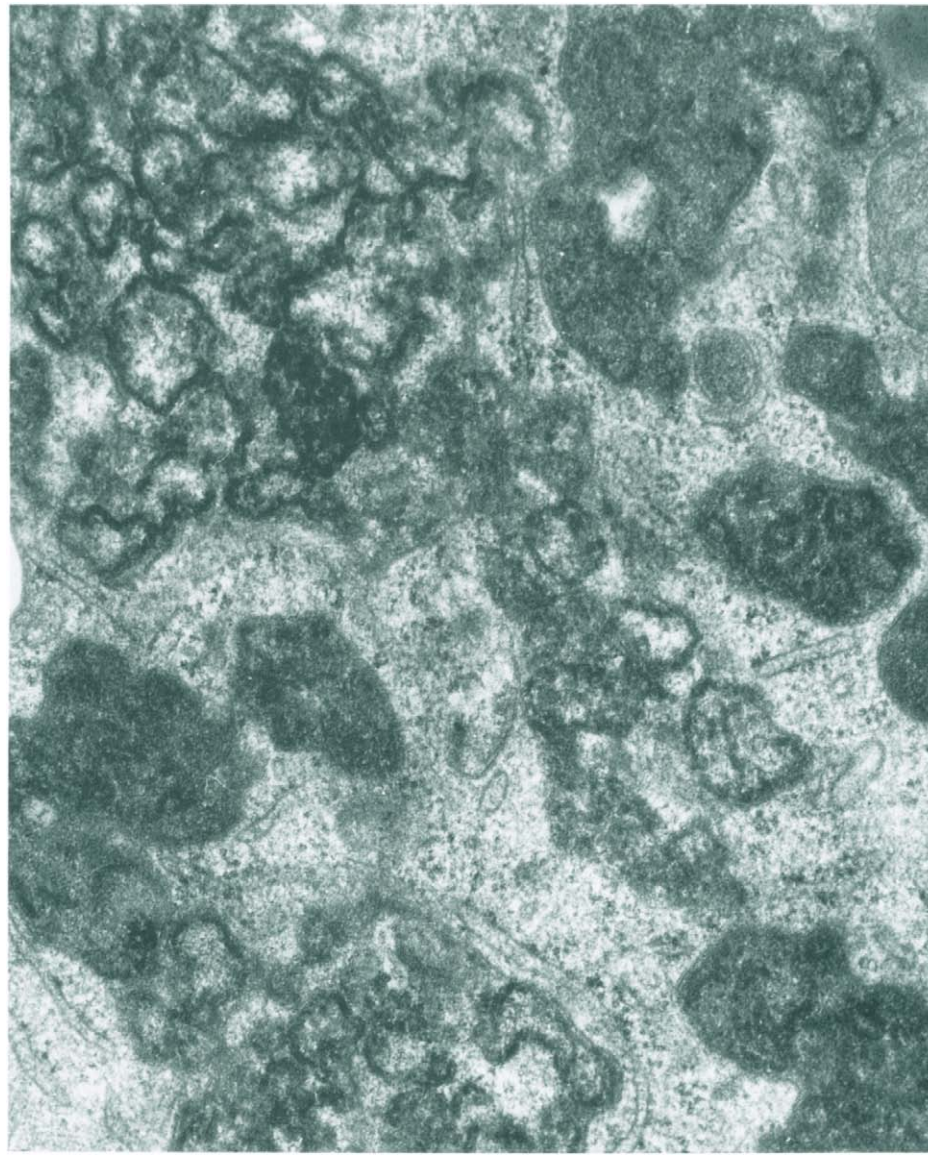


Fig. 152 Juvenile form of ceroid lipofuscinosis. Curvilinear structures in a macrophage in the rectal mucosa, ×60,000.

metachromatically with toluidine blue. All regions of the brain are affected, but various areas may differ in their degree of involvement. The essential features of the neurons affected by storage were already described in detail by the early authors and discussed at length in the literature of the following decades (Schaffer, 1935). The binding pattern of lectins may differ-

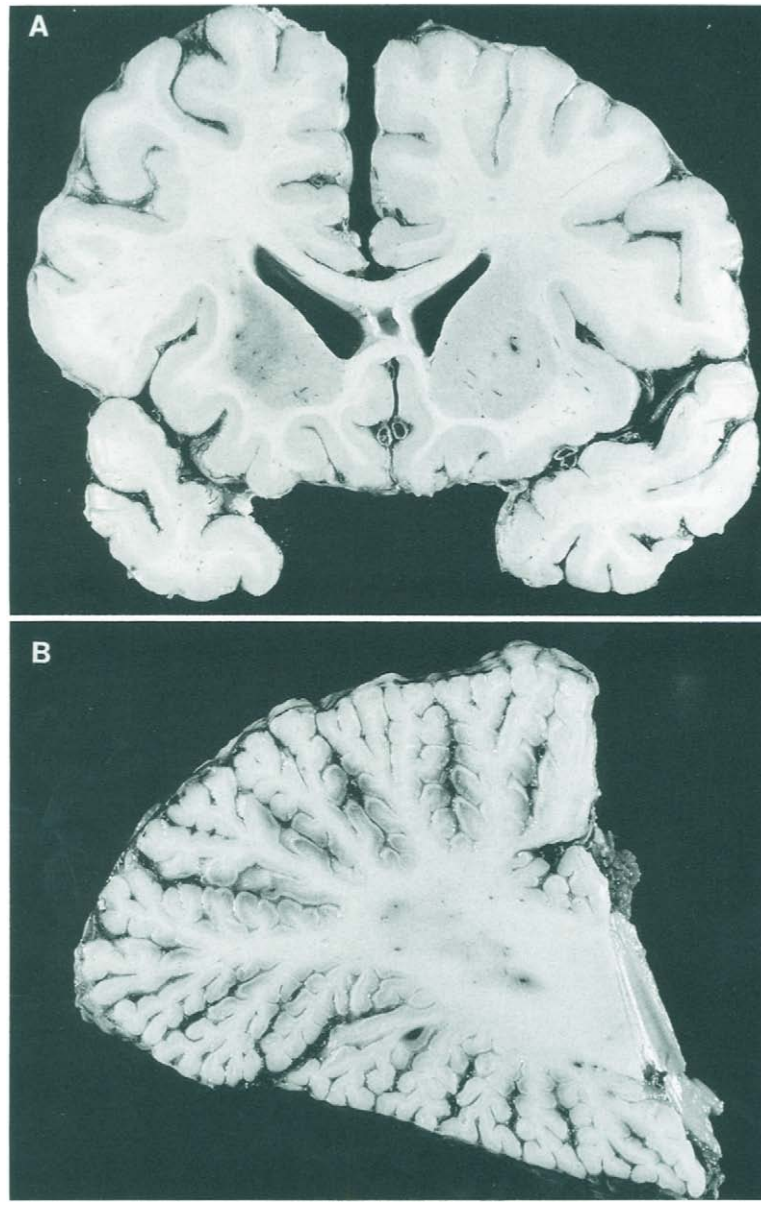


Fig. 153 Juvenile form of ceroid lipofuscinosis. Atrophy of (A) the cerebrum and (B) the cerebellum.

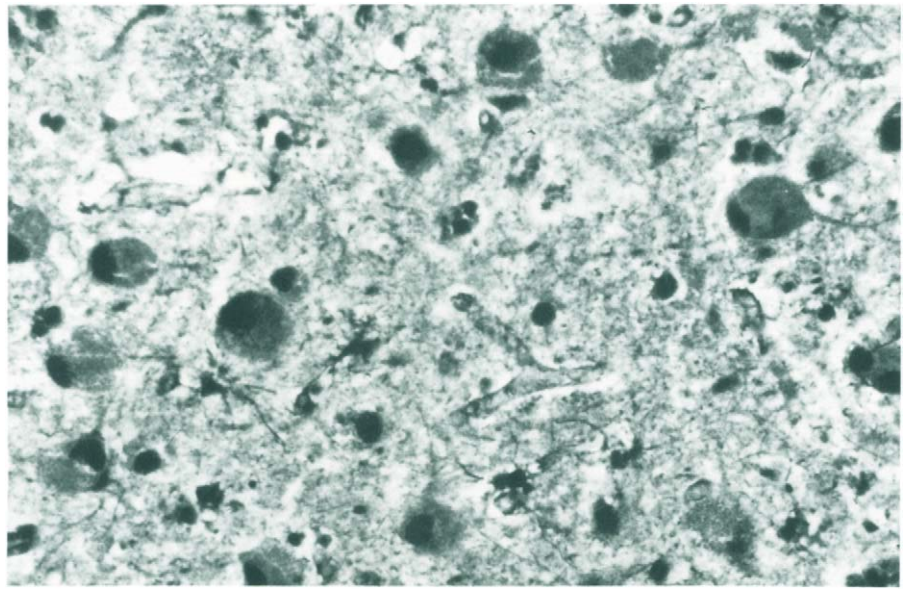


Fig. 154 Same case shown in Fig. 153. The cortical neurons are reduced in number and show a rounded cell body. Bodian stain, ×300.

entiate between storage materials of neuronal ceroid lipofuscinosis and aging brains (Wisniewski and Maslinska, 1990).

In sections stained by Nissl's method, no definite evidence appears of rarefaction of the neuronal population. In stains for the stored pigment (Braak and Goebel, 1978), however, axonal swellings are seen in the third and fourth layers and severe neuronal loss becomes apparent in layer V (Fig. 155A–E) as well as in the stellate cells of the striatum (Braak, 1984). The stored material displaces the nucleus to the periphery. It is often present in the proximal parts of the cell processes. This is particularly apparent in the Purkinje cells, where material may be stored in staghorn dendrites (Fig. 156). Degeneration of the granular layer of the cerebellar cortex is fairly common. The inclusions in the astroglia were particularly impressive because of their severe involvement in the striatum, where they correlated with the frequent extrapyramidal symptoms in Swedish patients. Other authors confirmed the presence of storage material in the astrocytes (Zeman *et al.*, 1970). Mesodermal structures may also be involved, including deposition of lipopigment in the endothelial and perithelial cells. Cerebral calcifications, situated near the outer and inner surfaces of the brain, were described by Bruun *et al.* (1991). Segmental demyelination and fragmentation of the axons was described in the peripheral nerves.

The histological appearance of the retina is characterized by the primary loss of the sensory epithelium. This is an essential difference between this disorder and Tay–Sachs disease. The rods and cones disappear completely; the external nuclear layer undergoes disorganization and rarefaction. The pigment epithelium is also damaged and may, in some places, extend deep into the retina. The neurons of the ganglion cell layer are reduced in number, with Sudan black- and PAS-positive material

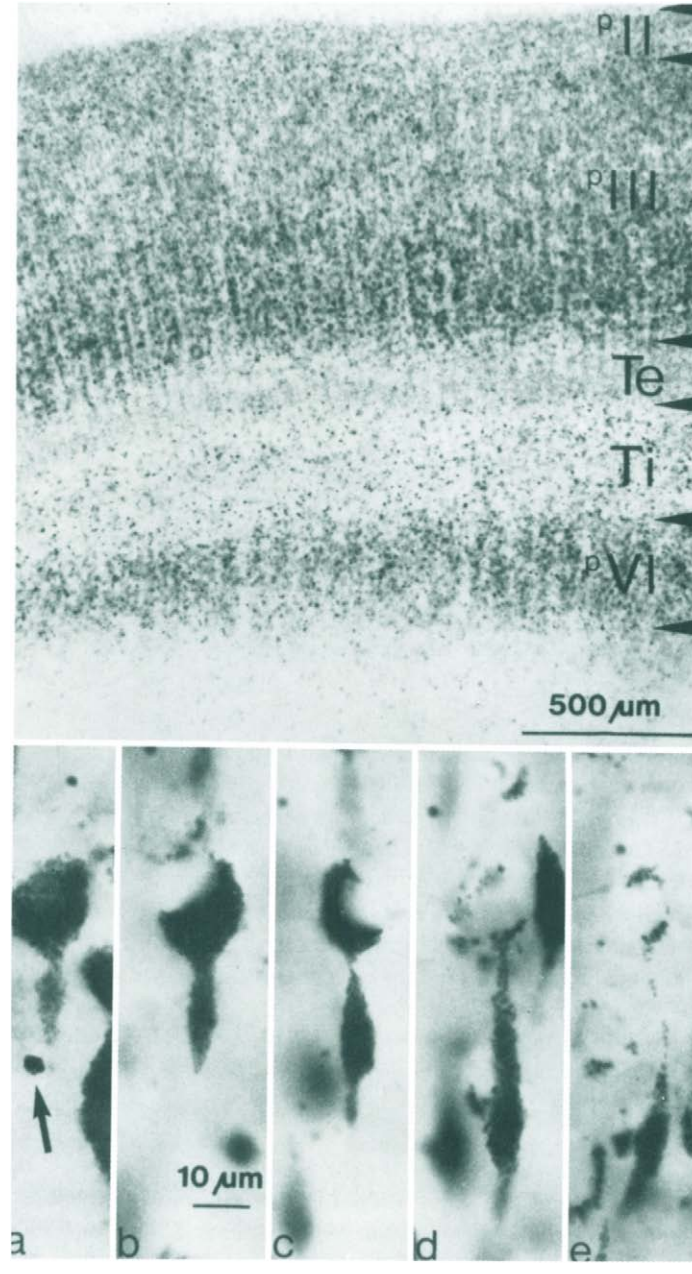


Fig. 155 Juvenile form of ceroid lipofuscinosis. (Top) A loss of cortical neurons in layer V. Pigment-laden axonal swellings in layer III. (A–E) Higher magnifications. (Reproduced from Braak, 1984.)

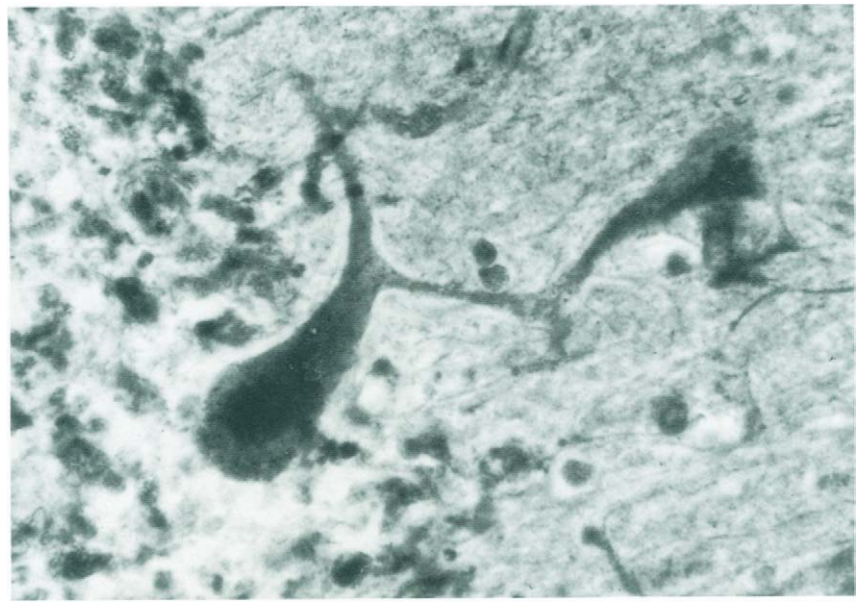


Fig. 156 Juvenile form of ceroid lipofuscinosis. Staghorn swelling of Purkinje cell dendrites by deposition of storage material. Bodian stain, ×500.

stored in the remaining cells. The optic nerve may be atrophic or may show normal myelinization.

Electron microscopy. Pleomorphic inclusions are present in the perikarya (Fig. 157A and B), axons, and dendrites (Fig. 158), which, at low magnifications, resemble lipofuscin, but at higher resolutions are seen to consist of fingerprint or curvilinear bodies. Fingerprint bodies (Fig. 159A) are more common in the juvenile than in the late infantile form of the disease (Towfighi *et al.*, 1973). The endothelial cells of the cerebral capillaries contain typical curvilinear bodies (Fig. 159B).

Skin and conjunctival biopsies show the same inclusions and make the diagnosis possible without recourse to a brain biopsy.

Inclusions of the fingerprint pattern have been observed in neurons of the myenteric plexus on rectal biopsies of two typical juvenile patients.

Adult Form (Kufs' Disease; Late Form of Amaurotic Idiocy)

Kufs (1925) described a storage disease of adult onset under the name *late form of amaurotic idiocy*. The term is a misnomer, as very few, if any, patients are blind, and some develop dementia only late in the course of the disease. The widely accepted eponymous term *Kufs' disease* acknowledges this author's important contribution, but not his priority, which belongs to Sträussler (1906). Many subsequent cases have been reported, but not all are acceptable based on strict clinicopathological criteria. In their

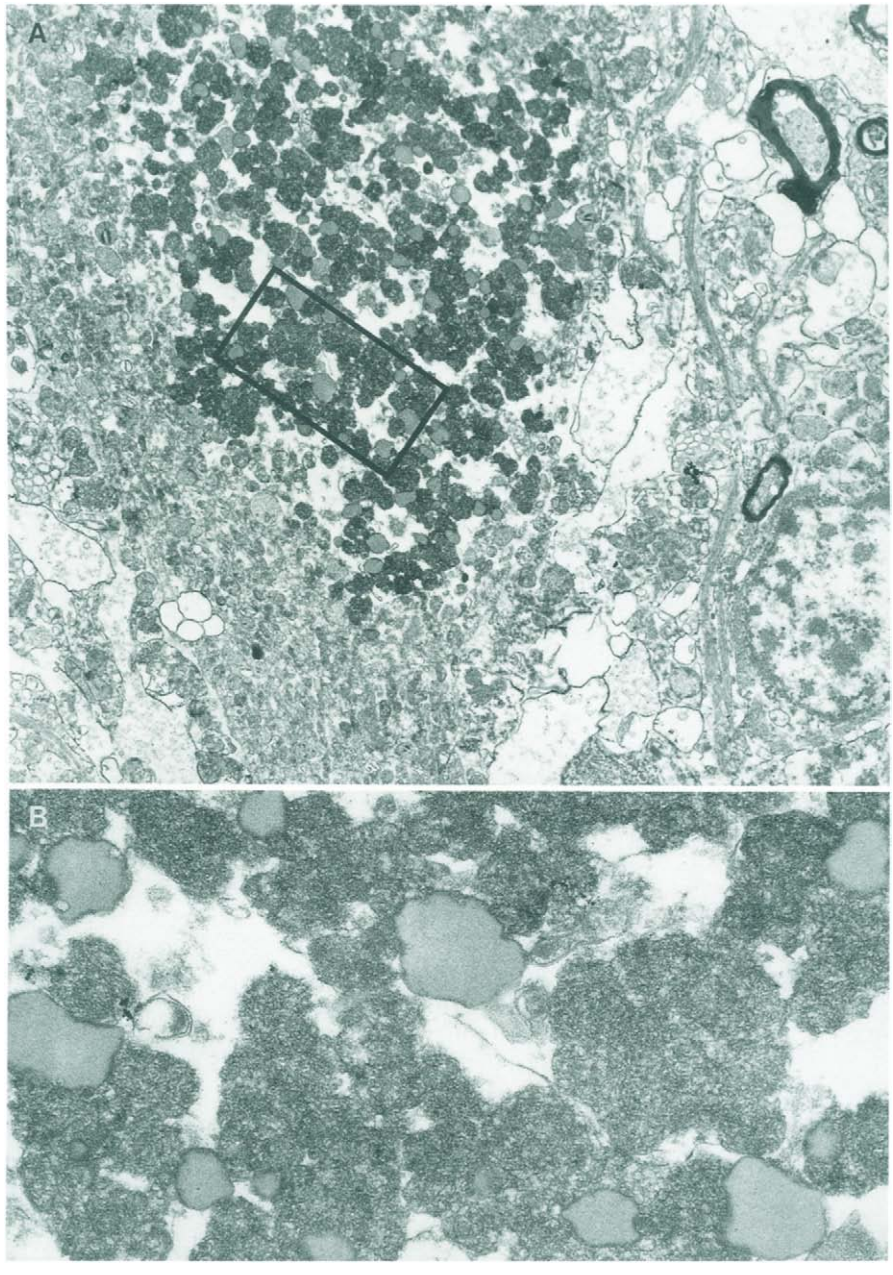


Fig. 157 Juvenile form of ceroid lipofuscinosis. A perikaryon of a neuron in the frontal cortex. Lipofuscin-like inclusions, (A) ×6000 and (B) ×20,000.

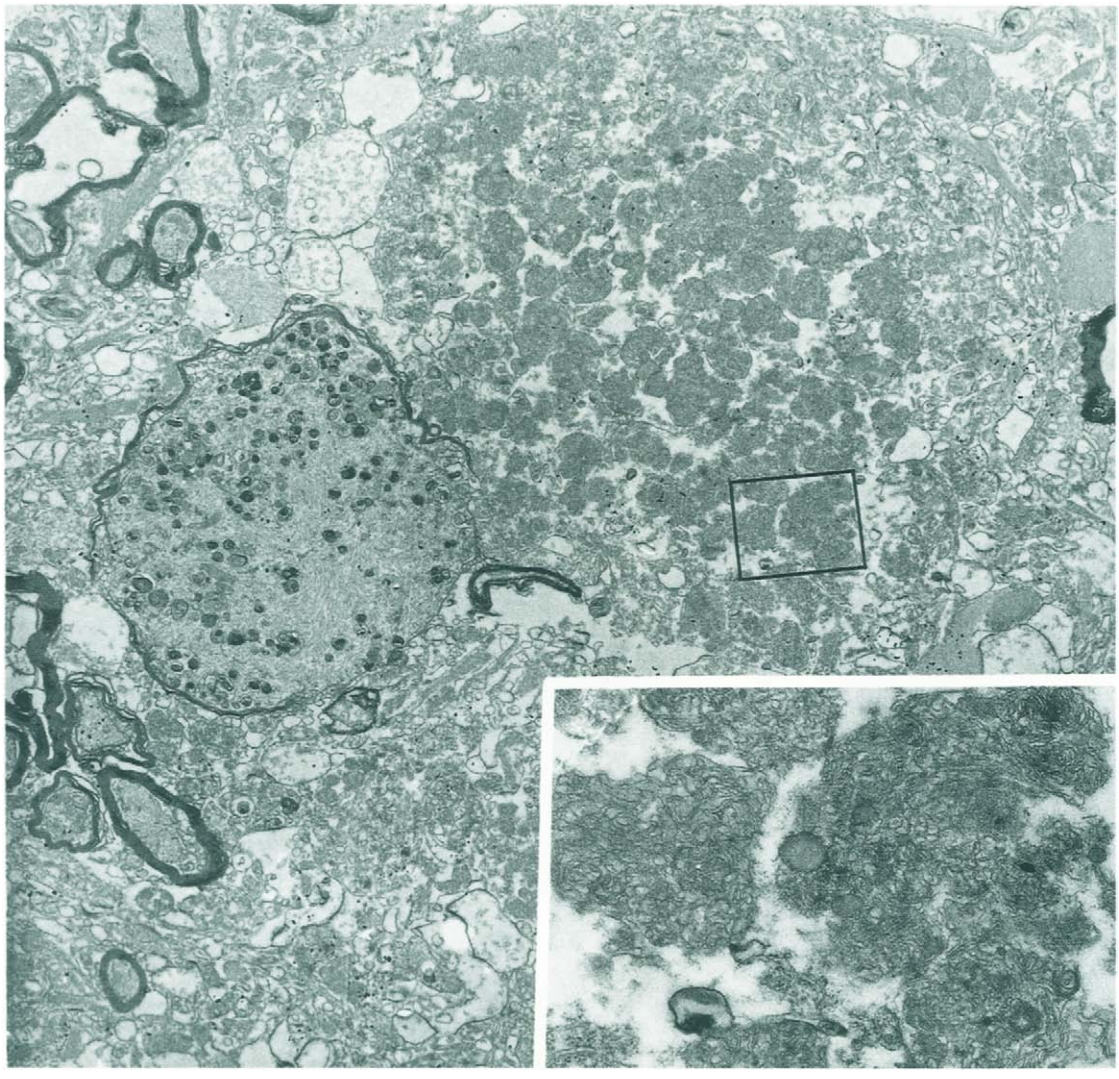


Fig. 158 Same case shown in Fig. 157. Curvilinear inclusions in a dendrite and an axon, ×8000 (inset ×24,000).

critical review Berkovic *et al.* (1988) listed 118 cases, of which they accepted only 50, the others either being inadequately documented or representing other storage diseases of late onset. A few more cases have recently been added (Goebel and Braak, 1989; Nakamura *et al.*, 1990; Vital *et al.*, 1990; Wisniewski *et al.*, 1991; Constantinidis *et al.*, 1992).

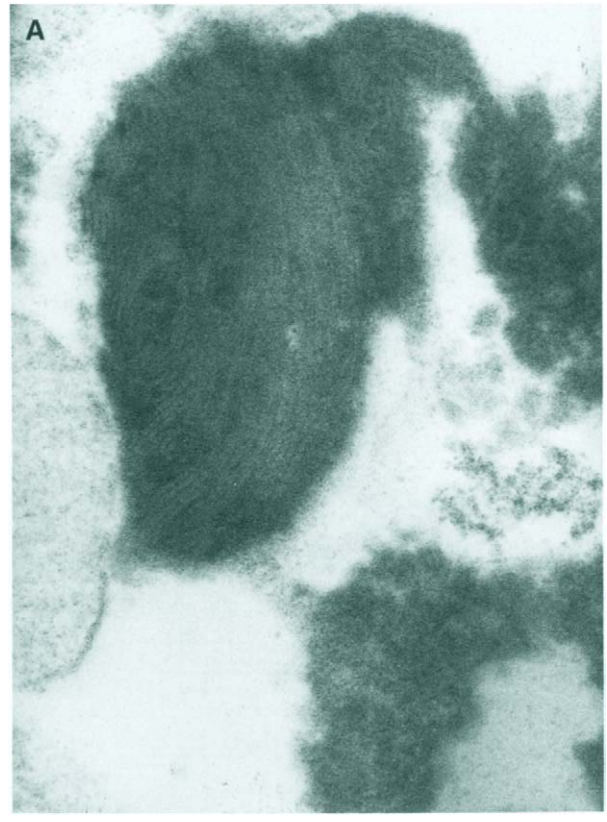


Fig. 159 Same case shown in Fig. 157. (A) A fingerprint body in the neuronal cytoplasm. Original magnification ×80,000. (B) Curvilinear inclusions in an endothelial cell of a cerebral capillary, ×30,000.

Clinical Picture The heterogenous spectrum of clinical and genetic phenotypes of adult neuronal ceroid lipofuscinosis are distinct from those of the other forms of this disorder (Martin, 1991). The age at onset is between 30 and 40 years, with a wide range from 11 years (Greenwood and Nelson, 1978) to 50 (Goebel *et al.*, 1982) or even 63 years (Constantinidis *et al.*, 1992). Several cases of early onset, particularly those with pigmentary degeneration of the retina, are examples of juvenile ceroid lipofuscinosis with a protracted course. Berkovic *et al.* (1988) outlined two distinct clinical patterns of the disease: one (type A), characterized by seizures, myoclonus, and neuropsychiatric disorders; the other (type B), by dementia and motor disorders. In type A the disease is usually ushered by a seizure followed by typical myoclonus epilepsy. In some cases the seizures are particularly photosensitive. Dementia appears later, as do ataxia and dysarthria. Some cases present with behavior disorders, and in these cases seizures are less prominent (Tobo *et al.*, 1984). Signs of involvement of

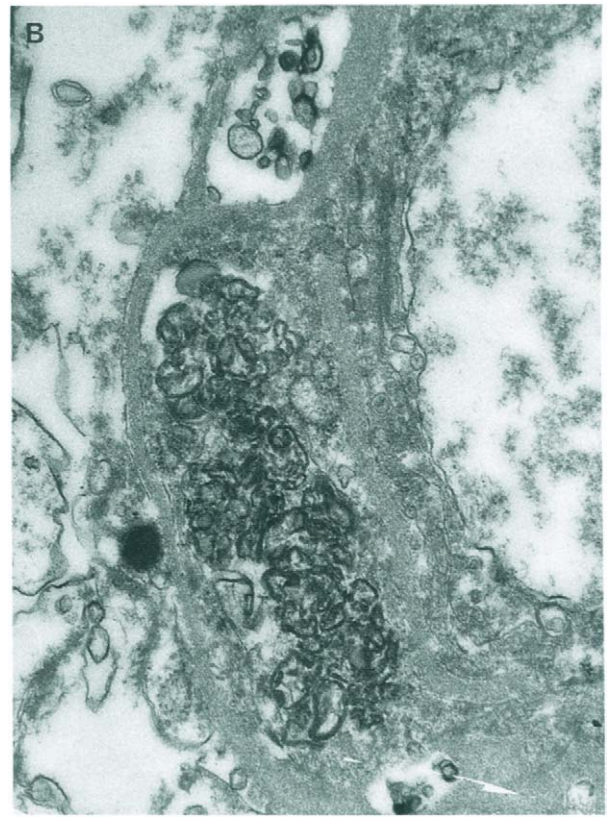


Fig. 159 Continued.

the pyramidal, extrapyramidal, and lower motor neuron systems are absent or develop terminally. In contradistinction to the juvenile and protracted juvenile neuronal ceroid lipofuscinoses, there is no pigmentary degeneration of the retina (Martin, 1991). Type B presents with behavior changes, rapidly developing into dementia, with movement disorders, mainly of the extrapyramidal or cerebellar type. Hyperkinetic disorders are more common than hypokinetic ones, with only one case of a parkinsonian syndrome having been recorded. A ticlike facial dyskinesia is present in many cases. Pyramidal signs were rarely prominent. Seizures are uncommon. Visual disturbances have not been reported. There is some overlap between the two types and they do not represent different nosological entities. Atypical cases also occur.

The clinical course of all cases is similar, being progressive over several years, with an average of 12 years. A subset of patients with late adult onset of the clinical symptoms and a shorter course has been reported (Constantinidis *et al.*, 1992). All patients are terminally demented.

The disease occurs worldwide and affects different races. Both sporadic and familial cases have been reported, the latter inherited as an autosomal-recessive trait, with

the exception of a few families in which the pattern of inheritance was dominant (Goebel and Braak, 1989).

Pathology Storage in reticuloendothelial cells of the liver and the spleen as well as in muscle was reported by several authors (e.g., Bignami *et al.*, 1969). Other authors state explicitly that the viscera are not involved (Chou *et al.*, 1970).

Neuropathology *Gross appearances.* The cerebrum may show mild atrophy, while in the cerebellum atrophy is marked (Fig. 160).

Light microscopy. The characteristic feature is the deposition of a granular, Sudan black- and PAS-positive, and strongly autofluorescent material in the neurons (Fig. 161A and B). The regional distribution of the storage varies considerably between cases. While the process is ubiquitous, it may be accentuated in some parts, and in places may even lead to the destruction of neurons. In most cases the cerebellum and the brain stem bear the brunt of the disease, while the cerebral cortex is relatively spared. Specific staining of the stored material reveals a predilection of the second, third, and fifth cortical layers (Goebel *et al.*, 1982). In the basal ganglia large cells of the striatum are selectively affected. In the thalamus the most prominent lesions are seen in the lateral nuclear complex; in the hypothalamus these lesions occur in the paraventricular nucleus. Further local accentuation is seen in Ammon's horn, where the most intense changes appear in the end plate and sectors H3 and H2 of the pyrami-

Fig. 160 Adult form of ceroid lipofuscinosis. Marked atrophy of the cerebellum.

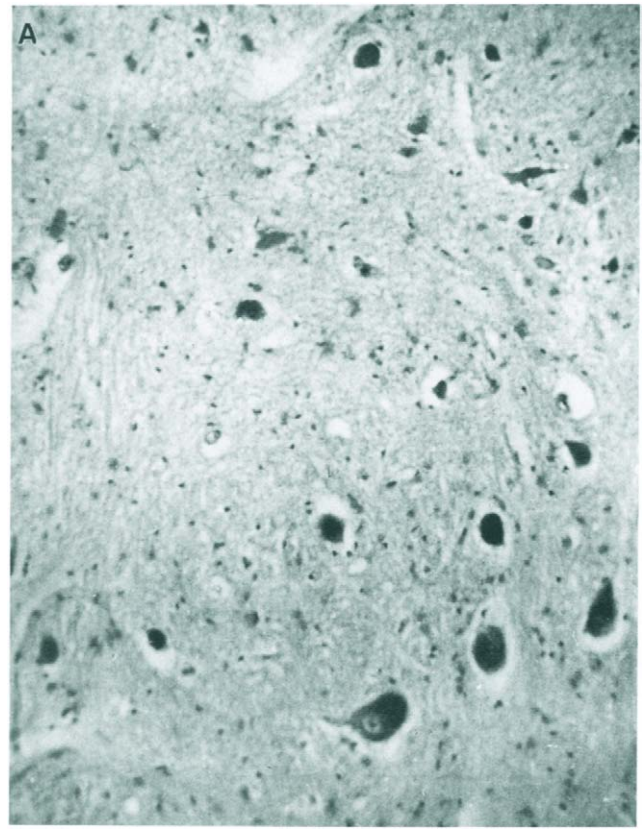


Fig. 161 Adult form of ceroid lipofuscinosis. (A) Neuronal perikarya laden with lipopigments. Hematoxylin–periodic acid–Schiff stain, ×120. (B) Autofluorescence in pigment-laden neuronal cell bodies, ×400. (Reproduced from Cervós-Navarro and Goebel, 1989.)

dal layer, while Sommer's sector H1 is relatively spared in contrast with vascular lesions. In some cases the cerebellum and the spinal cord are the most severely affected parts.

In the selectively affected region the granular material is distributed diffusely in the neurons, in the periphery of the astrocytes, and in the endothelia of the blood vessels. This material stains darkly with cresyl violet and positively with Sudan black. The Bial reaction may be positive or negative. Under ultraviolet light it has a bluish tinge to its autofluorescence, but this can be clearly distinguished from the yellow autofluorescence of lipofuscin only by spectroscopic analysis.

Alzheimer's neurofibrillary tangles (NFTs) have been observed in several cases (Chou *et al.*, 1970). They were found predominantly in Ammon's horn, particularly in sector H3, but also in the thalamus, hypothalamus, corpus striatum, substantia nigra, and pontine tegmentum.

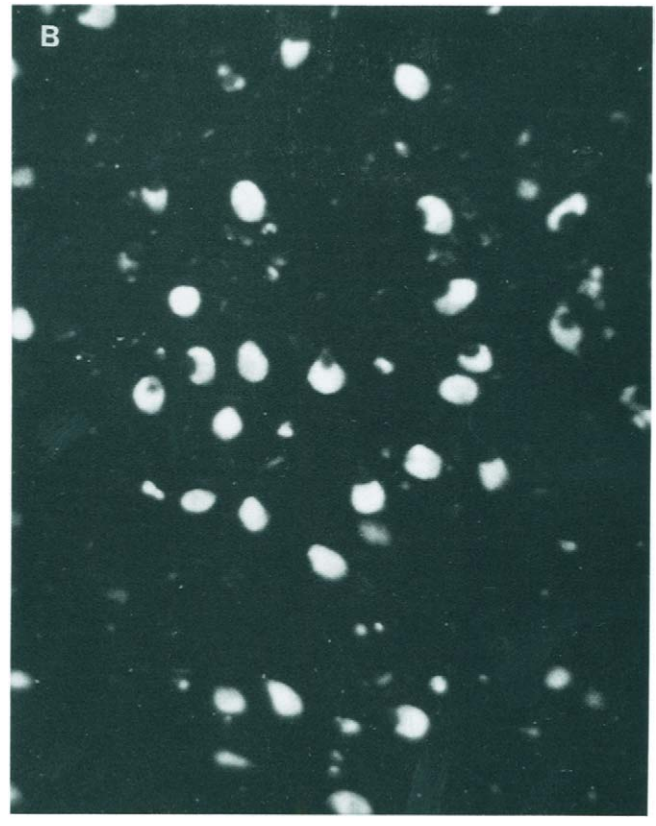


Fig. 161 Continued.

Slight changes have been found in the retina in the form of granular material in the neurons of the ganglion cell layer. Zeman *et al.* (1970) also observed Sudan black-positive lipopigment granules in the outer segments of rods. Ikeda *et al.* (1984) found prominent storage in the retina.

Electron microscopy. The neuronal inclusions (Fig. 162) have been described as "round lipofuscin-like bodies" or simply as "lipofuscin granules" (Chou *et al.*, 1970; Ikeda *et al.*, 1984). Similar granules are present in the glial cells (Fig. 163). Laminar structures, "miniature membranous cytoplasmic bodies," fingerprint patterns, and zebra bodies, as well as curvilinear profiles, have been observed occasionally (Constantinides *et al.*, 1992; Märzheuser-Brands *et al.*, 1992). The curvilinear bodies may be combined with lipid bodies of different structure, and may accompany typical lipofuscin complexes. Berkovic *et al.* (1988) recognize only fingerprint bodies and granular osmiophilic deposits.

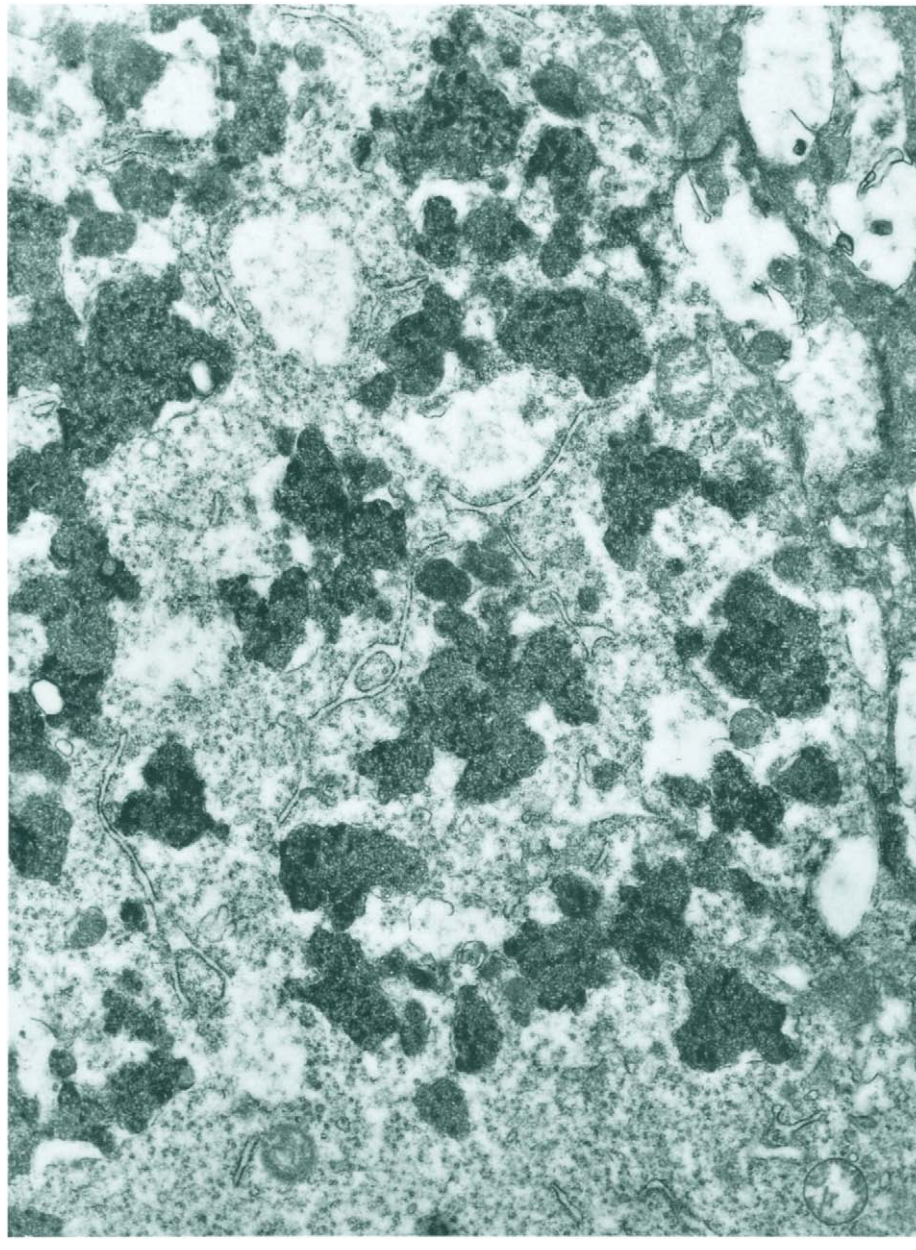


Fig. 162 Adult form of ceroid lipofuscinosis. Cytoplasm of a neuron in the parietal cortex with lipofuscin-like inclusions, ×26,000.

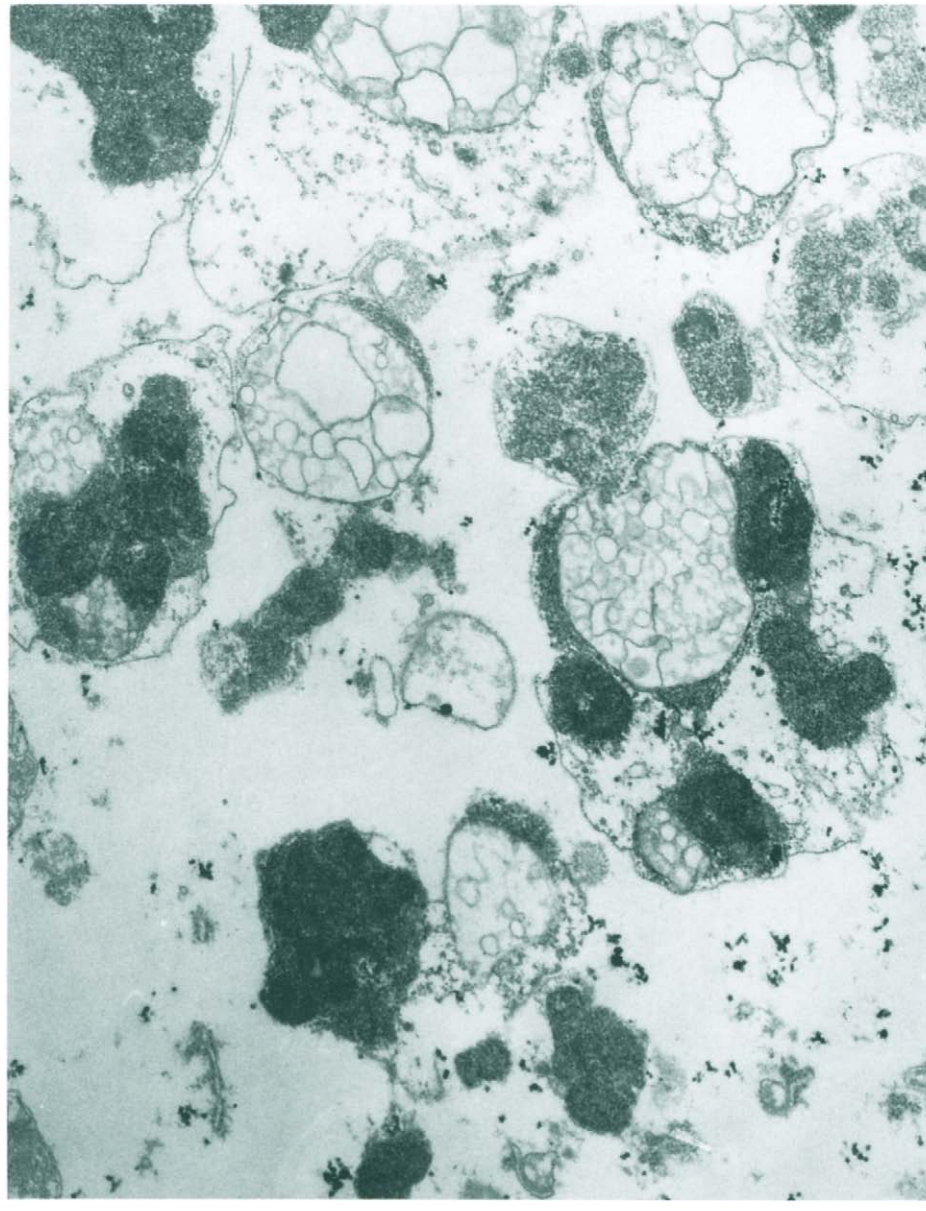


Fig. 163 Same case shown in Fig. 162. Cytoplasm of a macrophage, showing granulomembranous electron-dense inclusions associated with marginal vacuoles with loose membranous structures, ×30,000.

Pathogenesis Almost all ceroid lipofuscinoses are inherited as autosomal-recessive traits, with the exception of only a few families with Kufs' disease inherited as an autosomal-dominant disorder (Berkovic *et al.*, 1988). Identification of the genes began with the localization of the gene coding for the infantile form on chromosome 1 and that coding for the juvenile form on chromosome 16 (Siakotos *et al.*, 1991). Subsequent investigations confirmed these findings and made the information more precise (Callen *et al.*, 1991; Yan, 1993; Gardiner, 1993). The gene of the infantile form is located on chromosome 1p32 with a mutation between *D1S57* and *D1S79* (Jarvela *et al.*, 1992). The gene of the juvenile form is located on chromosome 16p12 in closest proximity to loci *D16S299* and *D16S298* (Mitchison *et al.*, 1994). The gene responsible for the classical form of late infantile ceroid lipofuscinosis has not been identified, but it is known not to be located on either of the above loci (Williams *et al.*, 1994). A variant subtype of the late infantile neuronal ceroid lipofuscinosis has been mapped to a well-defined region on chromosome 13q21.1–q32 (Savukoski *et al.*, 1994). No genes responsible for Kufs' disease have been identified as yet. The nature of the metabolic defect remains unknown. As the stored substance consists of about 20–40% lipid, the remainder being protein, attention has been directed to both groups of substances. The original theory that the pigment was derived from peroxidation of lipids (Tappel, 1973) has not stood the test of time, the results of subsequent investigations being highly contradictory. An increased peroxidation damaging the plasmalemma and the lysosomal membrane was demonstrated by some authors. A deficiency of peroxidases was found in some subsequent studies (Jensen and Clausen, 1983). Other studies, however, failed to show any decrease in peroxidase activity in the saliva, in the parotid gland, or in leukocytes. The activity of catalase and glutathione peroxidase was also found to be normal.

Despite problems in identifying individual storage material, it is believed that nonenzymatic oxidation of unsaturated fatty acids in phospholipids and inhibition of lysosomal proteolysis, leading to massive deposition of autofluorescent pigment, are the cause of the disease (Dawson *et al.*, 1990). Dolichols and dolichyl pyrophosphate oligosaccharides are present in all forms of ceroid lipofuscinosis (Pullarkat *et al.*, 1988). They are, however, nonspecific, as they also accumulate in age-related lipofuscin (Wisniewski and Wen, 1988) in the gangliosidoses and in Alzheimer's disease. They are components of normal lysosomal membranes and their accumulation may be an expression of the defective breakdown of membranes in the turnover of lysosomes. Nevertheless, Berkovic *et al.* (1988) considered the presence of large amounts of dolichols in the urinary sediment a useful pointer to the possibility of Kufs' disease in obscure neurological disorders in adulthood.

Ever since Palmer *et al.* (1988) demonstrated that the major component of the lipopigment in ovine neuronal ceroid lipofuscinosis was a low-molecular-weight protein, attention has been focused on abnormalities of protein metabolism. Palmer *et al.* (1989) subsequently identified the protein as the lipid-binding subunit c of the mitochondrial ATP synthetase. The same protein forms the principal fraction of the protein component in the late infantile, juvenile, and adult forms of neuronal ceroid lipofuscinosis, but is absent in the infantile form (Hall *et al.*, 1991a,b). These findings have

been confirmed and amplified by subsequent authors (Palmer *et al.*, 1992; Kida *et al.*, 1993; Wisniewski *et al.*, 1994b).

Other altered protein patterns include abnormalities in glycoprotein metabolism (Wisniewski *et al.*, 1988; Pullarkat *et al.*, 1992; Hall *et al.*, 1992; Daniel *et al.*, 1992; Heaney-Kieras *et al.*, 1992), defective processing of the β-amyloid precursor protein (Kitaguchi *et al.*, 1990; Wisniewski *et al.*, 1990a,b, 1992, 1993a), and overactivity of the protease inhibitor α_1-antichymotrypsin (Wisniewski and Kida, 1990).

For the recently discovered neuronal ceroid lipofuscinosis-like lesions associated with osteopetrosis, see p. 695.

Ceroid Lipofusinosis in Animals Ceroid lipofuscinosis occurs in various breeds of dogs, as well as in cats and sheep (Jolly *et al.*, 1980). Both the juvenile and adult types (Dowson *et al.*, 1982) have been described. The discovery that the so-called "motor neuron disease" mutant in mice (*mnd/mnd*) is, in fact, a ceroid lipofuscinosis (Bronson *et al.*, 1993) may provide a useful model for investigating the human disease (Faust *et al.*, 1994).

Chédiak–Higashi Syndrome (Steinbrinck–Chédiak Granulation Anomaly)

Beguez-César (1943) described three siblings of a consanguineous marriage and Steinbrinck (1948) reported on a child aged $2\frac{1}{2}$ years with an unusually protracted infection. All of these children had irregular dark blue inclusions in the cytoplasm of their neutrophil leukocytes. Two independent reports followed, that by Chédiak (1952) and that by Higashi (1954), and ignorance of the previous publications thus led to the eponym *Chédiak–Higashi syndrome.*

Clinical Picture The granulation anomaly is associated in 70% of the cases with an oculocutaneous albinism. There is a lack of uveal pigment, pale skin, and very fair hair, as well as excessive sweating, associated with other general symptoms. Anemia, leukopenia, and thrombocytopenia are accompanied by an increased susceptibility to infections. An accelerated lymphoma-like phase occurs in 85% of the cases (Dent *et al.*, 1966) and manifests itself by hepatosplenomegaly and lymphadenopathy.

The closely related Griscelli (or Griscelli–Prunieras) syndrome differs from Chédiak–Higashi syndrome by the absence of leukocytic granulations, but shares with it partial albinism ("silvery gray hair"), abnormal melanocytes, and a tendency to develop the same complications.

Neurological symptoms include photophobia, nystagmus, pareses (Haraldson *et al.*, 1991), paresthesias, and, in later stages, peripheral neuropathy (Misra *et al.*, 1991). Other reported features comprise diabetes insipidus, dysautonomia, and mental disorders. A case of parkinsonian, oculogyric crises, muscular atrophy, and loss of tendon reflexes was reported in a 24-year-old woman (Uyama *et al.*, 1994). Symptoms of spinocerebellar degeneration have been described (Salazar-Cabrera *et al.*, 1993). Most patients die before the age of 10 years. Gale *et al.* (1986) described patients with abnormal leukocytes of the Chédiak–Higashi type and psychomotor disturbances, but without susceptibility to infections, albinism, or photophobia.

CT and MRI generally show cerebral atrophy and rarefaction of the periventricular zone

(Ballard *et al.*, 1994). In the case reported by Uyama *et al.* (1994), there was additionally atrophy of the spinal cord.

Pathology The abnormal granules in leukocytes described by various authors differ little from the normal ones. They are 1–3 μm in diameter, sometimes up to 5 μm, and are sharply demarcated. The granules of eosinophils are also enlarged three- to fivefold, are round or elliptical, and are of variable size. The lymphocytes, plasma cells, and monocytes may also contain granules 1–2 μm in diameter, staining a brilliant red (Hansson *et al.*, 1959).

Aside from granulation anomalies in the blood, inclusions have also been seen in the histiocytes, endothelial cells, and renal tubules.

Besides the manifestations and sequelae of severe infections of the skin, tonsils, bronchi, lungs, and other organs, perivascular infiltrates may be found in many tissues. They consist of numerous small mononuclear cells resembling lymphocytes and larger elements with loosely woven nuclei and abundant eosinophilic cytoplasm. A few plasma cells and polymorphs may be included.

Neuropathology In some of the autopsy material, no lesions were found in the CNS. In most cases, however, a prominent lymphocytic and histiocytic infiltration was seen both in the CNS and in the peripheral nervous system. It affects preferentially the white matter and is conspicuous in the cerebellum and the posterior lobe of the pituitary. These infiltrates may also appear in the optic nerve, peripheral nerves, and spinal and sympathetic ganglia. Sparse infiltrates may be present in the leptomeninges, particularly in the sulci. Aside from the perivascular infiltrates, microgranulomas were found in the pons and the lumbar cord in two cases. Degenerative changes in neurons were confined to the areas in which microgranulomas were present. Inclusions of variable shape and size may also be found in the cytoplasm of neurons, astrocytes, Schwann cells, and epithelia of the choroid plexuses. They are barely visible in sections stained with H&E, but are strongly PAS positive.

Pathogenesis Forty-eight percent of the affected children come from consanguineous marriages. In families in which the disease occurs, 27% of the children are affected. The mode of inheritance is autosomal recessive.

To begin with, a genetically conditioned membrane insufficiency was suggested as a possible cause of the disease. A positive reaction for acid phosphatase in the granules pointed to a lysosomal disease. This was confirmed by ultrastructural investigations. The large granules in the neurons were thought to arise from confluence of the individual lipofuscin granules. However, fusion has been rejected as a mechanism of formation of the giant leukocyte granules and giant melanosomes (Valenzuela and Morningstar, 1981). The cytoskeletal abnormalities appear to be of a secondary nature and to play no part in pathogenesis.

Patients with Steinbrinck–Chédiak anomaly and analogous animal mutants have a reduced resistance to bacterial and viral infections. Diminished cytolytic activity was demonstrated in the natural killer cells (Brahmi, 1983). A reduced activity of β-glucuronidase and peroxidase in leukocytes was found by Stossel *et al.* (1972) and that of bactericidal or cytotoxic protein was noted by Ganz *et al.* (1988). The concentration of

3′,5′-cAMP in leukocytes is increased 10-fold (Hug, 1978). The defect in phagocytosis has been ascribed to faulty function of the cytoskeleton, particularly the microtubular system.

An overproduction of inhibitory substances appears to affect the intracellular proteins cathepsin G and elastase in leukocytes, which are of central importance in the defense mechanism against infection (Takeuchi and Swank, 1989).

In view of the paucity of recent neuropathological studies, it is difficult to account for the multiplicity of neurological manifestations. Most of them are probably due to inflammatory infiltrates, as described above. These, however, do not account for the cerebral atrophy as seen on CT and MRI.

Animal Models A syndrome resembling the Chédiak–Higashi anomaly has been observed in Aleutian mice (Sung and Okada, 1969), in partially albino Hereford cattle (Penner and Prieur, 1987), in cats (Creel *et al.*, 1982), in a killer whale (Taylor and Farrell, 1973), and in foxes (Fagerland *et al.*, 1987). The beige (*bg/bg*) mouse (Lutzner *et al.*, 1967; Biron *et al.*, 1987), a mutant of the C57BL/6 black mouse, is thought to be the closest model of the human disease. Cerebellar and hippocampal ectopias have been recorded in this model (Guo *et al.*, 1992).

Astrocytic Residual Body Encephalopathy (Towfighi's Disease)

Towfighi *et al.* (1975) described the first cases of this disease in two siblings.

Clinical Picture The symptomatology has not been uniform in the few cases reported so far. The common feature is the occurrence of epileptic seizures as few hours after birth. Psychomotor development may be almost totally absent in some cases (Towfighi *et al.*, 1975; Figols *et al.*, 1986); in others it may be near-normal during the first year. Skeletal muscles are hypotonic to begin with, but in later stages they become hypertonic with contractures. Some patients do not react to visual, auditory, or pain stimuli, either from birth or only in advanced stages of the disease. The course of the disease is chronic, unless it is cut short by intercurrent infections.

Pathology Aside from one case of congenital fibrosis of the liver (Figols *et al.*, 1986), no lesions were found in internal organs.

Neuropathology *Light microscopy.* Light brown granules are found in the astrocytes and occasionally in the perivascular macrophages in advanced stages of the disease. They stain intensely with PAS and weakly with oil red O. Occasional sparse granules are seen in the neurons. A slight increase in the number of astrocytes appears in the white matter of the cerebral hemispheres and the cerebellum (Figols *et al.*, 1986). The pyramidal tracts in the spinal cord show slight pallor without gliosis.

Electron microscopy. Some astrocytes, both in the cortex and in the white matter contain irregular inclusions, 1–4 μm in diameter, scattered through the clear homogeneous cytoplasm (Fig. 164). They contain paired membranes, straight or slightly curved, consisting of electron-dense lamellae, 2 nm in thickness, enclosing an eletron-

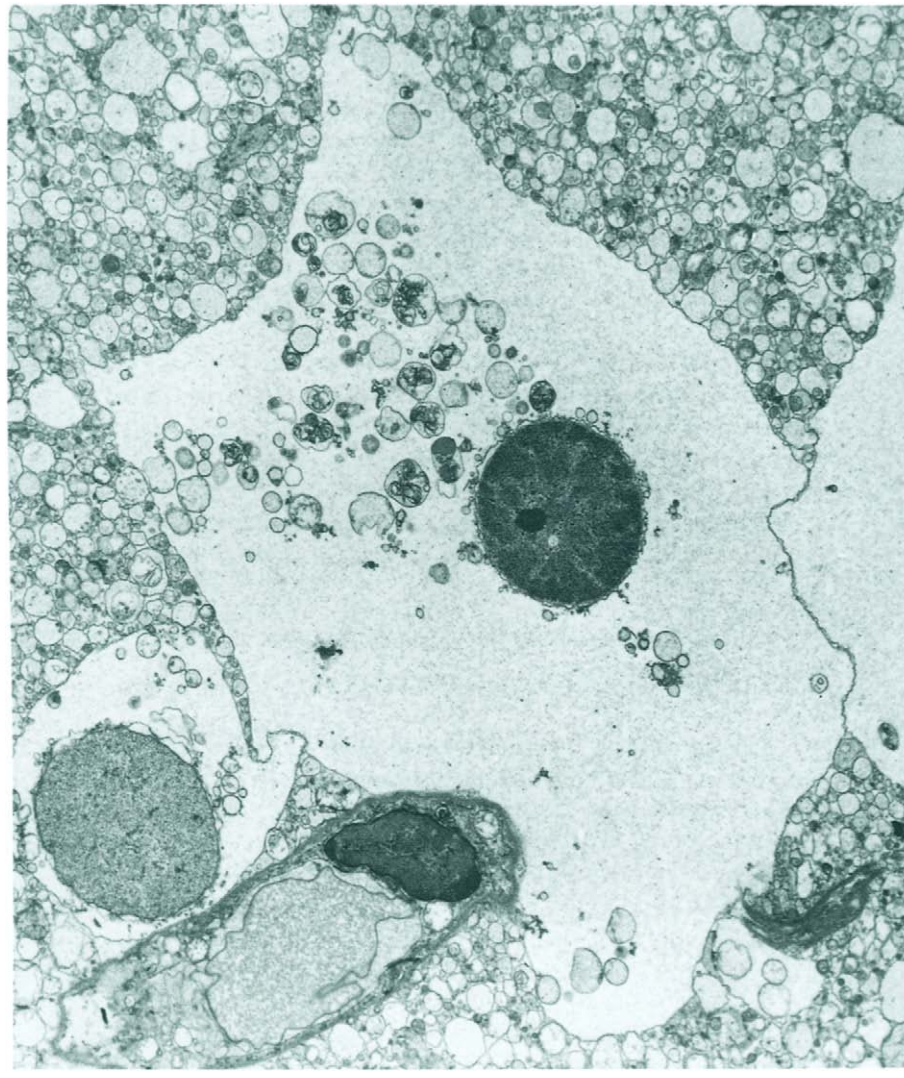


Fig. 164 Astrocytic lysosomal encephalopathy. An astrocyte with empty cytoplasm and collections of lysosomal inclusions in the parietal cortex, ×4500. (Reproduced from Cruz *et al.*, 1986.)

lucent space 3 nm wide (Figols *et al.*, 1986) (Fig. 165). The intervening homogeneous matrix varies in density. Similar inclusions are present in the perivascular macrophages. The lipofuscin granules in the neurons contain a few membranes besides their usual structure. These are identical to the astrocytic inclusions, but are obscured by the dense matrix of lipofuscin. Towfighi *et al.* (1975) mentioned the affinity of the membranous inclusions for silver proteinate. Ultrastructural examination of the peripheral nerves and the skeletal muscles revealed no abnormality.

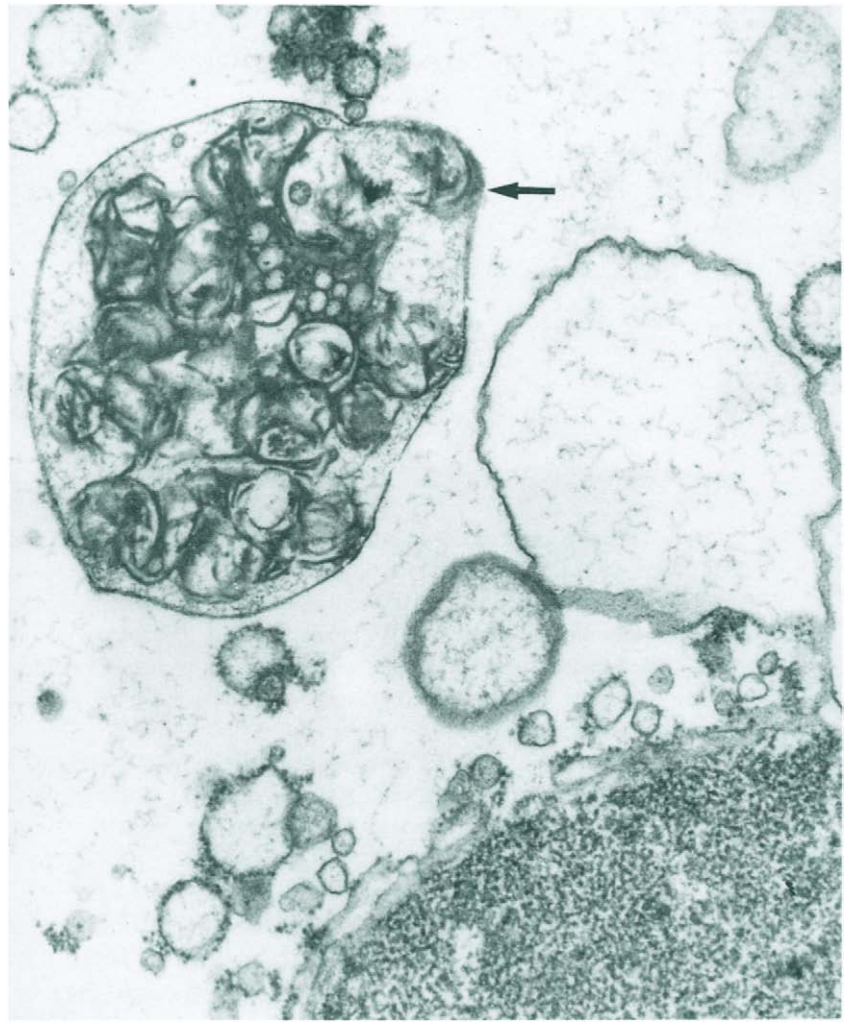


Fig. 165 Same case shown in Fig. 164. The membrane-bound inclusions (arrow) contain straight or irregular lamellae, ×30,000.

Pathogenesis The nature of the stored substance is unknown. Its positive reaction with silver proteinate suggests a polysaccharide structure. Caution is indicated, however, in the evaluation of histochemical reactions in glutaraldehyde-fixed material. The nature of the enzymatic defect is also unknown. This disease can be separated from the ceroid lipofuscinoses by its predilection for astrocytes and its ultrastructural appearances. Towfighi *et al.* (1975) assigned particular diagnostic importance to the affinity of the stored material for silver proteinate. Martin *et al.* (1977), on the other hand, could not obtain unequivocal results with the same impregnation.

Disorders of Purine Metabolism

Adults suffering from gout do not, as a rule, develop neurological symptoms. The involvement of the nervous system in hyperuricemia, confirmed clinically and morphologically, occurs only in patients with neurological disorders originating in childhood.

Secondary disturbances of purine metabolism can occur in a variety of conditions, such as increased tissue breakdown in leukemia, excessive neoformation of purines in Down syndrome, or diminished excretion of uric acid in the glycogenoses and other primary enzymopathies

The hypoxanthine–guanine phosphoribosyltransferase (HGPRT) deficiency may have two clinical forms: that of Lesch–Nyhan syndrome (complete HGPRT deficiency) and that of Kelley–Seegmiller syndrome (partial HGPRT deficiency).

Lesch–Nyhan Syndrome (Complete Hypoxanthine–Guanine Phosphoribosyltransferase Deficiency; Juvenile Gout with Cerebral Involvement; Catel–Schmidt Syndrome)

The complete deficiency of HGPRT leads to prominent neurological disturbances in the newborn. Lesch and Nyhan (1964) carried out a detailed study of the syndrome and established its familial incidence. Seegmiller *et al.* (1967) identified the missing enzyme.

Clinical Picture Soon after birth impairment of growth becomes apparent in the majority of the cases. Choreoathetoid movements, corticospinal motor system dysfunction, and mental retardation develop early (Heidelmann and Knauthe, 1982). At about the age of 2 years, the children develop a self-mutilating tendency by biting their lips and fingers. In a case of Lesch–Nyhan syndrome with delayed onset of self-mutilation, athetotic cerebral palsy and mental retardation were diagnosed at 1 year of age, but the disease was not suspected until the age of 8 years, when the patient began biting his lips

and fingers (Hatanaka *et al.*, 1990). With rare exceptions only boys are affected, the disease being inherited as an X-linked recessive trait. The aggressive self-mutilating behavior may be the first manifestation of the disease, but it may be absent or may appear later. Cardinal features are hyperuricemia and hyperuricuria, which may return to normal after appropriate treatment, without necessarily alleviating other symptoms. CT and MRI reveal cortical and subcortical atrophy in some patients (Jankovic, 1988), with a normal appearance in others.

A considerable range of variability in the residual activity of the HGPRT was established in patients from different families, pointing to a genetic heterogeneity of the HGPRT in humans. Sex-linked recessive gout and/or urolithiasis or the partial HGPRT deficiency syndrome may also be associated with minor neurological manifestations. In a partial deficiency of the enzyme activity, neurological involvement may be absent (Mizuno, 1986).

Recurrent episodes of coma have been reported. These may be explained by the disruption of the cellular energy metabolism due to purine depletion, consequent to lack of the purine salvage pathway normally provided by the HGPRT. The patients with Kelly–Seegmiller syndrome are very heterogeneous: some patients had psychomotor retardation with spastic movement, others are retarded with generalized dystonia, and occasionally patients had only gout with no neurological manifestations.

Pathology Macroscopically, the kidneys are atrophic and studded with chalky cysts. Under light microscopy numerous uric acid crystals are present; the glomeruli are sclerotic. The gingiva show macrophages around the blood vessels, and the cytoplasm of the macrophages contains stippled cytoplasmic inclusions (Mequid *et al.*, 1990).

Neuropathology *Gross appearances.* Microcephaly was seen occasionally (Warzok *et al.*, 1982), particularly in older patients. Petechiae in the white matter can be found upon sectioning the brain.

Light microscopy. Focal demyelination may be present in the cerebral and cerebellar white matter, as well as hyalinosis and fibrosis of the blood vessels with ball hemorrhages and fibrin exudation.

Urate crystals are not always demonstrable. When present, they are perivascular in distribution and strongly birefringent under polarized light (Fig. 166).

Degeneration of the granular layer and small infarcts were observed in the cerebellum with a predilection for the vermis. Warzok *et al.* (1982) found deposition of storage material in the neurons of the inferior olive (Fig. 167). In sections stained with H&E, the material appears foamy and displaces the nucleus to the periphery. It is Sudan II negative and PAS positive.

Reduction of the larger myelinated nerve fibers suggests a peripheral nervous disorder (Origuchi *et al.*, 1990).

Electron microscopy. The material has the structure of lipofuscin (Fig. 168).

Pathogenesis Nyhan *et al.* (1965) presumed that the absence of a blood–brain barrier in the immature brain may lead to prenatal damage in the CNS. A disturbed maturation of the brain is held responsible for the microcephaly.

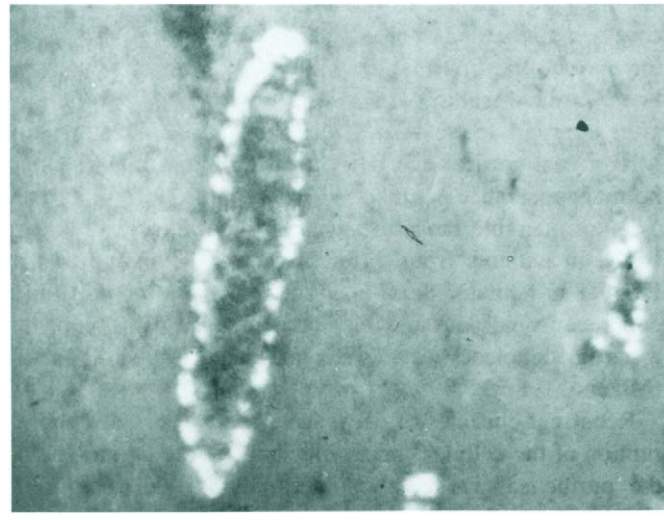


Fig. 166 Hyperuricemia. An arteriole in the frontal lobe. Perivascular crystals of uric acid are clearly recognized by their birefrigence under polarized light, ×40.

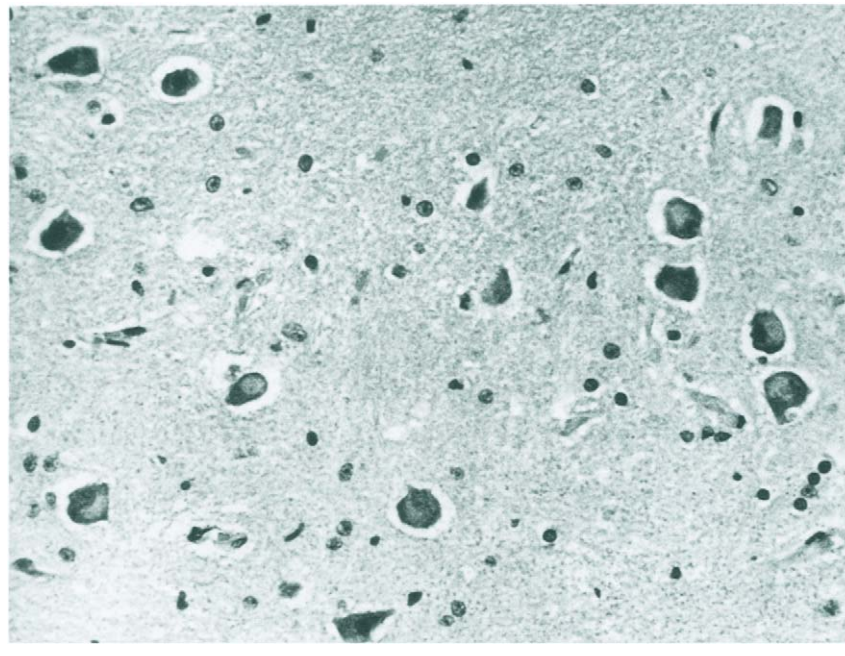


Fig. 167 Lesch–Nyhan syndrome. The neurons of the inferior olives show an excessive deposition of storage material. Nissl stain, ×500. (Courtesy of R. Warzok, Greifswald, Germany.)

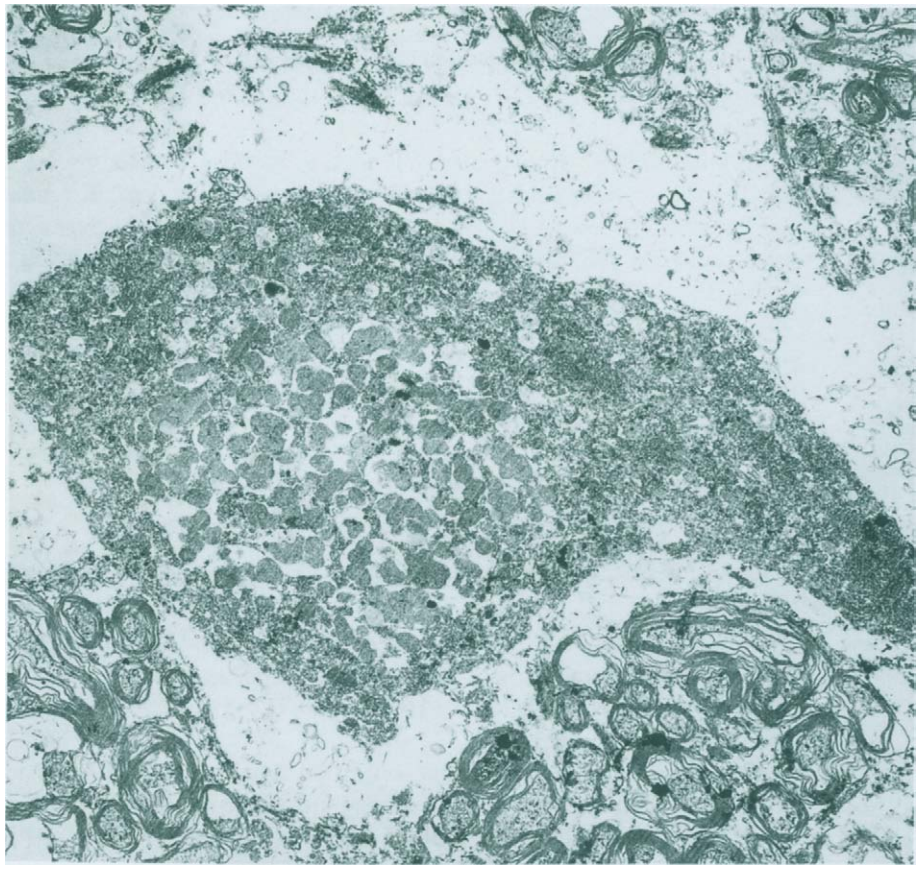


Fig. 168 Same case shown in Fig. 167. An intracytoplasmic accumulation of lipofuscin granules in a neuron of the inferior olive, ×4500.

Allsop and Watts (1980) studied the enzyme activities in various stages of development of the CNS in rats and reached the conclusion that there is sufficient synthesis of purine nucleotides in Lesch–Nyhan syndrome for the development of essential structures. There may, however, be a small group of neurons with extensive connections that have greater demands. A disturbance in dopamine metabolism was demonstrated in Lesch–Nyhan syndrome on the basis of CSF investigations (Silverstein *et al.*, 1985).

Mutations in the X-linked *HGPRT* gene result in deficiencies of HGPRT enzyme activity, which may cause either a severe form of gout or Lesch–Nyhan syndrome, depending on the residual enzyme activity. Mutations leading to these diseases are heterogenous and include DNA base substitutions, in the splicing consensus region splicing error (Yamada *et al.*, 1993), splicing of exons 1, 2, 3, 8, and 9 (Marcus *et al.*, 1993), DNA deletions, gene deletion (Fuscoe and Nelson, 1994), DNA base insertions, and errors in RNA splicing located within clusters of hot spots in exon 3 (Bouwens *et al.*, 1993). More than

50 mutations in the human *HGPRT* locus have been described (Davidson *et al.*, 1994). Other reported mutations have been a partial duplication of the *hort* gene (Marcus *et al.*, 1993). The abnormalities are absent in the dopamine metabolism in patients with partial HGPRT deficiency without a tendency to self-mutilation.

Animal Models Rats treated with high doses of methylated purine, caffeine, or theophylline began to bite themselves. Newborn rats fed 6-hydroxydopamine exhibited similar behavior (Breese *et al.*, 1984). The administration of dopamine agonists to monkeys with unilateral ventromedial tegmental lesions induced self-mutilating biting (Goldstein *et al.*, 1986). Goldstein *et al.* concluded that the deficiency of HGPRT caused an abnormal metabolism of guanine nucleotides, which, in turn, could lead to a disturbance in the regulation of dopamine receptors. Lesch–Nyhan syndrome is characterized by a deficiency of HGPRT and a loss of central dopaminergic neurons. In order to model the loss of central dopamine-containing neurons, neurotoxin 6-OHDA may given to neonatal pups 3 days of age. The lesioned rats exhibit an increased susceptibility for compulsive self-mutilatory behavior.

Other Hereditary Disorders of Purine Metabolism

Hyperuricemia with hyperactivity of phosphoribosyl-pyrosphosphate synthetase, observed in some families with gout, may be associated with deafness and aplasia of the lachrymal glands (Nyhan, 1981). Hyperuricemia, ataxia, and deafness occurred in several members of one family.

Because of the occurrence of self-mutilation in some patients with Gilles de la Tourette's syndrome (see p. 542), a relationship was postulated with Lesch–Nyhan syndrome. The anomalies of the HGPRT described by Van Woer *et al.* (1977) have not been confirmed (Merril *et al.*, 1979).

Disorders of Mineral Metabolism

The electrolytes sodium, potassium, and chloride play an essential role in the pathology of the nervous system. The cations magnesium and calcium and the anions phosphate and carbonate are also of considerable importance. Iron and the trace elements copper, zinc, chromium, manganese, cobalt, and molybdenum act as cofactors of some enzymes. The demand for these elements is usually adequately covered by nutritional intake. Disturbances can occur, however, through abnormalities of absorption, excretion, or regulation, as well as through local tissue changes. The CNS is affected almost exclusively by disorders of iron, copper, and calcium metabolism.

Disorders of Iron Metabolism

Aside from the changes in the CNS that may occur in hemochromatosis, disorders of iron metabolism were thought to play a part in siderosis of the dentate nucleus and in the cerebrohepatorenal syndrome of Zellweger. The raised level of iron in the latter, however, is an epiphenomenon that is not responsible for the cerebral lesions. Deposition of iron also occurs in the brain in conjunction with calcium and other minerals in Fahr's syndrome (see p. 419) as well as in the normal brain.

Iron in the Normal Central Nervous System

Understanding of the normal distribution of iron in the brain, which varies in different parts, is indispensable for the interpretation of a pathological increase or decrease of this element. Spatz (1922) divided the centers into four groups according to the rapidity and intensity of the iron reaction in unfixed brain material.

1. The globus pallidus and the substantia nigra show the fastest and most intense reactions.

2. The red nucleus, dentate nucleus, subthalamic nucleus, and striatum form the next group.

3. The thalamus and the cerebral and cerebellar cortices still display an appreciable reaction.

4. No reaction can be obtained in other structures, including the gray matter of the spinal cord, the spinal ganglia, and the inferior olives.

Other authors also emphasized the preeminence of the globus pallidus, the pars reticularis of the substantia nigra, the red nucleus, and the dentate nucleus as centers with the highest iron content. This was also confirmed by MRI (Drayer *et al.*, 1986). A similar localization was found in primates (Fran-çois *et al.*, 1981) and in rats (Hill and Switzer, 1984).

Iron does not have ready access to the adult brain, as it does to other tissues, since it does not cross the blood–brain barrier. All of the iron present in the brain is deposited before the closure of the blood–brain barrier at an early age and is sequestered and conserved there. Oligodendrocytes are the predominant brain cells that contain iron in humans (Morris *et al.*, 1992; Connor, 1993), monkeys (François *et al.*, 1991), rats (Hill and Switzer, 1984), and mice (Levine and Macklin, 1990). In areas such as the caudatum–putamen, substantia nigra, and deep cerebellar nuclei, the oligodendrocytes stain conspicuously for iron (Benkovic and Connor, 1993). Fibers in the neuropil stain intensely in the deep cerebellar nuclei and the substantia nigra; fibrous staining in the basal ganglia is confined to the white matter tracts that form the striations. Neurons, particularly pyramidal neurons in the cerebral cortex and the hippocampus, have small puncta or an iron reaction product in their somata, which increase in density in rats with age (Benkovic and Connor, 1993). Another cell type that stains prominently for iron are tanycytes, which line the third ventricle (Hill and Switzer, 1984; Connor, 1993). These cells may be involved in transporting iron between the brain and the CSF.

Hemochromatosis

The name *hemochromatosis* can be traced to Von Recklinghausen and the scientific meeting in Heidelberg in 1889, at the time when it was thought that most identified pigments had something in common with hemoglobin. The term is erroneous, however, as the iron storage in primary hemochromatosis is not derived from an increased breakdown of erythrocytes, but from excessive absorption in the gut. It is also important to avoid confusion with the superficial siderosis of the CNS (see p. 404), described as hemochromatosis in earlier publications.

Clinical Picture The disease manifests itself usually after the age of 40 years with loss of weight and general malaise. The main features are cirrhosis of the liver, skin pigmentation, diabetes mellitus, and hypogonadism. A juvenile form, in which endocrine disturbances predominate, and a neonatal form (Barnard and Manci, 1991) have also been described.

Associated neurological symptoms are due predominantly to peripheral neuropathy. Retinopathy, deafness, and mental changes may also occur (Cutler, 1991). A defect in pituitary function as well as in hypothalamic gonadotropism regulation is common in males (Siminoski *et al.*, 1990). A cerebellar ataxia, which regressed after treatment of the he-

mochromatosis, has been reported. Suppression of gastric secretion is present in 10–30% of the cases of hemochromatosis and may be complicated by subacute combined degeneration of the spinal cord or by Wernicke's encephalopathy.

Pathology *Gross appearances.* The main features are marked hepatomegaly and slight splenomegaly. Most organs show a brownish discoloration.

Light microscopy. On light microscopy hemosiderin and lipofuscin deposits are found in the parenchymal and mesenchymal cells (Vogt *et al.*, 1987). The liver shows a micronodular cirrhosis. It must be differentiated, however, from the hemophagocytic lymphohistiocytoses, in which erythrophagocytosis by benign-appearing histiocytes in the liver, spleen, and meninges is frequent (Schneider *et al.*, 1992).

Neuropathology *Gross appearances.* Cerebral hemorrhages may be present. The choroid plexuses, olfactory bulbs, region of the tuber, and area postrema are brown. Occasionally, iron deposition is also found in several periventricular structures as well as in the lentiform nucleus and the cerebellum. Cerebral infarcts occur frequently.

Light microscopy. The deposition of iron is confirmed in areas of increased permeability of the blood–brain barrier, as seen macroscopically. The finely granular iron pigment in these areas of predilection is deposited mainly in the glial cells (Fig. 169A,B). An in-

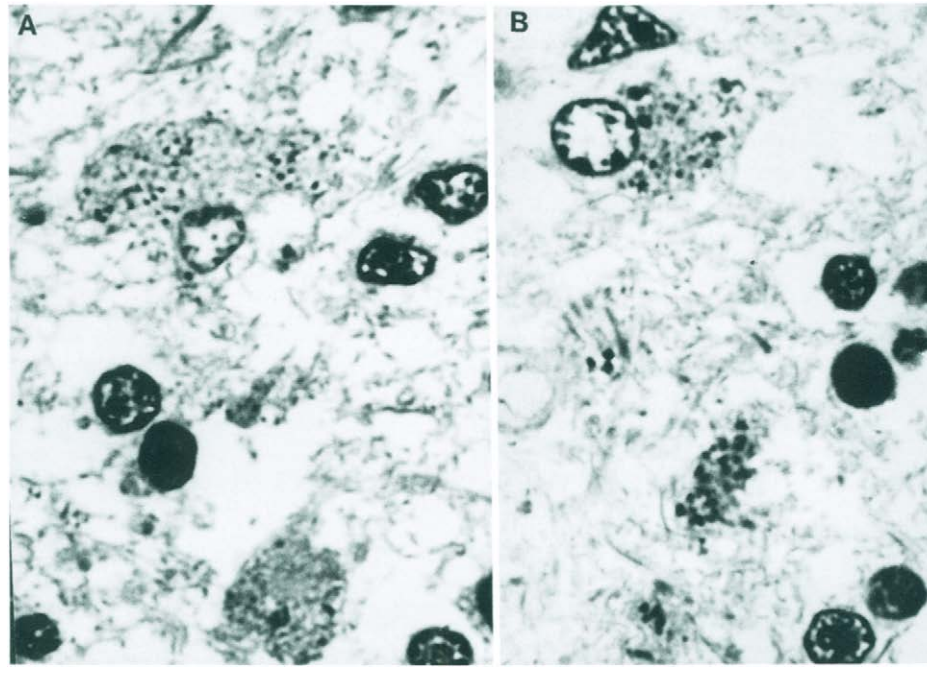


Fig. 169 (A,B) Hemosiderosis in the globus pallidus. Numerous hemosiderin granules are visible in the cytoplasm of astrocytes. Turnbull blue stain, ×800.

crease in the amount of physiological iron in the globus pallidus, substantia nigra, and dentate nuclei was found in only a few cases, and this pointed out the increase in the amount of lipofuscin throughout the brain. Iron deposits are present in all of the anterior pituitary, predominantly in the basophils.

Status spongiosus of variable severity is present more commonly than is implied by the literature. The putamen, the border of the cortex and the white matter, and the internal capsule are sites of predilection. Lesions in the white matter of the hemisphere have been observed occasionally. Changes in the glia take the form of Alzheimer's type II astrocytes (see p. 410). These have also been seen in the neonatal form. Transition forms to the Alzheimer's II glia with nonstainable intranuclear vacuoles can be seen. Their sites of predilection are the caudate nucleus, the putamen adjacent to the internal capsule, Ammon's horn at the junction of the dentate fascia and the pyramidal layer, and the deep layers of the cerebral cortex.

Acute neuronal changes, described in some cases, were ascribed to ischemia. In neonatal hemochromatosis hemorrhagic cerebellar infarcts and periventricular leukomalacia have been reported (Moerman *et al.*, 1990).

Electron microscopy. Iron particles are present in the cytoplasm, mainly in the lysosomes, neurons (Fig. 170A), glial cells, and perivascular macrophages. They are often associated with lipid droplets (Fig. 170B).

Pathogenesis The biochemical defect of the disease is unknown; the only fact that has been well established is the excessive iron absorption through the duodenal mucosa. However, it is not known whether this is a primary event (Le Gall *et al.*, 1993). A putative membrane carrier protein for non–transferrin-bound iron was identified, and preliminary data suggest its enrichment in the plasma membranes of human mucosal cells as well as in the liver and other organs that are affected in genetic hemochromatosis. The cellular accumulation of ionic iron leads to peroxidative decomposition of organelle membrane phospholipids, with the consequences of cell degeneration and cell death.

The hereditary hemochromatosis gene is tightly linked to the HLA complex on the short arm of chromosome 6 (6p21.3) Gasparini *et al.*, 1993). Neonatal hemochromatosis and hereditary hemochromatosis are similar in their patterns of iron loading, although they are not genetically related (Hardy *et al.*, 1990). Different cells have variable capacities for handling excess iron. Heavily laden cells (e.g., hepatocytes) undergo apoptosis. In contrast, cells without noticeable iron-storing capacity (e.g., neurons) are apparently more exposed to the toxic effects of unbound and unsegregated iron (Iancu, 1990).

Marginal Siderosis of the Central Nervous System (Subpial Siderosis of the Central Nervous System)

This syndrome was first described by Noetzel (1940) as the result of past subarachnoid hemorrhages. Rosenthal (1958) divided all cases of marginal hemosiderosis into two groups: one following subarachnoid hemorrhage, the other "idiopathic." In the first group he included only cases with a history of proven subarachnoid hemorrhage. The second group consisted of cases without evidence of past hemorrhage or of a possible source of bleeding. Such cases have been repeatedly observed.

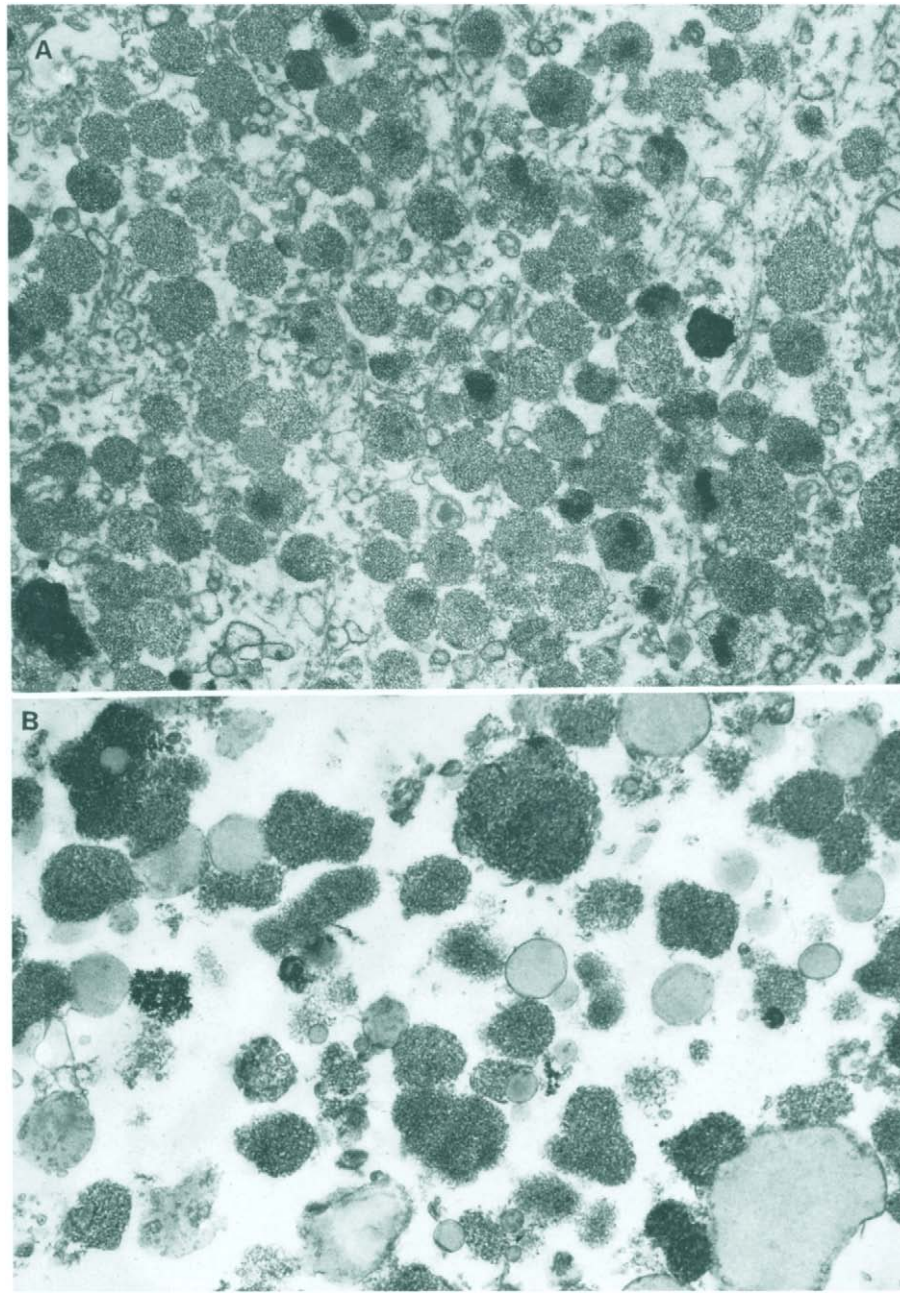


Fig. 170 Same case shown in Fig. 169. (A) A neuron with intralysosomal iron particles, ×15,000. (B) A glial cell with siderosomes interspersed with lipid droplets, ×24,000.

Clinical Picture The majority of the patients are adults over 50 years of age. Disorders of gait, ataxia, impairment of hearing, and loss of sphincter control are common symptoms (Revesz *et al.*, 1988). The course of the disease is chronic. More acute progression has been observed in younger patients, under 20 years of age. Pyramidal signs may be present in some cases, as well as sensory symptoms, and rarely a progressive dementia (Heye *et al.*, 1994). Intravital recognition is possible by reduced T_2-weighted signals on MRI.

Neuropathology *Gross appearances.* A variable distribution of the siderosis can be seen. In some cases the entire base of the brain may be involved, whereas in others only the basal parts of the frontal and temporal lobes are involved. Constant features include intense discoloration of the olfactory nerves and bulbs, the cerebellum, the entire surface of the brain stem, and the spinal cord (Revesz *et al.*, 1988). Upon sectioning the brain, one notices that the staining extends to a depth of 2–3 mm and decreases in intensity away from the surface (Fig. 171, see color plate).

Light microscopy. Hemosiderin granules are present in the leptomeninges and the underlying parenchyma. Most of the granules are found in perivascular macrophages, but some are taken up by the cytoplasm of neurons and glial cells (Fig. 172, see color plate). A reactive gliosis may be present in areas with intense iron deposits (Revesz *et al.*, 1988). Spheroids may also be present; these are GFAP positive. The cerebellum is the organ most severely affected. There is a loss of Purkinje and granule cells in the superficial parts of the folia. The tips of the folia may be completely destroyed and replaced by glial scars. In the spinal cord the iron deposits are present both in the superficial white matter and in the anterior horns. In most cases the neurons of the anterior horns are preserved, but a loss of motor neurons has been occasionally reported.

Electron microscopy. Ferritin particles, 5–6 nm in diameter, are present in the spheroids and the cytoplasm of the microglia (Koeppen and Borke, 1991).

Pathogensis Rosenthal (1958) pointed out the discrepancy between the frequency of subarachnoid hemorrhage and the rarity of marginal siderosis. He therefore postulated the presence of additional factors that facilitate the penetration of iron into the parenchyma. He suggested that one such factor may be impairment of absorption of the CSF, leading to delay in the evacuation of blood from the subarachnoid space. In the idiopathic disease form he assumed an increase in permeability of the meningeal vessels, leading to the escape of iron into the CSF with a simultaneous primary decrease in iron-binding proteins. The results of animal experiments do not support this hypothesis (Levine *et al.*, 1989). The common consensus is that marginal siderosis is always a sequel of subarachnoid bleeding, even if its source cannot be established by routine examination of the CNS. It is rarely the result of a massive subarachnoid hemorrhage; more often, it follows repeated small hemorrhages or continuous oozing.

Siderosis of the Dentate Nucleus

Reznik and Delwaide (1976) described the case of a man who, at the age of 76 years, developed dementia, akinesis, and focal neurological symptoms. He died a few months

after the onset of symptoms. A deep brownish discoloration was found in both dentate nuclei.

Light microscopy. Dense iron deposits stained with Turnbull blue and were not bleached by potassium permanganate. The granules aggregated around the vessels without penetrating into the vessel wall. There was diffuse demyelination in the dentate nuclei, the neurons remaining normal. The Purkinje and granule cells were slightly rarefied. A few pigment granules were also present in the striatum and in the external segment of the globus pallidus.

Disorders of Copper Metabolism

Copper is a trace element indispensible for the functioning of various oxidative enzymes. In human pathology disturbances of copper metabolism are responsible for two diseases: hepatolenticular degeneration (Wilson's disease) is due to flooding of the organism with excess copper; trichopoliodystrophy (Menkes' syndrome) is the result of a copper deficiency caused by disturbances of the transport mechanism. In both conditions neurological symptoms and neuropathological findings occupy a preeminent position. Aside from these, additional hereditary disorders have been described, characterized by low copper levels in the serum and severe neurological manifestation, but in which no neuropathological observations are available (Haas *et al.*, 1981).

Hepatolenticular Degeneration (Wilson's Disease; Westphal–Strümpell Pseudosclerosis; Wilson–Konowalow Disease)

Westphal (1883) described a clinical syndrome with intention tremor and spasticity, reminiscent of multiple sclerosis, in which, however, no plaques of demyelination were found at autopsy. He therefore called the condition "pseudosclerosis." Strümpell (1898) elaborated on the clinical symptomatology of the disease. Wilson (1912) presented a series of similar cases which, at autopsy, revealed softening of the lenticular nucleus and cirrhosis of the liver. He recognized the familial incidence of the disease and the similarity of the clinical picture to that described by Westphal and Strümpell.

Alzheimer (1911) described specific changes in the glial cells in cases of pseudosclerosis. These were thought to differentiate this syndrome from Wilson's disease until Spielmeyer (1920) demonstrated the presence of Alzheimer's glia in cases of Wilson's disease. Hall (1921) reviewed the entire published case material as well as some cases of his own, and coined the term *hepatolenticular degeneration* to embrace both apparent variants of the disease. A similar syndrome may occur occasionally as a sequel to chronic hepatitis (De Santi, 1986; Hanner *et al.*, 1988). The coincidence of Wilson's disease and excessive iron storage has been reported by Hafkemeyer *et al.* (1994).

Clinical Picture The patients present with extrapyramidal motor symptoms, coarse tremor, muscular rigidity, dysarthria, and dysphagia. Mental symptoms of various degrees of severity may also be present (Rosselli *et al.*, 1987).

MRI in 90% of the patients demonstrates symmetrical striatum and brain stem lesions with or without a thalamic lesion. Brain stem auditory evoked potentials were abnormal in 65% of the patients, indicating that subclinical sensory dysfunction is common in Wilson's disease and that auditory and somatosensory pathways are most severely affected at the brain stem level (Selwa *et al.*, 1993).

Four variants have been recognized:

1. An infantile form with early onset and a rapid course. Increasing rigidity is the main feature, accompanied by choreiform and dystonic movements, but without tremor
2. A rigid form with tremor, later onset, and a slowly progressive course
3. A tremulous or late form with even later onset, slower progression, and hypotonia instead of rigidity
4. An extrapyramidal or corticoextrapyramidal form

Parkinsonian symptoms are equally common in children and adults; a "pseudosclerotic" picture is much more common in adults, but dystonic and choreic symptoms are seen more often in children (Walshe and Yealland, 1992). Epileptic seizures are about six times more common in those with Wilson's disease than in the general population. A rare cerebellar form has been described (Madden *et al.*, 1985). Both the neurological and mental symptoms are reversible by appropriate treatment (Rosselli *et al.*, 1987).

In some cases ascites, jaundice, and gastrointestinal symptoms may be present from the onset of the disease. Urolithiasis has been documented in as many as 16% of the patients (Nakada *et al.*, 1994). In the purely hepatic form the main symptoms may remain for a long time, sometimes until death, even if the EEG is abnormal (Nevsimalova *et al.*, 1986).

To complete the clinical picture, a greenish brown pigmentation is present in the cornea, and was described by Kayser (1902) and Fleischer (1903). This Kayser–Fleischer ring can precede the other clinical manifestation. A clinical syndrome resembling hepatolenticular degeneration, but without the Kayser–Fleischer ring, has been described by Ross *et al.* (1985). Bones and joints may be affected in a few adult cases; this is more common among patients in Asia (Chu and Hung, 1993).

Changes in the basal ganglia can be seen on CT scans in some, and on MRI in almost all, cases. Cortical and white matter lesions may also be seen in some cases (Le Fort *et al.*, 1988). Sener (1993) demonstrated bilateral hyperintensity of the basal ganglia and thalami, and small nodular hyperintensities were superimposed that presumably represented cavitations secondary to the spongy degeneration. An MRI pattern consisting of symmetrical lesions of the red nuclei, the periaqueductal gray region, and, facultatively, the substantia nigra and the dentate nuclei has been considered almost pathognomonic (Willeit *et al.*, 1992).

Pathology *Gross appearances.* The liver is small, tough, and knobby. On cut sections areas of liver tissue are separated by fine and coarse strands of connective tissue. Splenomegaly may be considerable.

Light microscopy. In patients with longstanding liver disease, circumscribed large areas of hepatic parenchyma with macronodular cirrhosis are separated by collagenous septa.

In patients with fulminant liver failure, the cirrhosis is predominantly micronodular (Rela *et al.*, 1993). In the periphery of the nodules, copper pigments may be demonstrated histochemically. These stain greenish black with rubeanic acid and yellowish brown with sodium diethyldithiocarbamate. The substrate of Kayser–Fleischer rings consists of fine granules in Descemet's membrane near the corneal limbus. Their staining reactions are the same as those of the liver pigments.

Electron microscopy. The hepatocytes contain giant mitochondria with paracrystalline inclusions. Multivesicular rounded granules in the hepatocytes are thought to be characteristic of Wilson's disease. Analysis by X-ray absorption shows an increased copper content (De Santi *et al.*, 1986). For practical purposes absorption spectrophotometry carried out on liver biopsies of untreated cases yields sufficiently reliable results.

Sternlieb (1992) reported three distinct patterns of structural abnormalities of mitochondria. No correlation was seen between the type of mitochondrial abnormality and the patient's age, hepatic copper concentration, degree of hepatic steatosis, or serum aminotransferase level. However, siblings revealed remarkably similar types of abnormalities in each family.

Neuropathology *Gross appearances.* Sinking of the surface of the insula is frequently observed. A "pseudolegyric type of hepatocerebral disease" was described by Japanese authors. Severe atrophy is rarely observed, but occasionally it may assume the appearance of hydrocephalus. On coronal sections a shrunken and discolored putamen is frequently seen. The changes are almost always symmetrical. Areas of softening, involving parts of the white matter, the cerebral and cerebellar cortices, and the putamen (Horoupian *et al.*, 1988), are seen in patients with long-term survival. A rare form with degenerative changes in the midbrain and central pontine myelinolysis was described by Kida *et al.* (1985).

Light microscopy. The striking feature is the presence of the two types of glial abnormalities described by Alzheimer (1911). Type I consists of hypertrophic astrocytes with abundant cytoplasm and a nucleus with multiple bulges (Fig. 173). The connection between the bulges can often be appreciated only by moving the fine adjustment of the focus of the microscope. The nuclei are hyperchromatic and contain double the normal amount of DNA. In Alzheimer's type II glia (Fig. 174) the cells are smaller and their cytoplasm is barely visible, although it may contain fine yellowish brown granules. The nucleus is large and pale, contains one or two nucleoli, and often contains inclusions (Fig. 175) that stain strongly with PAS and Best's carmine. Type II cells lose their immunohistochemically demonstrable GFAP (Koo and Roessmann, 1988). The third type, present in small numbers, was described by Opalski (1930) and bears his name. These are glial cells with a large, spongy, dull-staining cytoplasm and a large centrally or peripherally placed nucleus (Fig. 176A and B).

Alzheimer's type I cells are pathognomonic for hepatolenticular degeneration, while type II cells are seen in Wilson's disease as well as in other types of hepatic encephalopathy (Mossakowski and Weinrauder, 1984). Opalski cells may occur in both circumstances, but are distinctly less common in hepatic encephalopathy. The Opalski astrocytes are strongly GFAP positive (Mossakowski and Weinrauder, 1984).

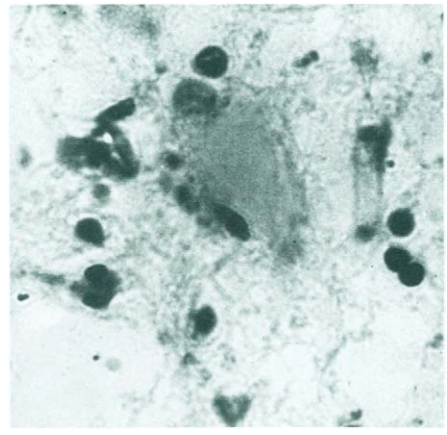


Fig. 173 Alzheimer's glia type I with hypertrophic cytoplasm. Hematoxylin–eosin stain, ×900. (Courtesy of M. Mossakowski, Warsaw, Poland.)

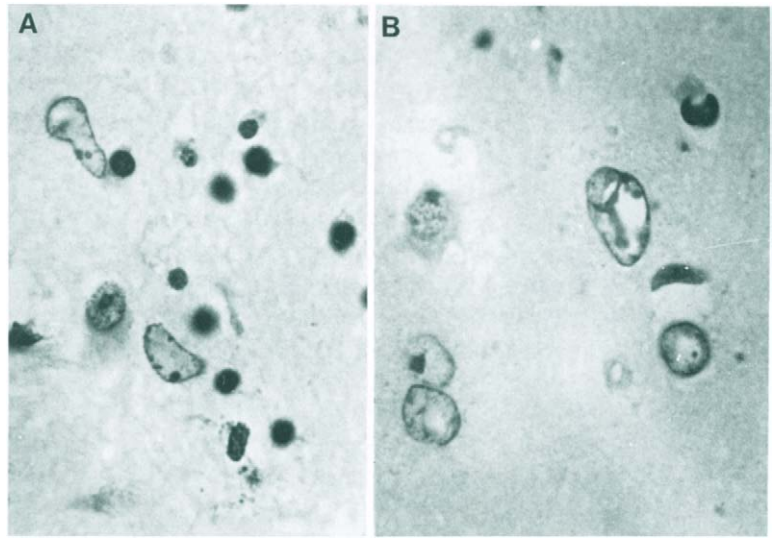


Fig. 174 (A and B) Alzheimer's glia type II, showing large pale nuclei and barely visible cytoplasm. Nissl stain, ×800. (Courtesy of W. Jänisch, Brandenburg, Germany.)

Status spongiosus may be present in the white matter (Miyakawa *et al.*, 1982), cerebral cortex, basal ganglia, and dentate nucleus. Fat granule cells are sparse and are seen in association with status spongiosus. These cells are more common in acute cases. They are considered evidence of an active process. They may persist for a long time in the foci of

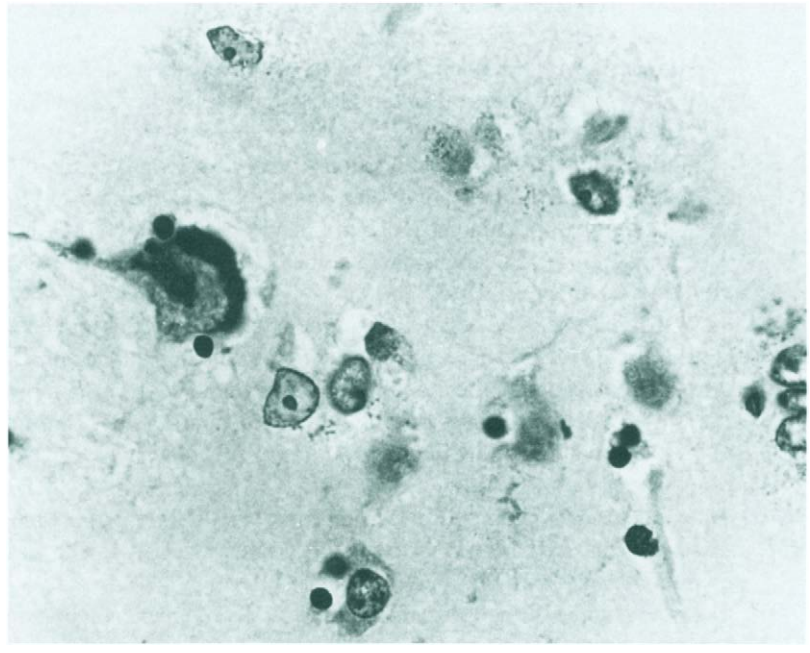


Fig. 175 Alzheimer's glia type II, showing fine granules in the cytoplasm. Nissl stain, ×700. (Courtesy of W. Jänisch, Brandenburg, Germany.)

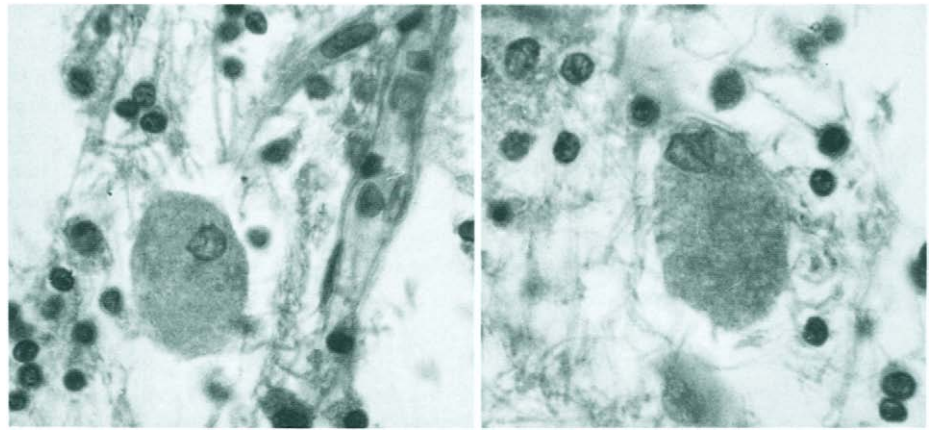


Fig. 176 (A and B) Opalski cells, showing hypertrophic cytoplasm with peripheral displacement of the nucleus. Hematoxylin–eosin stain, ×900. (Courtesy of M. Mossakowski, Warsaw, Poland.)

softening. Miyakawa and Murayama (1976) described extensive demyelination of the cerebral and cerebellar white matter.

Iron-laden phagocytes are found in the globus pallidus and the substantia nigra. Calcified neurons may be present in the globus pallidus and the medulla oblongata in juvenile cases as well as in older patients.

Endothelial swelling and rarefaction of the vessel walls, particularly of the capillaries, may be found occasionally. Vascular proliferation is commonly seen in association with status spongiosus, but may also occur independently.

Neuropathological changes can also be observed in patients successfully treated clinically (Horoupian *et al.*, 1988).

Electron microscopy. Alzheimer's type II glial cells contain clusters of lipofuscin bodies and numerous glycogen granules. The intranuclear inclusions also consist of aggregates of glycogen granules, occasionally surrounded by a membrane. Miyakawa *et al.* (1982) also found structures resembling amylopectin. Aside from lysosomes, other inclusions containing mucopolysaccharides in Opalski cells have been described.

Pathogenesis Strümpell and Handmann (1914) were the first to find an increased copper content in the livers of two of Fleischer's patients. The same observations were subsequently made on brain tissue.

Most authors assumed that disturbance of the copper metabolism in the liver led to a high copper concentration in various organs. The copper-binding ferroxidase is reduced to less than 25% of the normal values. This leads to a reduction in the total copper content in the plasma with a simultaneous increase in the albumin-bound fraction. The incorporation of copper into ferroxidase is also reduced, as is the excretion of this element in the bile (Frydman *et al.*, 1985). The low level of ferroxidase is ascribed to reduced biosynthesis caused by impaired transcription (Czaja *et al.*, 1987).

It is remarkable that in spite of the ubiquitous distribution of copper in the brain, only motor functions are affected, while sensation remains intact.

In cultured skin fibroblasts from patients with Wilson's disease, the addition of copper to the culture medium causes an abnormally high uptake of copper by the cells compared with fibroblasts from normal controls. This leads to the conclusion that the defective gene also causes abnormalities of copper metabolism in these cells. Hepatolenticular degeneration is inherited as an autosomal-recessive trait. The higher prevalence rate of the disease in Japan is presumably due to a higher consanguinity rate (Chu and Hung, 1993). The responsible gene was localized on chromosome 13 in the neighborhood of the esterase *D* locus between q14 and q21 (Bowcock *et al.*, 1988). It is a putative copper-transporting P-type ATPase functionally similar to the Menkes gene (Bull *et al.*, 1993; Tanzi *et al.*, 1993) and has been mapped in chromosome 13q14.3 (Petrukhin *et al.*, 1993). Using RFLPs in the 13q14.3 region supports the location between the markers *D13S31* and *D13S59* (Thomas *et al.*, 1994). The disease-containing region that spans these loci and orders nine highly polymorphic microsatellites provides evidence for strong allelic associations between *AFM084xc5* alleles and the Wilson gene alleles and suggests that the number of mutations accounting for the disease is lower than expected on the basis of the variety of clinical symptoms observed (Bowcock *et al.*, 1994).

Experimental Models A chronic industrial intoxication with copper is unknown in humans. In animals, however, a condition resembling Wilson's disease could be produced by excessive copper administration through a subcutaneous osmotic pump (Cook and Grubb, 1986). Intoxication with ammonia and urease as well as portocaval anastomosis (Norenberg, 1976) produced neuropathological changes analogous to human hepatic encephalopathy. A reproduction of the full clinical picture of Wilson's disease has not been achieved in animals.

Menkes' Syndrome (Trichopoliodystrophy; Kinky Hair Disease)

Menkes *et al.* (1962) described a new syndrome in five male members of a single family. It was characterized by abnormal stubbly hair, neurological symptoms in childhood, and stunted growth. Aguilar *et al.* (1966) called the condition "kinky hair disease." Ghatak *et al.* (1972) coined the term *trichopoliodystrophy*. This widely accepted term is not entirely accurate, however, as both the gray and white matter are affected in this condition (Tan and Urich, 1983).

Clinical Picture The infants develop normally during the first 2 months. The first symptoms appear between the ages of 2 and 4 months, and somewhat earlier in premature infants. Hair is sparse, twisted (pilus tortus), or fragile and constricted in regular intervals (trichorrhexis nodosa) or varying in diameter (monilethrix). Some children have micrognathos and occasionally an arched palate. A talipes equinovarus deformity is frequently observed. Psychomotor development ceases, and seizures, both focal and generalized, occur. Symptoms of progressive neurological deficit develop, with motor weakness and spasticity. A horizontal nystagmus and pallor of the optic disks have also been described. Appearances on CT scans vary from patient to patient, ranging from massive cerebral and cerebellar atrophy with ischemic softenings and subdural effusions to normal findings (Muramatsu *et al.*, 1984). MRI confirms the cerebral and cerebellar atrophy, subdural effusions, and rarefaction of the white matter (Ichihashi *et al.*, 1990; Johnsen *et al.*, 1991). Magnetic resonance angiography reveals tortuosity of the cerebral blood vessels (Jacobs *et al.*, 1993; Takahashi *et al.*, 1993). The course of the disease in progressive, punctuated by respiratory infections and episodes of hypothermia and terminating in decerebrate rigidity. Severe, sometimes fatal, gastrointestinal hemorrhage from gastric polyps occurs occasionally (Kaler *et al.*, 1993). Most patients die between the ages of 7 months and $3\frac{1}{2}$ years. Longer survival is rare (Okeda *et al.*, 1991). Inheritance is X-linked recessive.

Pathology Widening of the metaphyses is seen in the early stages of this condition. This disappears later, leaving behind an irregularity of metaphyseal plates, particularly in the ribs and the femur. Abnormalities in the arteries include fragmentation and reduplication of the elastica, sometimes associated with intimal proliferation. Ghatak *et al.* (1972) found glycogen accumulation, interfibrillar vacuolation, distortion of the tubular system, and abnormal mitochondria in the skeletal muscle.

Neuropathology *Gross appearances.* There is a wide range of appearances. As a rule, the brain is severely atrophic, its weight being reduced to less than one half of the normal

values. The gyri are narrow; the cortex is thin and of a firm consistency. The white matter is shrunken and the lateral ventricles are moderately dilated. The cerebral atrophy predisposes the patient to subdural hematomas (Menkes *et al.*, 1962).

Light microscopy. A reduction in the number of neurons is apparent in the cerebral cortex (Fig. 177). Areas of total devastation with microcystic rarefaction of the cortex and astrocytic proliferation may be present. A moderate loss of nerve cells is also found in the basal ganglia. The nucleus ventralis oralis of the thalamus and the red nucleus may show signs of severe degeneration (Martin and Leroy, 1985). Occasionally, the medial and lateral geniculate bodies showed an almost total loss of neurons. A status spongiosus with astrocytic proliferation can also be seen in the white matter, but frank cavitation is rare (Tan and Urich, 1983). The arteries, particularly the leptomeningeal ones, are tortuous, dilated, and degenerate, and may show aneurysmal expansion.

The cerebellum is severely affected in almost all cases. There is a striking loss of granule cells (Fig. 178). The Purkinje cells are also diminished in number and show striking dendritic abnormalities. The most characteristic feature is the presence of perisomatic dendrites (Fig. 179) radiating from the perikaryon (Reed *et al.*, 1984). The apical dendrites show deformities of the weeping willow or staghorn pattern. Dendritic swellings (Robain *et al.*, 1988) and axonal torpedoes may also be present. The perikarya of some Purkinje cells show coarse vacuolation. Basket cells and their fibers are also severely depleted. In young infants abnormalities can also be seen in the external granular layer. The abnormal thickness of this layer is suggestive of inhibited migration. Nodular

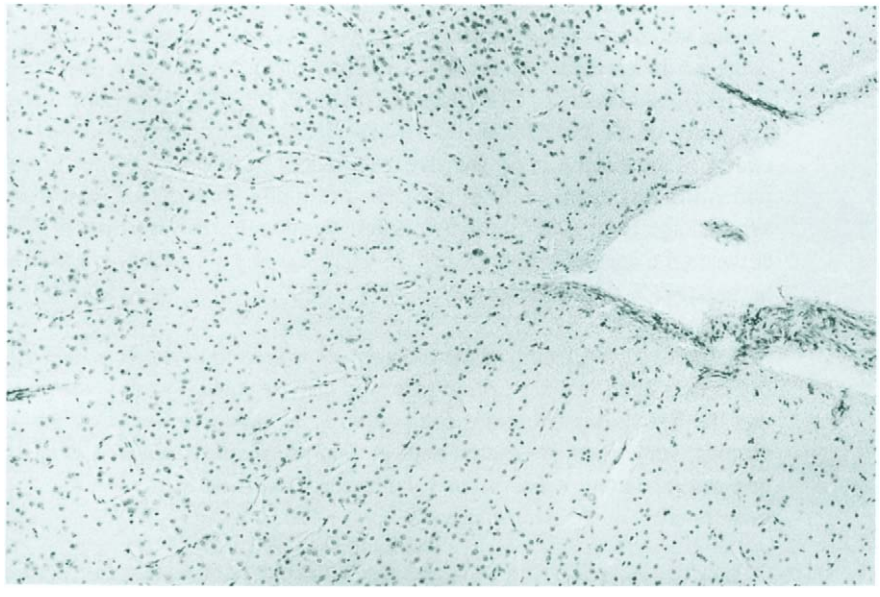


Fig. 177 Trichopoliodystrophy. A severe loss of neurons in the frontal cortex. Nissl stain, ×10.

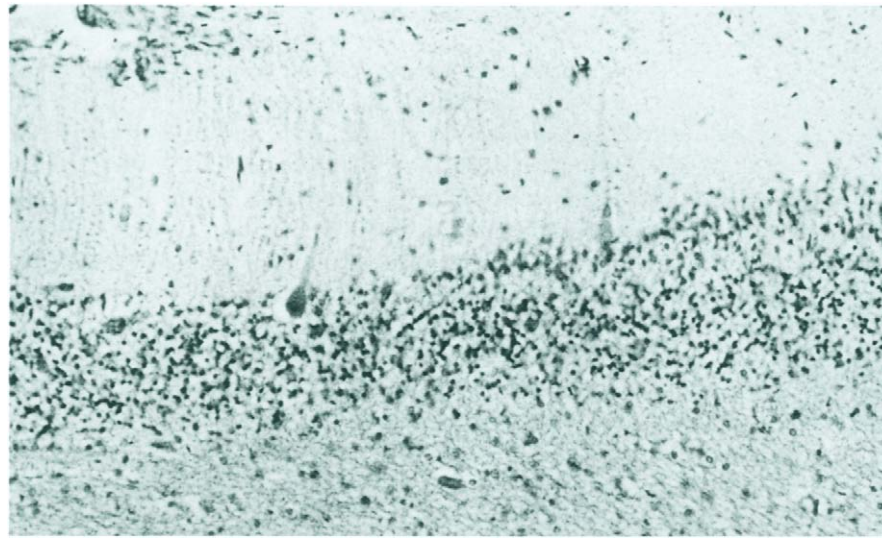


Fig. 178 Same case shown in Fig. 177. Rarefaction of the granule cells in the cerebellar cortex. Nissl stain, ×150.

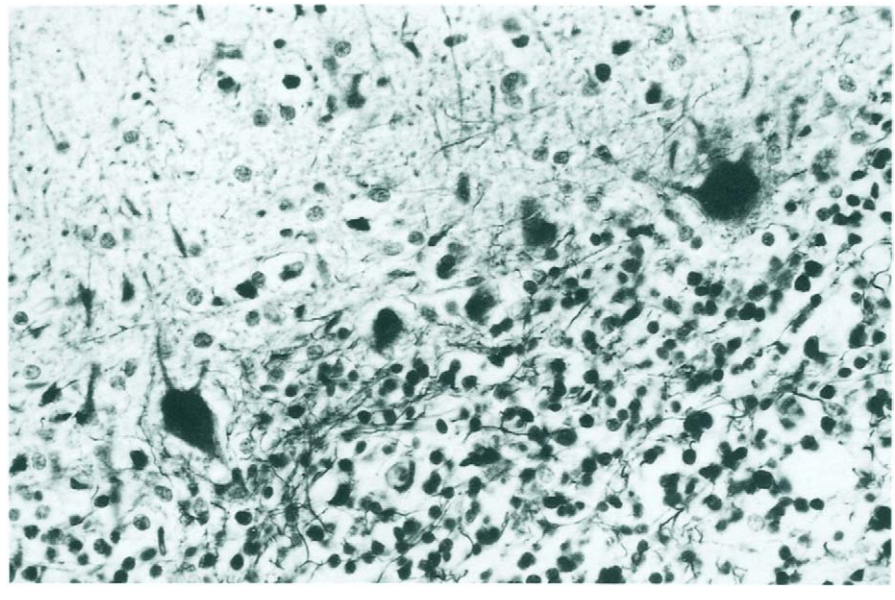


Fig. 179 Same case shown in Fig. 177. Dystrophic Purkinje cells with aberrant dendrites. Nissl stain, ×280.

cellular structures in the external granular layer have been seen occasionally (Tan and Urich, 1983).

Peculiar chromatolytic neurons were found scattered in small numbers in the brain stem and the spinal cord (Tan and Urich, 1983).

A loss of cells in Clarke's column with gliosis and degeneration of the spinocerebellar tracts may be seen in the spinal cord (Ghatak *et al.*, 1972; Okeda *et al.*, 1991). Lesions in the eye include microcysts in the pigmented epithelium of the iris and a loss of retinal ganglion cells with partial atrophy of the optic nerve.

Electron microscopy. Persistent perisomatic processes of Purkinje cells, only some of which formed synaptic connections, can be found. The axonal torpedoes contain accumulations of neurofilaments and other axonal organelles. Calcifications are present in the swollen dendrites (Fig. 180A and B), as well as hypertrophic mitochondria (Robain *et al.*, 1988). Aggregations of mitochondria are also found in the Purkinje perikarya (Ghatak *et al.*, 1972). Hypertrophic mitochondria (Fig. 181) may be seen in a variety of neurons. Concentric lamellar structures have been found in the expanded Purkinje dendrites (Okeda *et al.*, 1991).

Pathogenesis The disease is inherited as an X-linked recessive trait and the gene has been located in the region Xq12–13.3 (Tonnesen *et al.*, 1992). Both in the serum and in the plasma there is a reduced level of copper and ferroxidase. Presumably, a mutation of an intracellular copper-binding protein leads to disorders of transport and incorporation of copper into various tissues. The intracellular distribution of copper is abnormal. It is abundant in the cytosol, but deficient in the mitochondria. It appears that the Menkes mutation affects copper transport from the cytosol to the organelles (Kodama, 1993). Copper is essential for the formation of the disulfite links between the polypeptide chains of keratin and for the interlinking of lysine radicals in elastin. Copper deficiency leads to inactivation of the lysyl oxidase in the hair and the blood vessels. The brain is the only organ in which the copper content increases with age. The demand for copper is particularly high during the period of myelinization. In the pathogenesis of the lesions, one should take into account the diminished activity of various enzymes that require copper as a cofactor. Among others, a disturbance of oxidative processes has been observed, due to the reduced activity of cytochrome-*c* oxidase. Subunits II and IV of the cytochrome-*c* oxidase were found to be deficient, while complex III of the respiratory chain was normal (Sparaco *et al.*, 1993). A reduction in the protective function of superoxide dismutase for the prevention of peroxidation of lipids and the reduction in the activity of the dopamine β-hydroxylase in the conversion of dopamine to norepinephrine are to be expected.

Whatever the exact mechanism, there is no doubt that all lesions are produced by copper deficiency. Identical lesions, allowing for species-specific differences in severity and distribution, occur in "swayback," a purely nutritional copper deficiency in newborn sheep and goats (Tan and Urich, 1983). If the copper deficiency in Menkes' syndrome is due exclusively to copper malabsorption from the gut, these lesions must be postnatal in origin. On the other hand, the presence of perisomatic dendrites is frequently quoted in support of the prenatal origin of the lesions. Another argument in favor of a prenatal malformation is provided by the Purkinje cell heterotopias in the cerebellar white matter of

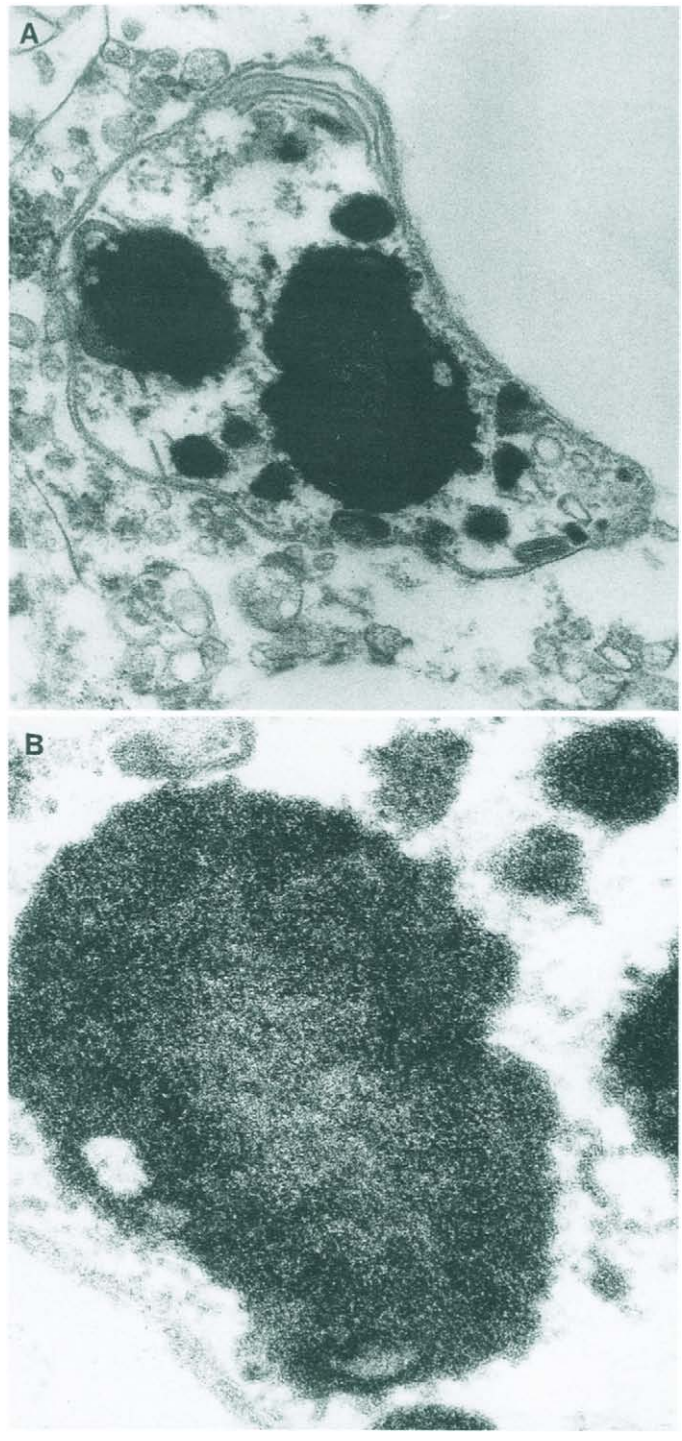


Fig. 180 Same case shown in Fig. 177. (A) Deposits of electron-dense material in a neuronal process, ×24,000. (B) Higher magnification (×120,000) reveals mineral particles.

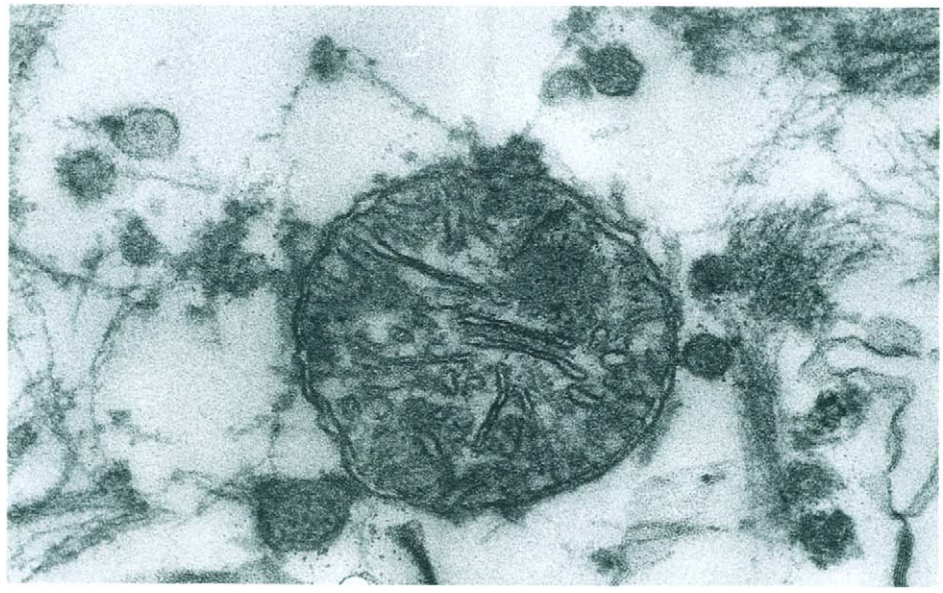


Fig. 181 Same case shown in Fig. 177. A hypertrophic mitochondrion in the cytoplasm of an astrocyte, ×70,000.

some cases. The problem of the prenatal versus postnatal origin of the cerebellar lesions thus remains unresolved.

The depletion of the internal granular layer may be due partly to disturbed migration and partly to degeneration. The bizarre ramifications of the dendritic tree of the Purkinje cells are commonly seen in all conditions associated with an absence or loss of granule cells and may be a specific response of the Purkinje cell to partial deafferentation (Urich, 1984).

Trichopoliodystrophy in Animals A metabolic disorder homologous to human trichopoliodystrophy is present in the *brindled mottled* mouse, an allele of the heterosomal *mottled* mouse mutant (Yamano and Suzuki, 1986) that is also highly sensitive to acute toxic copper intoxication (Shiraishi *et al.*, 1994). Another useful model is the X-linked copper-deficient *macular* mouse, either as a male hemizygote or as an artificially bred female homozygote (Iwane *et al.*, 1990). Similar lesions are seen in the nutritional enzootic ataxis (swayback) of lambs (Tan and Urich, 1983).

Disorders of Calcium Metabolism

Deposition of calcium-containing substances in the walls of cerebral blood vessels occurs in a variety of diseases as well as in normal brains. It has been reviewed in

large series of CT examinations. The combination of neuropsychiatric manifestations with symmetrical calcification of the basal ganglia and the dentate nuclei led to the concept of striatodentatal calcification of Fahr's disease, after a paper by Fahr (1930), although his observations were preceded by those of Delacour (1850). This condition is often associated with hypoparathyroidism or its variants. Symmetrical calcifications in the white matter occur in PKU, in dihydropteridine reductase deficiency, and in various infections and intoxications. They are one of the principal features of Cockayne's syndrome (see p. 501). In this section we consider, first, the idiopathic form, that is, striatodentatal calcification without obvious hypoparathyroidism or other metabolic disorders.

Striatodentatal Calcification (Fahr's Disease; Striatopallidal Calcification; Systemic Calcification of the Basal Ganglia; Idiopathic Nonarteriosclerotic Calcification of the Blood Vessels; Cerebrovascular Ferrocalcinosis)

Familial cases of symmetrical cerebral calcification without leukodystrophy have been reported repeatedly (Ellie *et al.*, 1989). Sporadic cases are also known, and in some of these a familial incidence may be suspected because of similar clinical histories in relatives. Some of the cases were associated with hypoparathyroidism (Cheek *et al.*, 1990). Symmetrical calcification of the basal ganglia was also reported in siblings or several generations of a family suffering from moniliasis and adrenal insufficiency or in combination with hemochromatosis and porphyria (Beall *et al.*, 1984).

Clinical Picture Neurological symptoms usually appear in adolescence or early middle age. In most patients the first symptoms are those of mental weakness or inefficiency (Trautner *et al.*, 1988). Slowness and paucity of movements, lack of facial expression, bent posture, and indistinct speech resemble the symptoms of parkinsonism (Morlan-Gracia *et al.*, 1993) and are the expression of damage to the basal ganglia. Choreiform and choreoathetoid movements have been observed. With extensive calcifications hemiplegia or paraplegia may be added to the extrapyramidal symptoms, as well as cerebellar disturbances in the form of ataxia, dysmetria, and abnormalities of speech. Seizures of various types, most commonly grand mal, may occur. The calcifications may be detected radiologically and on CT and MRI scans (Manyam, 1992), sometimes even in childhood.

There is no definite correlation between the neurological deficit and the extent of calcification or the level of calcium in the serum.

Neuropathology *Gross appearances.* Atrophy of the frontal and temporal lobes has been described in cases associated with dementia. Upon sectioning the brain, a roughening of the cut surface, resembling sandpaper, is felt in the globus pallidus and sometimes in the adjacent internal capsule. This is due to the protrusion of small calcified vessels. Calcium deposits are sparse in the corpus callosum and the medial parts of the centrum ovale. They are abundant in the striatum, however, where they occupy the entire putamen and the outer two thirds of the caudate nucleus (Fig. 182A, see

color plate). Small circumscribed areas of calcification may be seen in the cerebral cortex and the thalamus. In the case reported by Norman and Urich (1960), the cortical deposits were confined to the arterial boundary zones. In the cerebellum the calcification extends from the dentate nucleus into the white matter (Matsui *et al.*, 1992a), which may be converted into a solid calcified mass. The areas of calcification appear brownish. Cystic changes are sometimes found at the margin of the calcifications.

Light microscopy. Calcium deposits are seen in the walls of all blood vessels in the affected areas. These may range from concentric deposits to total obliteration of the vessel. Not only the media, but also the intima and adventitia, may be calcified, and the laminar structure of the vessel wall may no longer be recognizable (Fig. 183). Apart from these, droplet calcification may be seen in the tissue, mainly along capillaries, where they resemble strings of beads (Fig. 184A and B). Larger deposits may form grapelike or branching structures. The deposits stain dark brown with von Kossa's method. With Turnbull blue they give a strong reaction for iron in the pallidum, and a weaker one elsewhere (Fig. 182B, see color plate).

The term *pseudocalcium* is rarely in use in the English literature (Norman and Urich, 1960), but is a common concept in German neuropathology. It refers to the in-

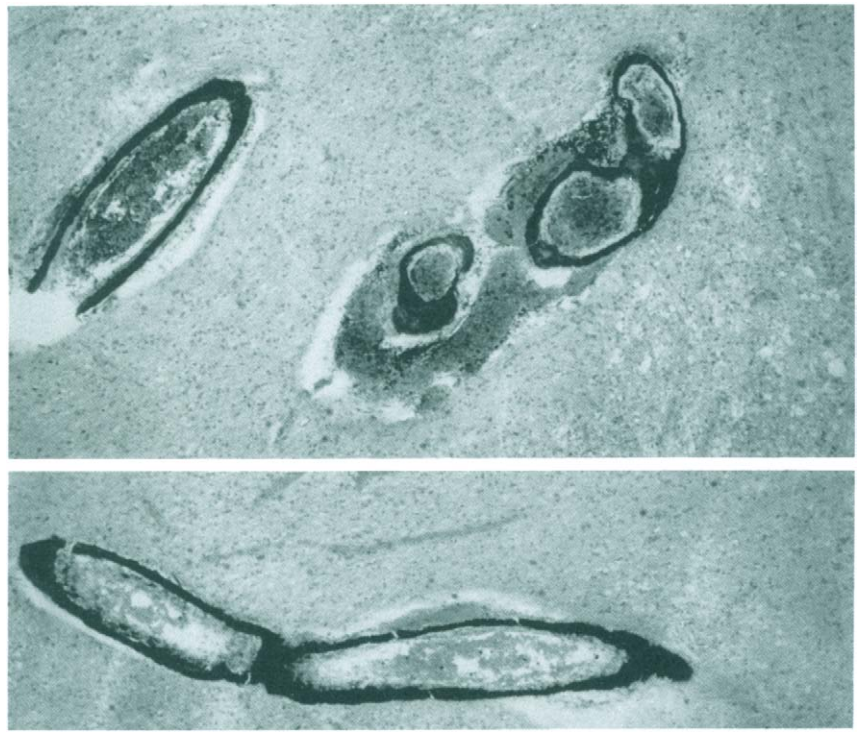


Fig. 183 (A and B) Same case shown in Fig. 182. In the globus pallidus rigid blood vessels appear as a result of homogeneous calcium deposition. Nissl stain, ×40.

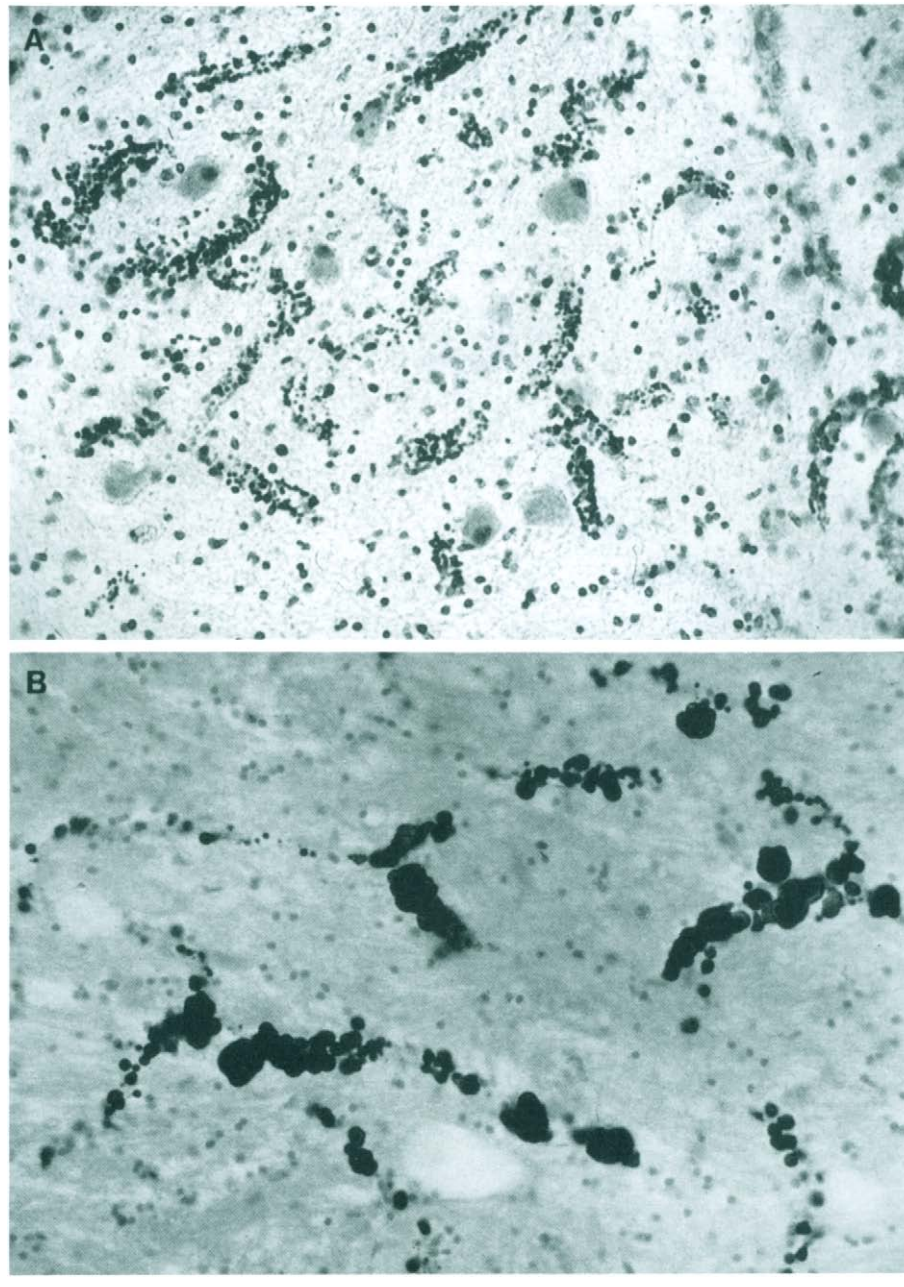


Fig. 184 Same case shown in Fig. 182. Droplet calcification arranged in the form of strings of beads. (A) Nissl stain, ×80. (B) von Kossa's stain, ×120.

soluble, basophilic, PAS-positive residue that remains after the decalcification of the material. It has the histochemical characteristics of an acid mucopolysaccharide or mucoprotein, perhaps related to basement membrane material. Its independent existence has been debated.

Electron microscopy. The apparently free calcium deposits are seen to be defined by a basement membrane (Cervós-Navarro and Matakas, 1974). Electron-dense inclusions, consisting of calcium granules, are seen in the neurons and the glial cells (Fig. 185). The deposits are associated with blood vessels and are surrounded by their basal membranes.

The concrements either appear as amorphous, electron-dense, homogeneous material or are formed by fine needlelike crystals (Fig. 186). On scanning electron microscopy the concrements appear as rounded nodules with a smooth surface (Fig.

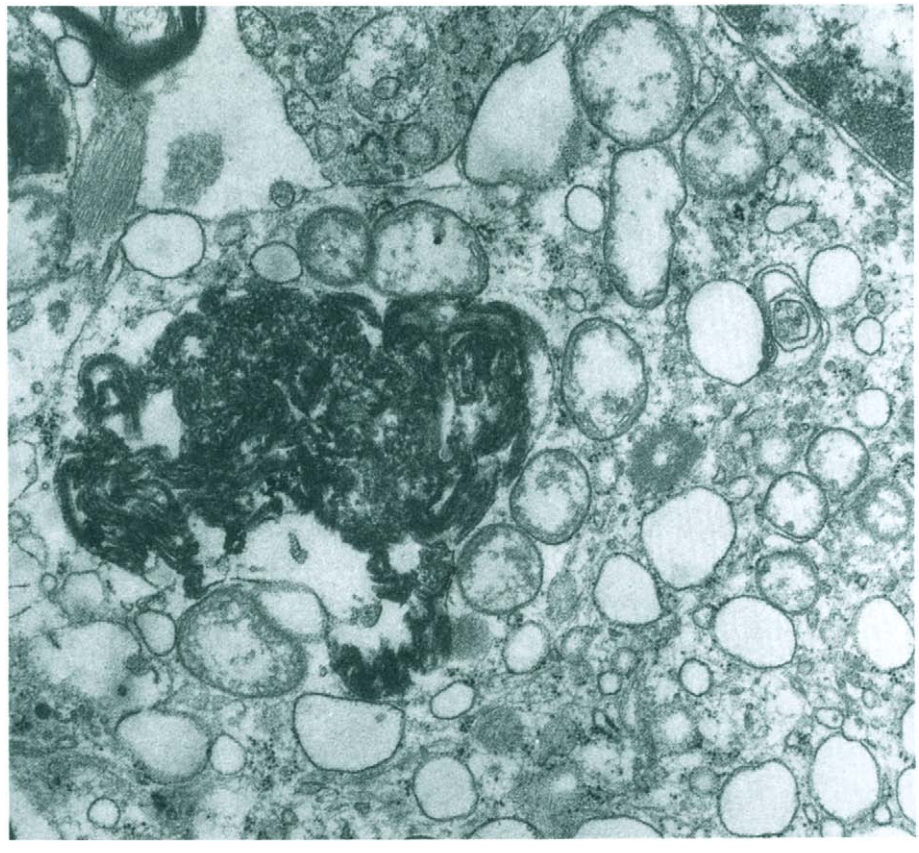


Fig. 185 Same case shown in Fig. 182. The parietal cortex, showing an electron-dense inclusion with calcium granules in the neuronal cytoplasm, ×20,000.

187). Heavily calcified vessels have a bumpy appearance corresponding to the round beadlike droplets.

In x ray energy dispersion analysis (EDAX) the deposits show an abundance of calcium (Fig. 188). They also contain phosphate and a moderate amount of iron (Cervós-Navarro and Matakas, 1974) as well as small amounts of zinc, aluminum, and magnesium (Duckett *et al.*, 1977).

Pathogenesis The electron microscopic appearances of tightly packed needlelike crystals do not support the view of a secondary impregnation of a pseudocalcium matrix by calcium. In the familial cases the inheritance is autosomal dominant (Manyam *et al.*, 1992). Reduced ornithine transcarbamylase activity was found in the liver by Matsui *et al.* (1992a), which was probably not related to the cerebral calcifications.

Cerebral Calcification in Animals Spontaneous calcifications have been seen in aging mice (Morgan *et al.*, 1982) and rats (Schmidt, 1978). Experimentally, calcium deposits can be produced by injuries to the spinal cord (Happel *et al.*, 1981) or by injection of kainic acid into the striatum (Korf and Postema, 1984), this being a nonspecific deposition in areas of necrosis and breakdown of the blood–brain barrier.

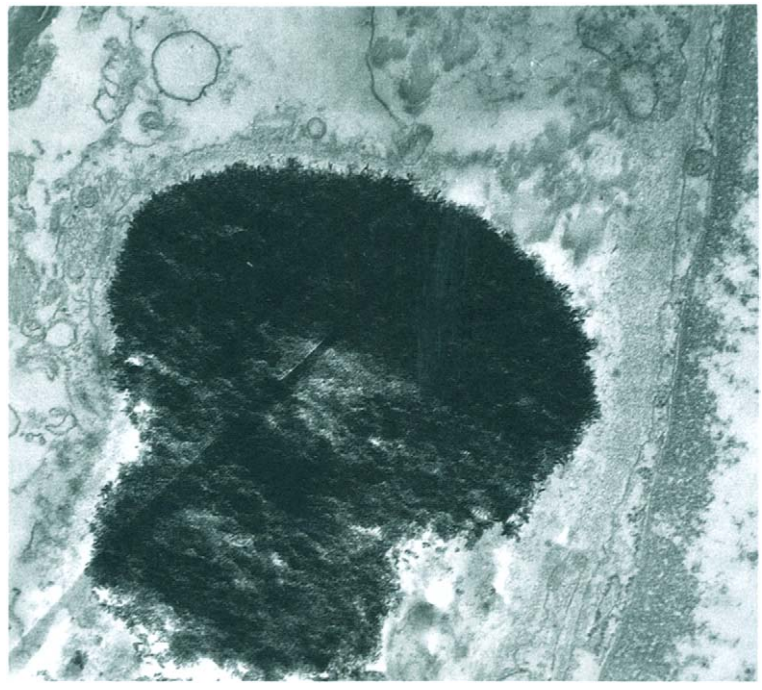


Fig. 186 Same case shown in Fig. 182. The globus pallidus, showing an endothelial cell (right). There is a calcium deposit with peripheral spikes in the perivascular space, ×17,000.

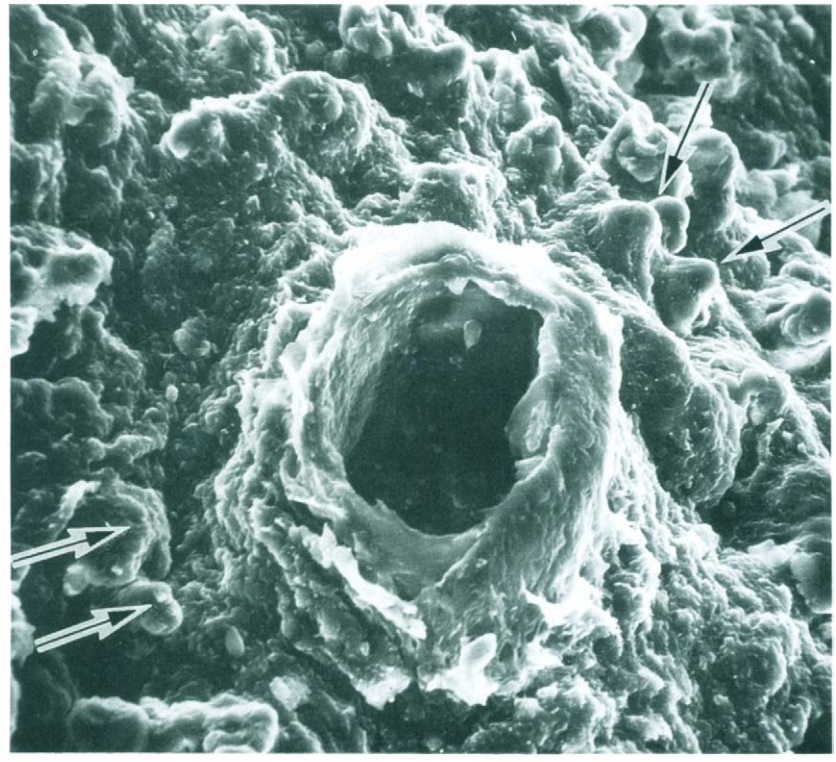


Fig. 187 Same case shown in Fig. 182. Scanning electron micrograph showing lumpy calcium deposits (arrows), ×1200.

Primary Hyperoxaluria

Besides toxicity-induced oxalosis (Heye *et al.*, 1991), there are two rare genetic disorders that manifest themselves by repeated attacks of calcium oxalate: nephrolithiasis and nephrocalcinosis.

Clinical Picture The renal symptoms usually appear before the age of 5 years, sometimes as early as in the first year. They lead to progressive renal failure and death before the age of 20 years. The inheritance of both types of disorders appears to be autosomal recessive.

Pathology Aside from the renal lesions, calcium oxalate crystals are deposited in the bones, cardiac muscle, and testes, and less commonly in other tissues (oxalosis).

Neuropathology In the CNS calcium oxalate crystals sometimes are deposited in the leptomeninges and the perivascular spaces (Haqqami, 1977). In peripheral nerves

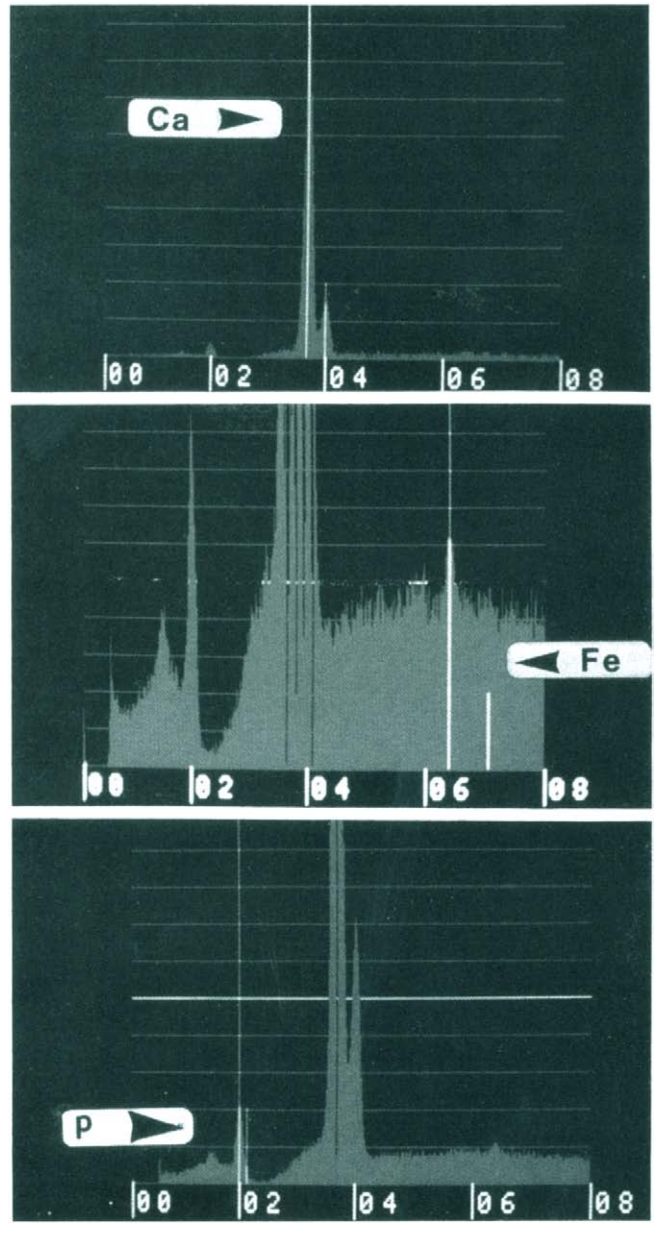


Fig. 188 Same case shown in Fig. 182. EDAX analysis of calcium deposits. Aside from calcium and iron, there is a significant amount of phosphorus.

intraaxonal deposition of crystals is accompanied by axonal degeneration and segmental demyelination.

Pathogenesis In type I the hyperoxaluria is caused by excessive synthesis of oxalate and glycolate through the inhibition of breakdown of glyoxylate. A deficiency of the peroxisomal enzyme alanine–glyoxylate aminotransferase was found in the liver, spleen, and kidney (Danpure and Jennings, 1986).

The metabolic defect in type II consists of an excessive reduction in hydroxypyruvic acid to L-glyceric acid caused by an absence of D-glyceric dehydrogenase.

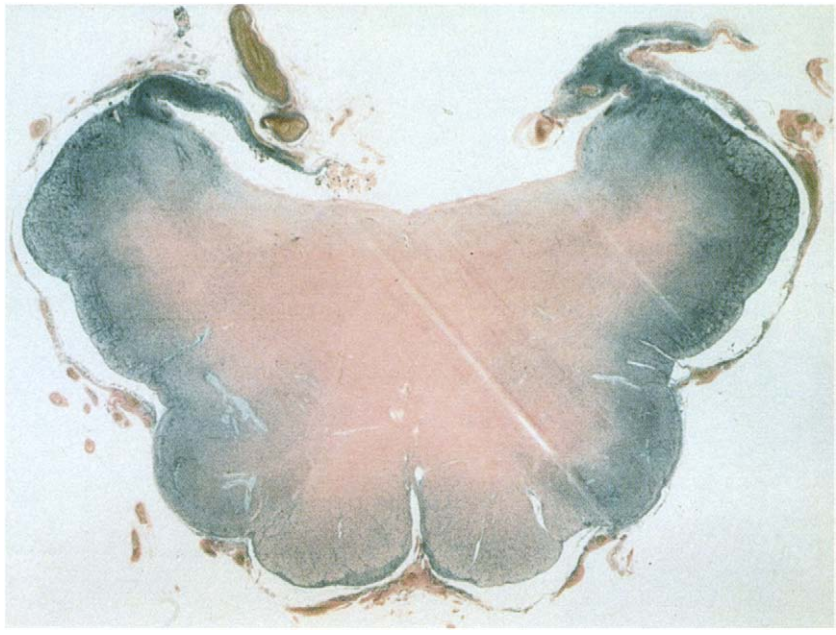


Fig. 171 Marginal siderosis of the central nervous system. The intensity of staining decreases with depth. Turnbull blue stain.

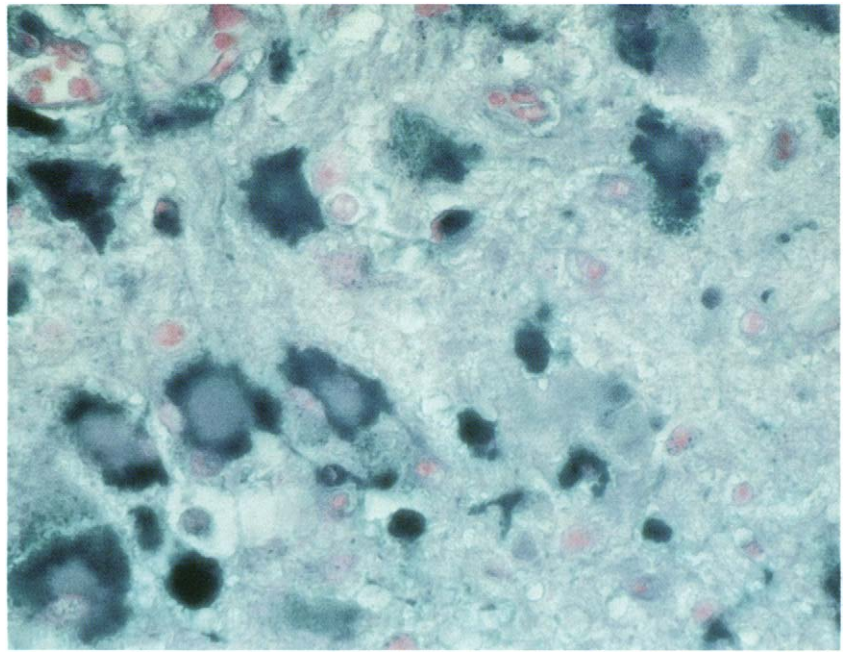


Fig. 172 Same case shown as Fig. 171. Intense staining of the neuronal and glial cytoplasm with diffuse staining of the neuropil. Turnbull blue stain, ×350.

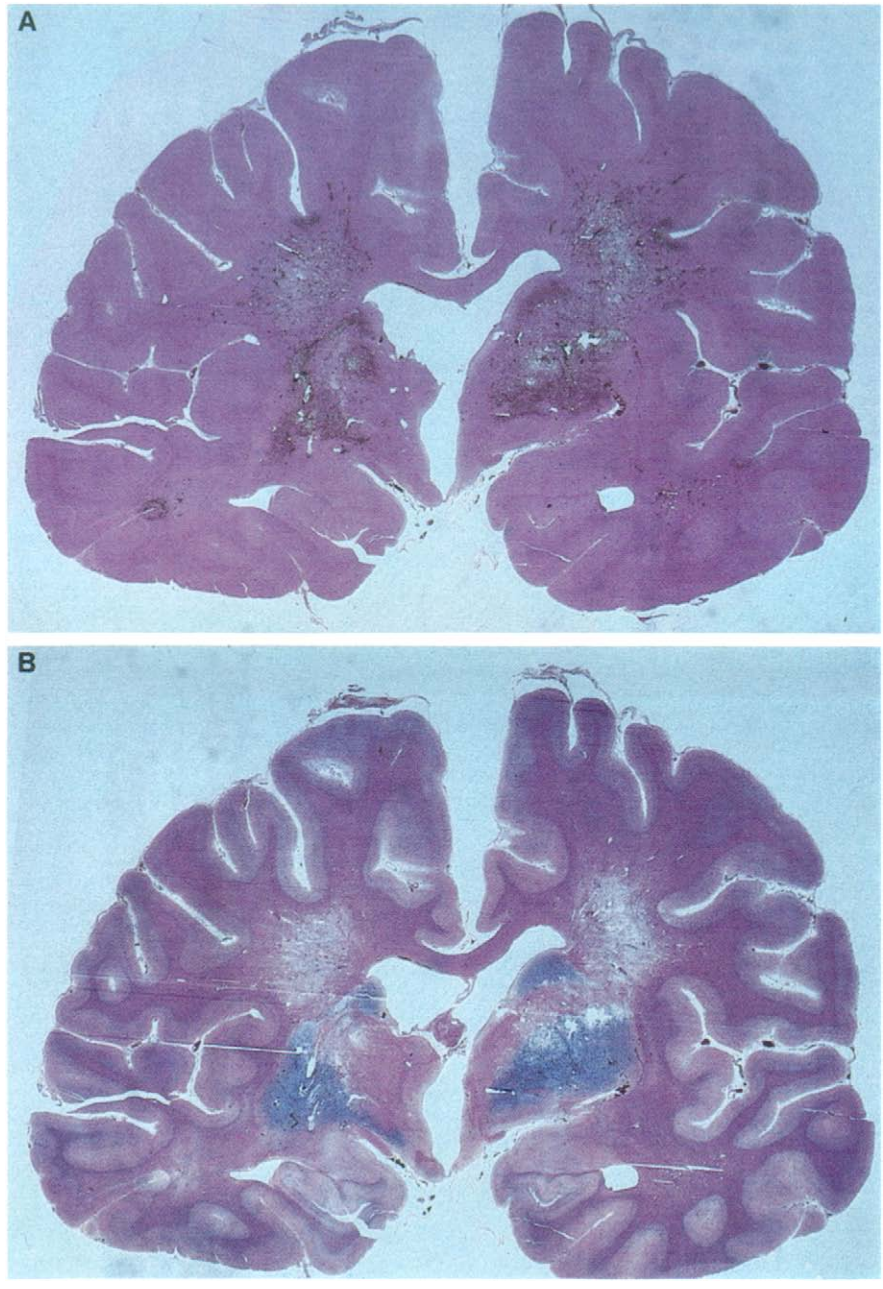


Fig. 182 Striatodentatal calcification. The calcium deposits occupy the putamen and the caudate nucleus, as well as part of the thalamus and the centrum ovale. (A) von Kossa's stain. (B) Turnbull blue stain.

Disorders of Pigment Metabolism

Pigments may be defined as colored substances found in the living body. They vary considerably in their chemical constitution, in their origin, and in their biological importance. The feature they have in common is that they absorb electromagnetic radiation in the narrow band of 400–800 nm visible to the human eye. Some of these substances have already been dealt with in the chapters devoted to disorders of lipid or mineral metabolism in view of the chemical identity of their main component. Not all pigments are lysosomal structures, as are those mentioned above, although some, such as melanin and bile pigments, may be taken up by lysosomes and broken down or stored in them.

Porphyrias

Symptomatic disorders of porphyrin metabolism associated with excessive excretion of coproporphyrin and caused by infections, blood diseases, liver failure, vitamin deficiencies, or poison must be distinguished from true porphyrias. The latter are disorders of porphyrin synthesis and are associated with excretion of uroporphyrin or its precursors.

The human porphyrias can be divided into two groups: the rare erythropoietic type and the more common hepatic type. The latter are subdivided into acute intermittent, chronic, combined, and latent forms.

Neurological manifestations are found almost exclusively in acute intermittent porphyria, an autosomal-dominant metabolic disorder affecting the enzyme porphobilinogen deaminase in the heme biosynthetic pathway. The highest prevalence of this disorder has been observed in Scandinavia, especially northern Sweden (Lapland), where it occurs with a prevalence of 1:1500 (Lee *et al.*, 1991). Severe ptosis without ophthalmoplegia due to selective involvement of oculomotor nuclei has been reported (Tan *et al.*, 1990).

Meningeal calcifications have been observed in congenital erythropoietic porphyria (Levesque *et al.*, 1988).

Protoporphyria is a genetic disorder characterized by a defect in the enzyme ferrochelatase, which catalyzes the chelation of iron into protoporphyrin. The predominant clinical feature is photosensitivity. Progressive and fatal liver disease occurs in a small percentage of the cases. A syndrome of neurological dysfunction with varying degrees of severity has been observed in all patients with end-stage protoporphyric liver disease (Rank *et al.*, 1993).

Clinical Picture Acute intermittent porphyria manifests itself by a deep red urine, severe abdominal pain reminiscent of ileus, and neurological deficits. These may occur concurrently with the abdominal crises, may follow them, or, occasionally may precede them (Mercelis *et al.*, 1990). The neurological symptoms are mainly peripheral (McEneanny *et al.*, 1993). Sensory loss is uncommon (Goren and Chen, 1991), but symptoms of sensory irritation in the form of severe pain or paresthesias are prominent. Motor involvement may lead to neurogenic atrophy of the skeletal muscles, particularly the small muscles of the hands (Fernandez-Barreira *et al.*, 1993). Cranial nerves may also be affected, producing a picture of acute bulbar palsy.

Acute, primarily motor, neuropathy and gastrointestinal symptoms can occur in several forms of porphyria, including acute intermittent porphyria and variegate porphyria (Barohn *et al.*, 1994). Occasionally, neurological manifestations may occur in combined porphyria during acute episodes, or in toxic and secondary porphyrinurias. CNS deficits have been observed occasionally, mainly in the form of pyramidal signs and disturbances of bladder function, occasionally mimicking multiple sclerosis (Macy *et al.*, 1993). Epileptic seizures occur in about 10% of the cases (King and Bragdon, 1991). Sever autonomic dysfunction may be present (McLeod, 1993).

Psychiatric manifestations are characterized by their great variety. They range from anxiety (Patience *et al.*, 1994) to depressive states. Even schizophrenic symptoms, including catatonia, can be mimicked (Stölzel *et al.*, 1987).

The course of the disease is rapidly progressive, reaching its peak in 1–4 weeks. Progression over several months is rare. Recovery extends over several weeks after the disease has reached its peak. Fatalities may occur during the acute stage, mainly from cardiac—or, less commonly, from respiratory—failure. Porphyric neuropathy can, on rare occasions, also be life threatening (Christensen and Rasmussen, 1991).

The disease is inherited as an autosomal-dominant trait with variable expressivity.

Pathology *Light microscopy.* Under light microscopy pigment deposition in hepatocytes, testicular atrophy, and neurogenic atrophy of the skeletal muscles may be present.

Neuropathology *Gross appearances.* Cerebral infarcts may be present, particularly in the occipital lobes (Chi-Wan *et al.*, 1977). Hemorrhages (Fig. 189) may be seen in the cortex and the underlying white matter (Stölzel *et al.*, 1987). A yellowish discoloration of the white matter or of the anterior horn of the spinal cord has been observed in a few cases (Agostini *et al.*, 1955).

Light microscopy. Areas of perivascular demyelination in the cerebral white matter

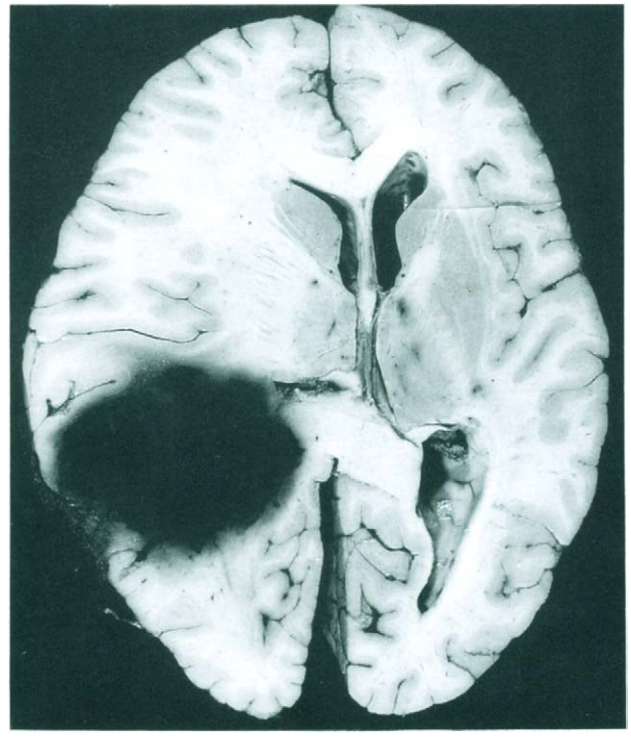


Fig. 189 Porphyria. Hemorrhage in the occipital cortex and the white matter.

have often been reported. The number of Purkinje cells may be reduced. A loss of anterior horn cells with reactive gliosis is seen in the spinal cord. The remaining neurons may show central chromatolysis (Fig. 190). The latter change has also been found in some nuclei of the pons and the medulla. Deposits of yellowish brown pigment may be seen in the neighborhood of the hemorrhages (Fig. 191, see color plate), in the stroma of the choroid plexus, in the leptomeninges, and in perivascular histiocytes in the cerebral and cerebellar white matter. They are particularly noticeable in the phagocytes of organizing infarcts (Fig. 192, see color plate). It is a coarsely granular brownish yellow pigment, which may also be seen in the motor neurons of the brain stem and the anterior horns of the spinal cord.

Changes in preganglionic parasympathetic neurons have occasionally been reported. In the peripheral nerves the changes are those of a dying-back process with a loss of axons and disintegration of the myelin sheaths (Ridley, 1969).

Electron microscopy. A wallerian-type degeneration was seen in thin and thick nerve fibers, and was ascribed to a dying-back axonal degeneration (Di Tripani *et al.*, 1984).

Pathogenesis Various substances may be affected by the activation of porphobilinogen and may release an acute episode. Hunger and alcohol may be contributory factors.

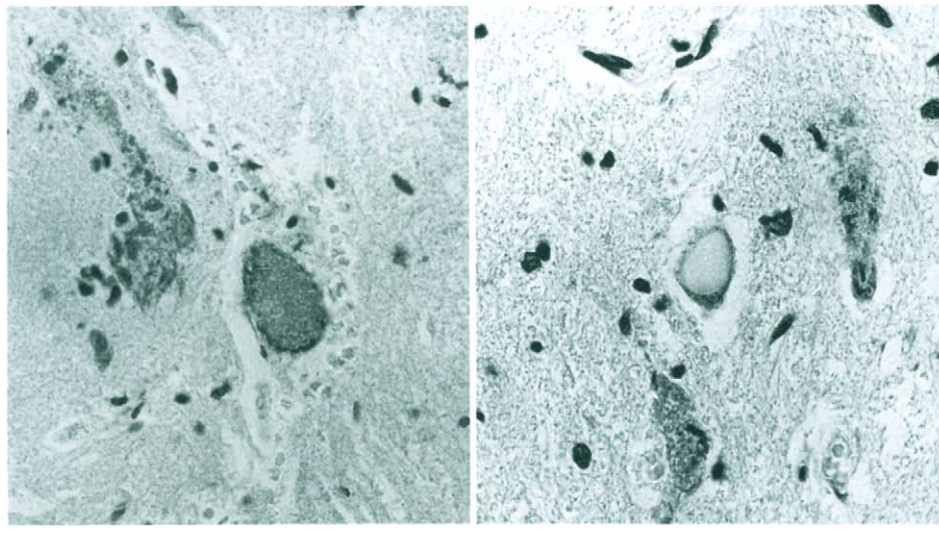


Fig. 190 Same case shown in Fig. 189. The spinal cord, showing chromatolytic neurons in the anterior horn. Nissl stain, ×500.

The increases in tryptophan and serotonin associated with faulty heme synthesis have been held responsible for the psychiatric manifestations (Litman and Almira Correia, 1985). A reduction in GABA release at the synapses has been also implicated. The neurotoxicity of porphyrias was demonstrated in tissue cultures by Riopelle and Kennedy (1982). The polyneuropathies of porphyria are also the consequence of disturbed heme synthesis (Laiwah *et al.*, 1985). A blockage of the cholinergic terminals has been discussed.

Acute intermittent porphyria is an autosomal-dominant disease characterized by mutations of the gene coding for porphobilinogen deaminase. The majority of the mutations have been detected in exon 10 and 12 (Ngone *et al.*, 1993; Daimon *et al.*, 1993). Mutations of the gene resulting in a cross-reacting immunological material-positive form of acute intermittent porphyria have been identified (Schreiber *et al.*, 1994). Sixteen different mutations had been identified as of 1994, when Gu *et al.* (1994) found 11 new mutations documenting the molecular heterogeneity of the disease.

Hyperbilirubinemia

Bilirubin, the degradation product of hemoglobin, can appear in abnormally high concentrations in the blood in severe hemolysis or as a result of a familial enzymopathy. In the former situation neurological symptoms and neuropathological lesions appear almost exclusively in neonates in the context of hemolytic jaundice of the newborn. These problems are extremely rare in adults as a result of acquired hemolytic

anemias. The higher incidence of hyperbilirubinemia in schizophrenics than in patients suffering from other psychiatric disorders has not been confirmed (Muller *et al.*, 1991).

The classical features of kernicterus were seen in the acute phase of hemolytic jaundice of the newborn. Improved therapy has virtually eliminated fatalities from this condition, but kernicterus still occurs in premature infants, even with relatively low levels of bilirubin in the serum.

Kernicterus of the Newborn (Icterus Hemolyticus Neonatorum)

Orth (1875) reported the first case of icteric discoloration of the cerebral gray centers in an appendix to his paper "On the Occurrence of Bilirubin Crystals in Newborn Infants." Schmorl (1903) coined the term *kernicterus* to denote the focal discoloration of brain tissue, particularly of the basal ganglia, in neonates.

Clinical Picture The icterus gravis develops within 24 hours of birth. Somnolence, apathy, and feeding difficulties follow within the next 2 days (Sherker and Heathcote, 1987). Head retraction is the first neurological symptom. This is followed by opisthotonos and muscular rigidity. Respiratory problems soon appear, first in the form of tachypnea, followed by pathological respiratory rhythms and finally by apnea. Uncoordinated spontaneous movements give way to severe convulsions. Cranial nerve pareses, particularly oculomotor ones, are observed occasionally. Death commonly occurs from respiratory failure. Subclinical or transient forms of bilirubin encephalopathy may be detected by detailed neurological examination (Perlman and Frank, 1988).

Neuropathology *Gross appearances.* The focal yellow discoloration affects various gray areas and the neighborhood of the CSF space. The distribution and intensity of the yellow staining vary from case to case. In some cases practically the entire gray matter may be stained, with accentuation in the basal ganglia, Ammon's horn, floor of the fourth ventricle, and deep cerebellar nuclei. In other cases the involvement is more selective and may be limited to Ammon's horn, subthalamic nuclei, globus pallidus, and individual nuclei in the floor of the fourth ventricle (Friede, 1989). Staining may be conspicuous in the thalamus as well as in the cerebral and cerebellar cortices (Turkel, 1980). Cortical pigmentation can be seen in only about 30% of the cases and is generally not uniform, but focal. The yellow patches are seen particularly in the temporal lobe near the uncus, in the central cortex, at the edge of the frontal cortex, in the cingulate gyrus, in the cortex of the insula, and in the depth of the occipital sulci. In the cerebellar cortex the areas of predilection are the inferior vermis and the flocculi. In about one quarter of the cases staining is apparent in the choroid plexuses, ependyma, and leptomeninges. The appearances resemble those seen in meningeal icterus of adults (see p. 436). The blood vessels stand out and cerebral edema is common. Focal softenings may occur occasionally in the acute stage.

Light microscopy. Selective neuronal necrosis and reactive gliosis are seen in the affected areas. Liquefaction and shrinkage of the neuronal cytoplasm may be present, as well as changes resembling ischemic or homogenizing processes. Incrustation of the cell

processes is seen particularly in the striatum, where the large neurons are mainly affected. These cells are often an intense yellow and have been described as "yellow ganglion cells." Both the cytoplasm and the nucleus are stained and usually show the appearances of the homogenizing change of Spielmeyer. The neuronal changes may be more extensive than the areas of yellow staining, but even in the pigmented areas only some neurons are stained. On the other hand, neurons and microglial cells containing bilirubin are far more numerous in frozen sections.

A proliferation of microglia and a focal increase in astrocytes can be seen in all areas of neuronal necrosis, particularly in patients who died after the age of 4 days or those with exceptionally severe seizures. Granules of bilirubin pigment may occasionally appear in the astrocytes. Glial scarring is distinct 3–4 weeks after the acute icteric phase.

The vasodilatation observed macroscopically is not confined to the areas of selective parenchymal necrosis. It can be seen in the cerebral and cerebellar white matter, and particularly in the floor of the fourth ventricle.

Kernicterus of Prematurity

Zuelzer and Mudgett (1950) observed yellow staining of the brain in premature infants with relatively low concentrations of bilirubin in the blood. This was subsequently confirmed by different authors. An attempt to find risk factors that predispose premature infants to kernicterus was unsuccessful (Connolly and Volpe, 1990) and led to the conclusion that this disorder is due to nonspecific staining of the damaged brain, perhaps caused by a defective blood–brain barrier (Turkel *et al.*, 1982). In view of the absence of characteristic symptoms, the diagnosis is made almost exclusively at autopsy.

Neuropathology *Gross appearances.* The yellow discoloration of the basal ganglia (Fig. 193A and B) does not differ from that seen in classical kernicterus. Harper *et al.* (1986) found a more severe involvement of the thalamus in some cases. Ahdab-Barmada and Moossy (1984) emphasized the staining of the cranial nerve nuclei and the absence of staining of the dentate nuclei and the inferior olives. The ventricular surface may be heavily stained and may present a coarsely nodular appearance (Fig. 194).

Light microscopy. Spongiosis of the neuropil is an early change. Vacuolation of the neuronal cytoplasm and incrustation with yellow pigment can be seen in frozen sections, but rarely in paraffin-embedded material.

Electron microscopy. Ahdab-Barmada and Moossy (1984) found lamellar inclusions in affected neurons.

Kernicterus in Glucose-6-phosphate Dehydrogenase Deficiency Several cases of kernicterus have been observed in full-term infants in the absence of evidence of blood group incompatibility. The underlying abnormality in these cases was glucose-6-phosphate dehydrogenase deficiency. Erythrocytes deficient in this enzyme are unduly susceptible to environmental hemolytic agents, and ingestion or inhalation of otherwise innocuous substances may lead to massive hemolysis. The condition is familial and does occur in siblings. Most affected infants are Chinese, but isolated examples have been reported in other ethnic groups (Kaplan and Abramov, 1992). This jaundice

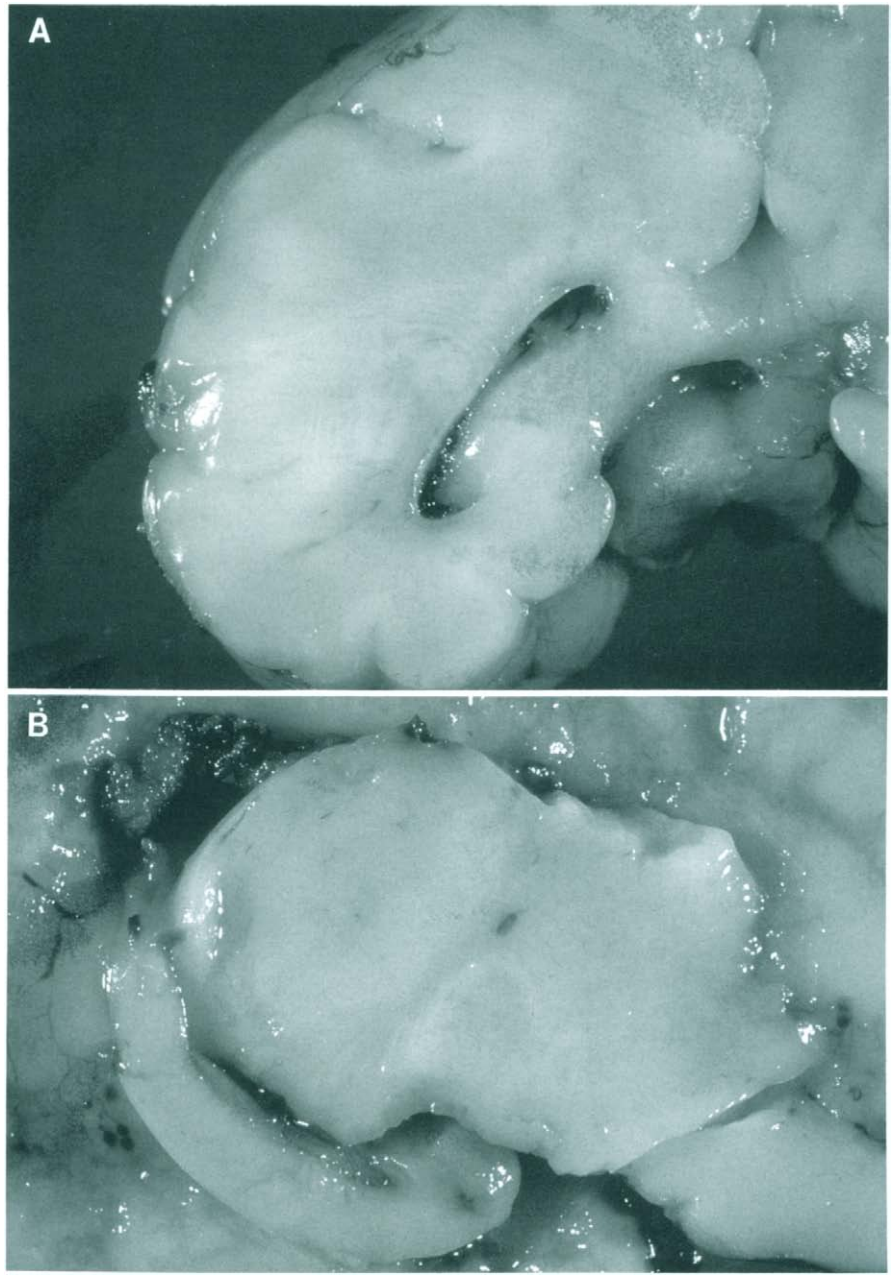


Fig. 193 Kernicterus of prematurity. Yellow discoloration (A) in the white matter and the ependyma and (B) in the basal ganglia.

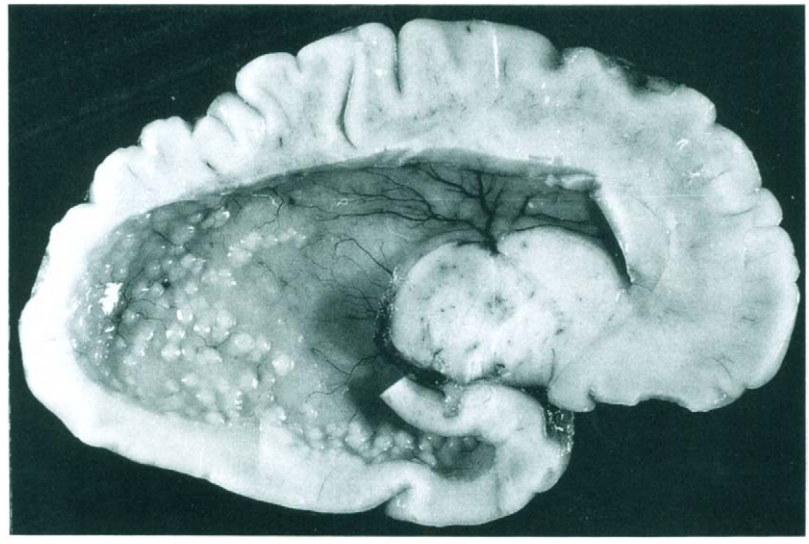


Fig. 194 Same case shown in Fig. 193. A lateral ventricle with a coarsely nodular surface.

may be severe, and as such has led to kernicterus, spastic cerebral palsy, or death (Beutler, 1991).

Late Sequelae of Kernicterus (Posticteric Encephalopathy of Pentschew)

Clinical Picture The sequelae of kernicterus manifest themselves in the form of cerebral palsy with asymmetrical spasticity, choreoathetosis, and nerve deafness (Foley, 1992). Children or young adults with athetotic-type cerebral palsy have a high risk of sudden death (Matsui *et al.*, 1992b). An absence of auditory brain stem responses was observed in patients who had suffered from severe neonatal hyperbilirubinemia (Hayashi *et al.*, 1992).

Moderate hyperbilirubinemia in full-term infants has been assumed to affect both infant behavior and brain stem conduction time (Vohr *et al.*, 1990). However, the effect of moderate hyperbilirubinemia on the IQ, postulated by some authors, has not been confirmed. A critical review of six studies involving more than 30,000 infants reveals essentially no evidence of the adverse effects of bilirubin on IQ, neurological examination, or hearing (Newman and Maisels, 1990).

Neuropathology In long-term survivors the yellow staining is no longer apparent. Atrophy can be seen in the damaged gray structures.

The brunt of the lesions falls on the globus pallidus and the subthalamic nucleus, with almost a total loss of neurons and myelin and symmetrical focal losses in the dorsal parts of the dentate nucleus as well as in the end plate of Ammon's horn. All of these lesions are accompanied by fibrillary gliosis.

Pathogenesis In an attempt to unravel the complex pathogenesis of kernicterus, the following factors should be taken into consideration: the origin of excessive bilirubin, the failure of conjugation with glucuronic acid, the binding capacity of serum albumin, the permeability of the blood–brain barrier, and the toxicity of bilirubin.

Hyperbilirubinemia in neonates arises from the excessive breakdown of red blood cells. As the fetal blood contains a higher proportion of erythrocytes than is needed in postnatal life, a considerable number of them are broken down in the first few days, an event that occasionally manifests itself in a mild "physiological" jaundice. More severe jaundice (icterus gravis neonatorum) appears as a result of massive hemolysis in blood group incompatibility.

In the normal adult bilirubin is conjugated in the liver with glucuronic acid by the action of β-glucuronidase (more precisely, glucuronosyltransferase) into a water-soluble product excreted as bile pigment. The level of the enzyme is very low in full-term infants, and even lower in those born prematurely, and does not reach normal levels until the age of about 3 months. Any bilirubin formed is circulated in an unconjugated state. Part of it is bound in the serum and only the free bilirubin is toxic. The binding capacity of albumin is low at birth, but rises rapidly in the full-term infant in the first 24 hours and reaches a plateau in 60 hours. The process is much slower in premature infants, which is a contributory factor in the kernicterus of prematurity with relatively low bilirubin levels. The binding capacity may be considerably reduced by drugs that compete with bilirubin for binding, such as salicylates and sulfonamides. Administration of these drugs has been known to precipitate or aggravate kernicterus.

Permeability of the blood–brain barrier is an essential factor in the pathogenesis of kernicterus (Wennberg *et al.*, 1991). Bilirubin is not lipid soluble, but tends to attach itself to lipid membranes, and it does not cross the intact barrier. It was assumed that the immature barrier is more permeable, but this is true only for some substances. Anoxia may be an important factor in damage of the blood–brain barrier. The toxicity of unconjugated bilirubin causes an inhibition of oxidative phosphorylation and depression of DNA and protein syntheses. The bilirubin attaches itself particularly to the mitochondrial membranes, causing vacuolation and glycogen deposition in the mitochondria (Hansen *et al.*, 1988). This may lead to destruction of multiple organelles and total disorganization of the cytoplasm, with subsequent cell death. Bilirubin also interacts with synaptic membranes (Vazquez *et al.*, 1988; Amit *et al.*, 1992). Bilirubin first seems to affect neuronal conduction before energy metabolism is impaired. Unchecked, this may lead to failure of ATP synthesis, resulting in the breakdown of all active intracellular processes (Palmer and Smith, 1990).

Kernicterus in Adults

Aside from the few patients with familial deficiency of glucuronosyltransferase, kernicterus in adolescents and adults is extremely rare. Cattan *et al.* (1952) described a case of kernicterus in a middle-aged patient with an acquired hemolytic anemia, cold agglutinins, complex neurological manifestations, and Sjögren's syndrome. Ho *et al.* (1980) found kernicterus and central pontine myelinosis in a 14-year-old boy with fulminating

viral hepatitis. Waser *et al.* (1986) saw yellow staining of the subcortical gray matter in a 47-year-old woman with severe liver disease. In all three cases there was generalized jaundice of the skin and the inner organs, as well as yellow staining of the surface of the cerebral hemispheres and of the cortical and subcortical gray matter with considerable variation in intensity. There was also marked cerebral edema and severe vasodilatation with petechial hemorrhages. Meningeal icterus is not uncommon in jaundice, as the blood–CSF barrier is permeable to bile pigments. The cranial nerves and the spinal nerve roots, the surface of the pituitary, the mamillary bodies, and the ganglion habenulae may be more deeply stained than other parts of the cerebral surface. Ischemic and hemorrhagic infarcts stain green in jaundiced patients because of the breakdown of the blood–brain barrier, which becomes permeable to bile pigments.

Light microscopy. Perivascular foci of demyelination are seen against the background of the generalized pallor of myelin. The neurons show ubiquitous degenerative changes. The glia shows reactive changes, including the oligodendroglia in the edematous parts of the white matter (Fig. 195, see color plate).

Familial Nonhemolytic Kernicterus (Crigler–Najjar Syndrome; Glucuronosyltransferase Deficiency)

Crigler and Najjar (1952) described a congenital familial nonhemolytic jaundice with kernicterus. The enzyme defect was demonstrated in the nonhemolytic bilirubinemia of Gunn rats by Carbone and Grodsky (1957). This syndrome has been subdivided into type I, which is transmitted as an autosomal-recessive trait, is generally severe, and is associated with jaundice at birth. Serum bilirubin levels vary from 300 to 735 μM and do not respond to an autosomal-dominant trait with variable penetrance, which is characterized by less severe bilirubinemia of 65–385 μM that responds to porphobilinogen administration and by absence of kernicterus. However, clinical parameters such as neurological signs do not unequivocally discriminate between types I and II (Persico *et al.*, 1991).

Clinical Picture In type I neurological symptoms appear in some patients in adolescence or adulthood after years of persistent jaundice (Galbraith *et al.*, 1992). These consist of chorea, myoclonus, spasticity, tremor, ataxia, epileptic seizures, progressive dementia, and coma. Other patients die soon after birth with typical kernicterus. Still others never develop kernicterus, although they may have some neurological disturbances.

Pathology Biliary thrombi are frequently seen in the bile canaliculi of the liver. Hemosiderosis of the spleen has been observed on rare occasions.

Neuropathology The lesions vary according to the patient's age at the time of death.

Gross appearances. Icteric staining of the cortex, thalamus, striatum, mamillary bodies, dentate nucleus, and inferior olives is seen in young patients. No macroscopic lesions are apparent in older patients.

Light microscopy. Moderate to severe neuronal loss is present in the basal ganglia. In some cases a severe loss of neurons has been observed in the lateral nucleus of the thalamus (Gardner and Konigsmark, 1969). The red nucleus is usually severely depleted. The

substantia nigra and the cerebellum are only slightly or moderately affected. Neuronal loss is accompanied by dense gliosis.

Pathogenesis In Crigler–Najjar syndrome type II point mutations were found on exon 1 of the *UGT1A* and *UGT1D* genes (Aono *et al.*, 1993). The abnormalities were single-nucleotide substitutions of G and T by C at base position 211 of *UGT1A* and at base position 395 of *UGT1D*. Patients can be homozygous for all defects. In Crigler–Najjar syndrome type I mutations in the *UGT* gene complex are the cause of the disease. A nonsense mutation was identified in exon 3 (Moghrabi *et al.*, 1993).

Kernicterus in Animals Gunn (1938) described a mutant in rats in which jaundice was inherited as a recessive trait. During postnatal development Gunn rat homozygotes exhibit marked cerebellar hypoplasia. During light microscopic examination of the neuropathological lesions, the bilirubin toxicity is particularly apparent in the cerebellum (Takagishi and Yamamura, 1993). Electron microscopy showed changes in the mitochondria, as well as an accumulation of glycogen and multilamellar cytoplasmic bodies and lipid droplets (Keino *et al.*, 1986).

The homozygotic rats show a deficiency of hepatic glucuronosyltransferase, which conjugates bilirubin and converts it into water-soluble bile pigments. The Gunn rat is a good model for investigating the bilirubin encephalopathy, and many studies discussed in the pathogenesis section were carried out on this animal.

Effects of bilirubin infusion on glucose utilization in the immature rat (Roger *et al.*, 1993) are in agreement with clinical observations that bilirubin mostly accumulates in the striatum and the cranial nerves and that the neurological sequelae of kernicterus is very often hearing loss as well as motor problems.

Melanosis of the Cerebellum (Melanosis of the Dentate Nucleus; Astrocytic Melanosis)

Melanosis of the dentate nucleus is a very rare condition devoid of clinical interest. Since its first description by Hiller (1941), several cases have been reported (Best *et al.*, 1981). Aside from the dentate nucleus, pigmentation is also found in the granular layer, particularly of the deeper parts of the lobules.

Gross appearances. The dentate nucleus and the parts of the cerebellar cortex closest to the central white matter are conspicuous in their symmetrical black discoloration. When the pigmentation of the granular layer is pronounced, it can be recognized with the naked eye. In the case reported by Best *et al.* (1981), the cerebral cortex was also visibly pigmented, admittedly only in the occipital lobe, which is usually selectively affected. The pigmentation is most marked in the depth of the sulci and may, in places, be associated with cortical atrophy.

Light microscopy. Blackish brown granules and globules of pigment are present in the dentate nucleus. Upon careful examination these are found in the granular layer in most cases. The pigment is distinctly extraneuronal and lies in close proximity to the glial nuclei, but cannot be localized with certainty in glial cytoplasm by light microscopy. Their

astrocytic localization can, however, be demonstrated in Cajal impregnations. The color of the pigment ranges from golden brown to nearly black. The granules are over 30μM in diameter, the largest being found in the dentate nucleus. The larger granules usually appear singly, while the smaller ones form clusters. They reduce ammoniacal silver nitrate (Masson–Fontana), are bleached by potassium permanganate, and are not autofluorescent. Iron stains are negative. They show the same ultraviolet absorption and X-ray diffraction patterns at 0.493 nm as melanin synthesized from dopamine. Small granules with the lipofuscin characteristic are also present. They are autofluorescent, reduce ammoniacal silver nitrate, and are not bleached by potassium permanganate.

Electron microscopy. The membrane-bound pigment particles show irregular round or polygonal profiles and can, in most cases, be localized in the cytoplasm. They have a fairly uniform electron density. This applies particularly to the larger granules. Under higher magnifications they are seen to consist of a homogeneous matrix with irregularly distributed higher densities, approximately 30 nm in diameter, as well as marginal structures lying partially in the matrix and partially in the submembranous cleft. They are round or oval, measure up to 100 nm in diameter, and resemble lipids of high electron density. The matrix also contains threads or networks of membranous, tubular, or honeycombed structures (Ule and Berlet, 1979). In other cases typical trimodal complexes of neuromelanin have been seen (Fan *et al.*, 1978; Best *et al.*, 1981).

Other Sites of Astrocytic Neuromelanosis Friede (1979) described two cases of astrocytic melanosis, in the striatum and the substantia nigra, in unrelated subjects. Both men were asymptomatic and showed no other lesions. Neuromelanin is also an important component of the astrocytic pigment in the putamen of striatonigral degeneration (see p. 565).

Pathogenesis The pigment has been identified as melanin by histochemical methods (Hiller, 1941) as well as by infrared absorption and X-ray diffraction (Ule *et al.*, 1979). The site of production is not in the normally neuromelanin-containing neurons, but in the cerebellar astrocytes. It has been assumed that this pigment arises from melanization of lipofuscin by pseudoperoxidation in the presence of a metallic catalyst. The cause of this melanization remains unknown. In view of the fact that normal neuromelanin is invariably associated with catecholamine-producing neurons, Friede (1979) suggested that a disturbance of catecholamine metabolism may be responsible for astrocytic neuromelanosis.

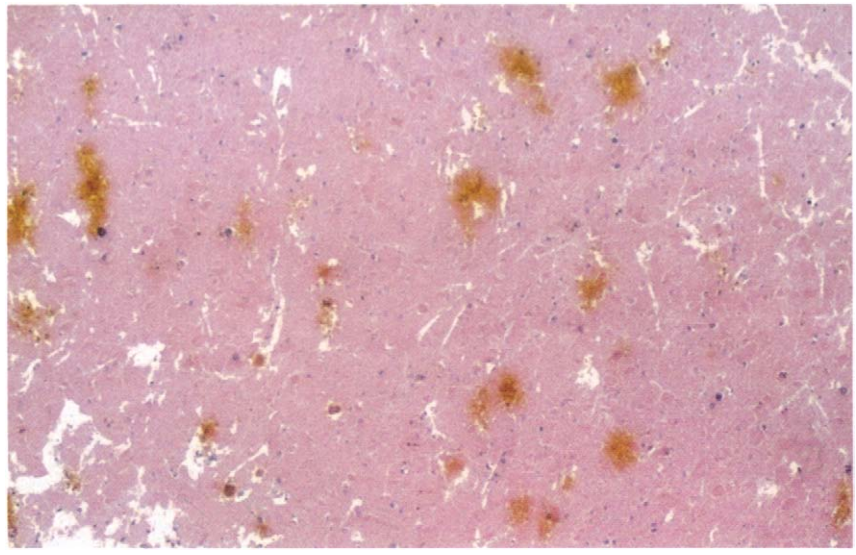


Fig. 191 Same case shown in Fig. 189. Yellowish brown pigment is visible in the area of hemorrhage. Hematoxylin–eosin stain, ×100.

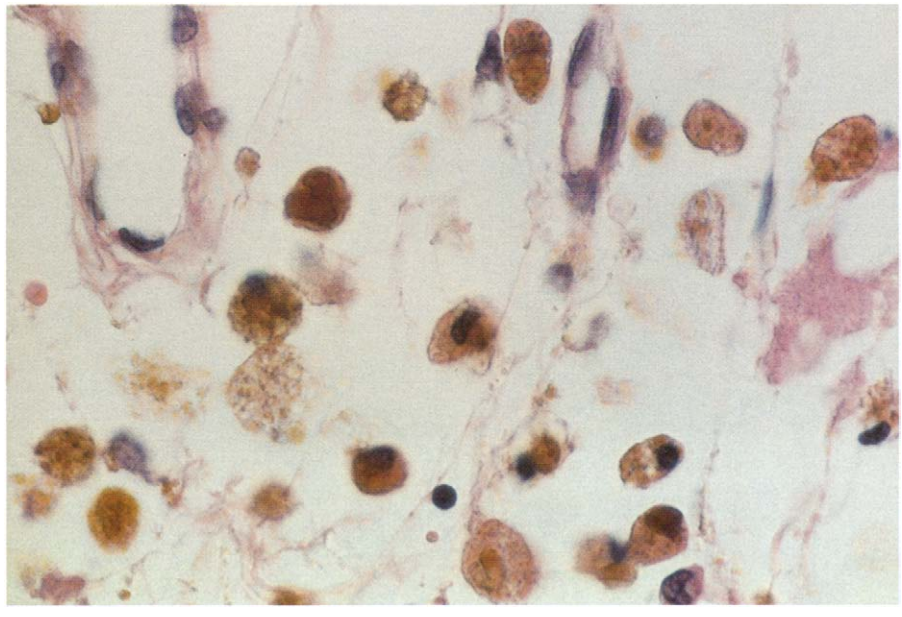


Fig. 192 Same case shown in Fig. 189. An infarct in the stage of phagocytosis. Granules of brownish yellow pigment are seen in the macrophages. Hematoxylin–eosin stain, ×700.

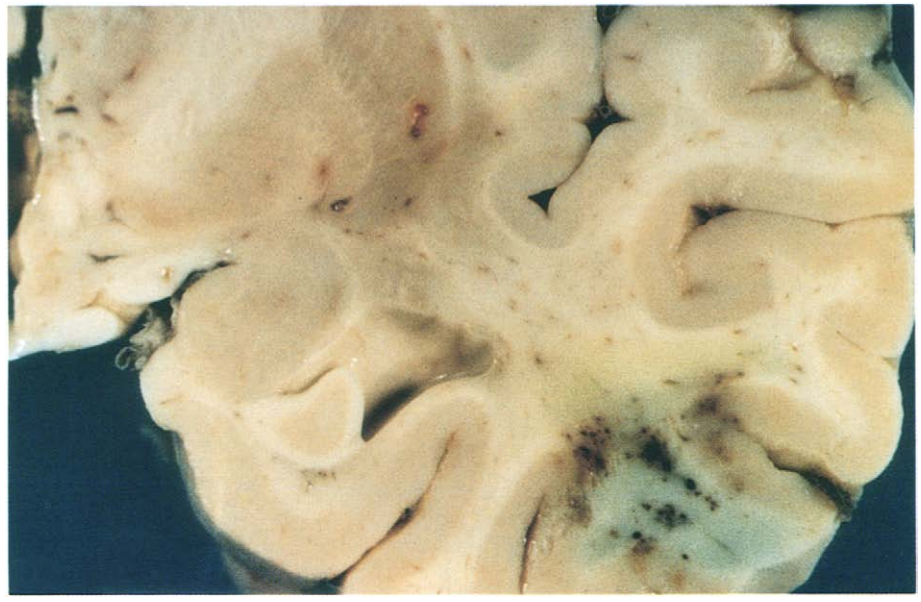


Fig. 195 A 66-year-old patient with myeloblastic leukemia. Hemorrhagic foci and areas of edema lightly stained by bilirubin. (Courtesy of E. Caputi, Buenos Aires, Argentina.)

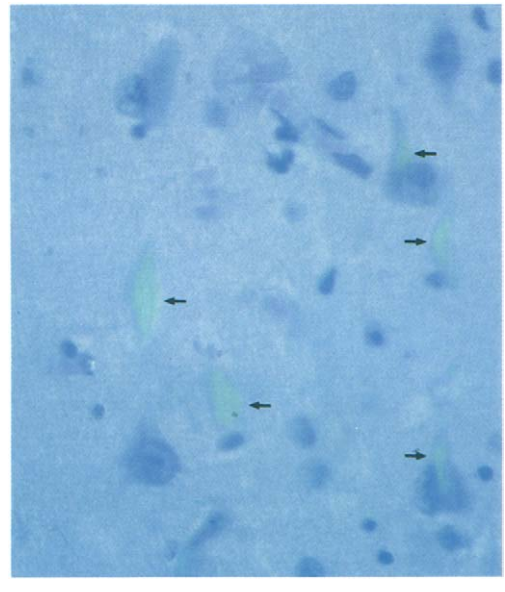


Fig. 200 Neurofibrillary tangles appear greenish under polarized light (arrows). Congo red stain, ×400.

Introduction

Within the concept of heredodegenerations, the subgroup of system degenerations occupies a special position. These are slowly progressive processes, with little evidence of active destruction and tissue reaction. These are usually symmetrical and affect selective functional structures or systems. The slowly progressive degeneration, corresponding to the protracted clinical course, ends in systemic atrophy (Spatz, 1938). Gowers (1902) introduced the term *abiotrophy* to denote the reduced vitality of a circumscribed group of neurons as an expression of premature senescence.

In spite of recent progress in genetics, our knowledge of the etiology and pathogenesis of degeneration disorders remains fragmentary. For the time being, therefore, it is impossible to classify these diseases on an etiological or pathogenetic basis. Peiffer (1984) preferred to classify them based on general pathological criteria, while Hirano and Frias-Llena (1983) and Schoene (1985) favored classification based on localization of the lesions. The latter is preferable because it facilitates correlation with the clinical symptomatology, particularly in the group of system degenerations. It is worth noting, however, that even in this group the lesions are rarely confined to a single system, and the allocation of any particular condition must be based on the system that is primarily and most severely affected.

In the evaluation of system degenerations, the problem may arise as to whether the involvement of certain neuronal chains may be the result of transneuronal (transsynaptic) degeneration. Both anterograde and retrograde transneuronal degeneration may occur in certain specific situations (Cowan, 1970). The best-known examples are atrophy of the lateral geniculate body after destruction of an optic nerve or tract and atrophy of the nuclei pontis after the loss of corticopontine tracts. A distinction is sometimes made between transneuronal atrophy and transneuronal degeneration, the former consisting of shrinkage and changing of staining properties of the perikarya and attenuation of their axons and the latter involving loss of the deafferented cells. As both processes may occur simultaneously or consecutively, the terms are often used interchangeably. Transneuronal degeneration may, in turn, lead to secondary, tertiary, or even quaternary changes (Strefling and Urich, 1982). Many degenerative diseases, similar to metabolic disorders, are associated with seizures.

In an attempt to correlate the clinical symptoms with specific lesions, the following facts must be taken into account:

1. The pathological process, whether multifocal, multisystemic, or diffuse, tends to affect more or less the entire CNS.
2. Only a limited number of lesions express themselves clinically, while others may remain asymptomatic.
3. Other factors, such as age, temporal progression, or evolution, may influence the interaction of lesions and render them symptomatic or asymptomatic (Jacob, 1982).

Furthermore, in genetic disorders affecting several members of the same family, there may be a wide range of expressivity, both in the clinical picture and in the extent and localization of the lesions. No useful purpose is served by covering this multiplicity of manifestations with the blanket term *multisystem atrophy*.

The concept of *systems* does include not only well-defined groups of neurons, along with their projections and connections, but also all those components of the nervous system that share a common neurotransmitter. Some degenerative disorders may also be associated with lesions in other organs and tissues.

Apoptosis and Growth Factors

Neuronal death, other than that due to acute necrosis, falls into two morphological patterns: the apoptotic, characterized by cell shrinkage and disintegration of the nuclear DNA, and the degenerative, which features cell swelling and disorganization of the cytoplasmic organelles (Wyllie *et al.*, 1990). The term *apoptosis* was applied originally to programmed cell death during development (Kerr and Harmon, 1991). Delayed neuronal death is characterized by primary degeneration of the cytoplasm, followed by punctate chromatin condensation (Ferrer *et al.*, 1994a). Early involvement of the cytoplasm in apoptosis is demonstrated by the direct ultrastructural observation of abnormal organelles, together with reduced MAP-2 immunoreactivity, and early destruction of tubulin, microtubules, and neurofilaments. Fragmentation of nuclear DNA into oligonucleosomal fragments occurs as a result of endonuclease activation. *In situ* labeling of nuclear DNA fragmentation is a useful tool for recognizing DNA fragmentation even in nuclei that appear normal in conventional stains, as well as in cells with punctate chromatin condensation and karyorrhectic cells, in addition to apoptotic cells (Gavrieli *et al.*, 1992).

An excess of cells is produced in the early embryonic stages, which must be reduced by elimination of large amounts of these cells. In the CNS only those neurons that survive will establish contact with their target organs, while the remaining ones undergo apoptosis. The survival of neurons depends on growth factors produced by the target organs and perhaps also by some supporting cells. Of the large number of known growth factors, the family of neurotrophins is of particular importance to the nervous system (Mendell, 1994). This consists of four closely related proteins: the nerve growth factor (NGF), the brain development neurotrophic factor (BDNF), and the neu-

rotrophins NT3 and NT4/5. Each of these binds to receptors on neuronal processes, which fall into two groups: the nonspecific low-affinity receptor P75 and the specific high-affinity receptors Trk A, B, and C. NGF binds to Trk A, BDNF and NT4/5 bind to Trk B, and NT3 binds mainly to Trk C, although it also has some affinity for Trk A and B. Both the high- and low-affinity receptors are essential for the full functional capacity of neurotrophins. Only the neurons dependent on NGF for their growth and maintenance have been adequately mapped out. These include the neurons of the sympathetic chain (Koike *et al.*, 1994), the small sensory neurons of the cholinergic root ganglia (Vogel, 1993), and the neurons of the cholinergic basal forebrain nuclei (the nucleus basalis of Meynert, the nucleus of the diagonal band of Broca, and the medial septal nucleus). Work on the identification of other growth factor–receptor symptoms is in progress.

In a degenerative, rather than developmental, situation loss of a previously established contact with the target organ may lead to apoptotic neuronal death. Experimentally, the destruction of a growth factor or its receptor by the use of specific antibodies will cause apoptosis in the appropriate neuronal system (Deckwerth and Johnson, 1993). The possibility that loss of a neurotrophin or its receptor may occur spontaneously, or may be genetically programmed, in human degenerative disease requires further investigation.

Repair Mechanisms of DNA

A breakthrough was made with the knowledge that many diseases that impair the repair of DNA play a part in pathogenesis. Evidence of faulty repair was obtained by exposing fibroblast cultures of patients with xeroderma pigmentosum to ultraviolet or ionizing radiation (Cleaver, 1968).

A further milestone in the pathogenesis of the degenerative diseases of the nervous system was achieved as early as the assessment in Huntington's chorea of an autosomal gene disorder linked to a chromosomal region. After this step the number of the search for the genetical links proceeded at an accelerated pace. The complete physical characterization of a gene involves three essential steps: (1) mapping, (2) cloning, and (3) sequencing.

Meanwhile, for most of the metabolic and degenerative diseases of the CNS, the characterization of the responsible genes has been established. Rapid advances in molecular genetics may further elucidate variants of already nosologically defined neurodegenerative diseases. Thus, the spectrum of neurodegenerative diseases could still increase unforeseeably.

1. In photoreactivation the damaged DNA reverts to its normal chemical state without the removal or exchange of any material. The existence and importance of this pathway in humans are controversial.

2. In excision repair damaged single strands of DNA are sequestrated and replaced with a new sequence of bases using the opposite strand of DNA as a template. Various enzymes of different specificities and mechanisms are required for the removal of the excised segment.

3. Postreplication repair is a complex system in which replication can take place despite the presence of damaged or incompletely excised sequences of DNA. The incorporation of these sequences may lead to local mutation, favoring neoplastic transformation.

Faulty repair of DNA has hitherto been established in three conditions affecting the nervous system: xeroderma pigmentosum, ataxia–telangiectasia, and Cockayne's syndrome. Doubts have been expressed, however, as to whether the disorder fully accounts for the neurological manifestations (Thomas, 1992). In view of these reservations, we have refrained from treating these conditions in a separate chapter and have adhered to the principle of morphological classification.

Degenerative Diseases of the Cerebral Cortex and the White Matter

Alzheimer's Disease (Presenile Dementia; Alzheimer's Dementia; Senile Dementia of the Alzheimer Type)

Alzheimer (1907) described the brain of a demented 51-year-old woman in whom he found, in addition to numerous SPs, the NFTs, which are now known by his name. The relatively young age of this patient led to the concept of "Alzheimer's disease" (AD) being equated with presenile dementia and opposed to senile dementia (Kraepelin, 1910). Meanwhile, all senile cases characterized by the presence of numerous plaques and NFTs are called "senile dementia of the Alzheimer type" (SDAT), as there seems to be no consistent morphological difference between the presenile and senile forms and because the clinical manifestation also forms a continuum, with transitional cases between the two types. Nevertheless, several authorities still accept the validity of a separation of presenile disease with onset of symptoms before the 65th year of age from senile dementia. Celsis *et al.* (1990) postulated that the old clinical distinction between senile and presenile dementias deserves new consideration.

There are some clinical, and perhaps neuropathological, criteria to distinguish subgroups of AD. On neurobiological grounds AD has been divided into two types: AD1, with quantitatively less severe neuropathological and neurochemical abnormalities, and AD2, with more pronounced ones. The clinical separation into mild and severe forms (Bondareff *et al.*, 1987), however, appears less justified, as these may simply represent different stages of the same disease process. Recent molecular genetic findings appear to justify a distinction between early- and late-onset cases, at least in familial AD.

Clinical Picture Clinically, AD is characterized by progressive dementia that manifests itself by a gradual loss of intellectual faculties, impairment of social and professional performance, and disturbance of memory. In addition, there may be early deficits in odor detection and discrimination (Talamo *et al.*, 1989), impairment of abstract thinking, and loss of judgment. Focal symptoms of aphasia, apraxia, agnosia, and increasing personality changes complete the picture. The CSF is normal; routine EEG recording shows no specific abnormalities. Cranial CT and nuclear MRI may initially be normal, but on repeated examination usually show progressive brain atrophy, most severely of the temporal and parietal lobes. Occasionally, brain imaging investigations may suggest that one hemisphere is more severely affected than the other.

The disease may begin at any age between 35 and 90 years, but in most cases manifests itself after the age of 65. According to the criteria proposed by the U.S. National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the clinical symptoms allow only for a diagnosis of "probable Alzheimer's disease." This may be supported by a positive family history if the disease had been confirmed neuropathologically in other family members. A diagnosis of definitive AD requires neuropathological confirmation. While these criteria are now widely accepted, there are still considerable discrepancies between the clinical and morphological diagnoses (Joachim *et al.*, 1988b). In only one study was a clinical diagnostic accuracy of 100% obtained in 26 neuropathologically confirmed cases of AD after extensive clinical, laboratory, and CT investigation.

The average duration of the disease is about 7 years. In the Western Hemisphere AD is the fourth or fifth most common cause of death in the elderly. Findings in centenarians (Fayet *et al.*, 1994) indicate that the prevalence of AD is not increased in people of very advanced age, as compared with that found between the ages of 80 and 90. It has been demonstrated that a large percentage of very old people show no clinical signs of AD and that the disease is not a necessary feature of the normal aging process (Wernicke and Reischies, 1994; Ebly *et al.*, 1994). Given the frequency of AD in the aging population, from 10% of those over 65 years of age up to 47% of those over 85, occasional coincidence with other diseases is to be expected.

Patients with idiopathic Parkinson's disease develop dementia more frequently than the general population. In many cases this may be explained by the simultaneous presence of Alzheimer-type changes. The frequent coincidence of both Lewy bodies and Alzheimer-type pathology in the same brain led to speculations that one type of change may accelerate or predispose the brain to the other (Bancher *et al.*, 1989). However, these assumptions were not confirmed by others (Jendroska *et al.*, 1994; Quinn *et al.*, 1986). Cortical changes of AD have been described in "Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy" (Pericak-Vance *et al.*, 1991). Coexistence of AD with CJD is a rare phenomenon, but has been reported on several occasions (Brown *et al.*, 1990; Powers *et al.*, 1991; Muramoto *et al.*, 1992).

Neuropathology *Gross appearances.* Generalized cortical atrophy is apparent (Fig. 196) and may reach a loss of one third of the brain weight. In some cases there is frontotemporal or parieto-occipital accentuation of atrophy. Occasionally, no atrophy

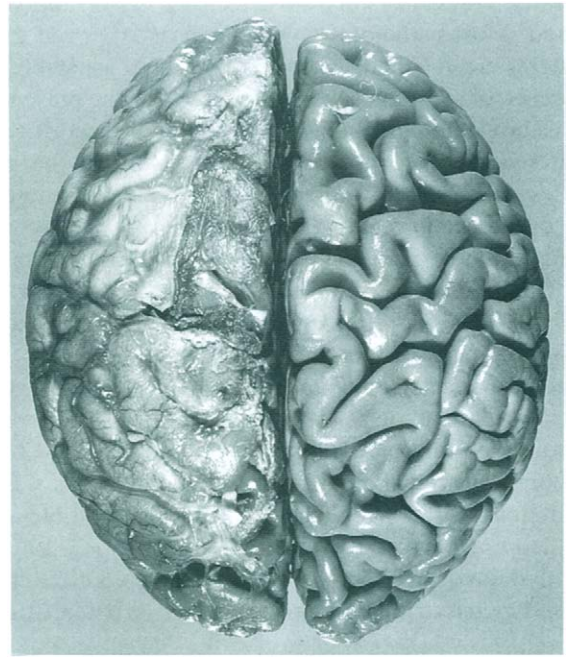


Fig. 196 Alzheimer's disease. The meninges have been stripped from the right cerebral hemisphere to show the narrow gyri and gaping sulci.

is obvious; in other cases atrophy does not exceed that expected per the age of the patient. Atrophy is generally more severe in cases with early-onset disease. In some patients brain atrophy is distributed asymmetrically. The topography of the most severe atrophy is consistent with the earliest clinical signs of localized brain dysfunction (Bugiani *et al.*, 1991).

Light microscopy. The characteristic histopathological feature of AD is the presence of Alzheimer's NFTs in the neuronal perikarya and the dendrites and SPs ("neuritic" plaques) in the neuropil. Less disease specific but pathogenetically important are the loss of cortical and subcortical neurons and synapses. Additional features are granulovacuolar neuronal degeneration (GVD), mild gliosis, and amyloid angiopathy. Khachaturian (1985) attempted to define the criteria necessary for a histological diagnosis of AD. His proposals require examination of the frontal, temporal, and parietal cortices, hippocampus, amygdala, basal ganglia, substantia nigra, cerebellar cortex, and spinal cord. For the diagnosis of AD, plaques with or without tangles must be found in any field the size of 1 mm^2. In patients under the age of 50 years, two to four plaques per field are sufficient. Between 50 and 65 years eight or more plaques and some tangles are required. Between 66 and 75 years the minimal plaque count is 10 per field. In patients over 75 tangles may be absent, but plaques must exceed 15 per field. Based on these histopathological criteria, the diagnosis of AD may be made with reasonable certainty even in the absence of clinical data. In cases with a well-docu-

mented clinical history of dementia, the histological criteria may be somewhat relaxed. Most pathologists will diagnose AD even in the absence of dementia if these criteria are fulfilled, since those cases presumably represent preclinical disease; the absence of symptoms would not preclude the presence of disease.

Neuropathological diagnosis is particularly difficult in the higher age groups, as the differences in quantitative findings between the demented and some nondemented cases with "age-related" changes decrease with age. Hansen *et al.* (1988) could find no difference in brain weight, numbers of plaques and NFTs, and densities of the neurons and the glia in AD patients aged over 80 years compared with nondemented age-matched controls. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has developed a practical and standardized neuropathology protocol for the postmortem assessment of dementia. A minimum of five anatomical regions are designated for microscopic study: the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, hippocampus and entorhinal cortex, and midbrain, including the substantia nigra (Mirra *et al.*, 1991). Comparison of the assessments of 24 different neuropathology centers that applied the CERAD protocol for 3 years showed significant differences. This indicates the need for improvement in the standardization of neuropathological evaluation (Mirra *et al.*, 1994). An analysis of several widely used staining methods showed that plaque differentiation may be severely compromised by tissue processing and staining protocols (Halliday *et al.*, 1992, 1994).

Neurofibrillary Tangles NFTs are best demonstrated in frozen sections by the silver impregnation techniques of Bielschowsky or von Braunmühl (Fig. 197) and, in paraffin sections, with one of the modifications of Palmgren's method (Cross 1982). NFTs are flame shaped in the pyramidal cells of the cerebral cortex (Fig. 198A,B), but usually globoid in neurons of the basal ganglia (Fig. 199). NFTs are not specific for the AD process; globoid intraneuronal tangles occur in subcortical neurons in other diseases such as progressive supranuclear palsy, postencephalitic parkinsonism, or subacute sclerosing panencephalitis without accumulation of SPs. In some elderly patients with AD, NFTs may be largely or entirely absent.

After cell death NFTs remain visible extracellularly as "ghost tangles" for some time while they are slowly dissolved. In H&E stains they appear bluish and, in later stages, weakly eosinophilic. They take up Congo red stain and show the characteristic birefringence under polarized light (Fig. 200, see color plate). Some authors prefer to use thioflavine S fluorescence under ultraviolet light (Rudelli *et al.*, 1984) for their identification. Lately, the silver impregnation method after Gallyas (1971) has found favor in some research centers. This technique demonstrates the finest fibrils that form the subunits of the NFTs and its sensitivity is surpassed only by immunohistochemistry for specific components of the NFTs. The CERAD group recommends the widely used modified Bielschowsky silver impregnation technique as the standard method for the detection of SPs and NFTs. The thioflavine S preparation viewed under ultraviolet light is accepted as an alternative stain for plaques and tangles as well as for CAA (Mirra *et al.*, 1991). NFTs initially occur in the transentorhinal region, where spare tangles occur almost ubiquitously in the aged population. From here the pathological process spreads to the entorhinal region (Braak and Braak, 1993). The site of predilection of the NFTs is the limbic

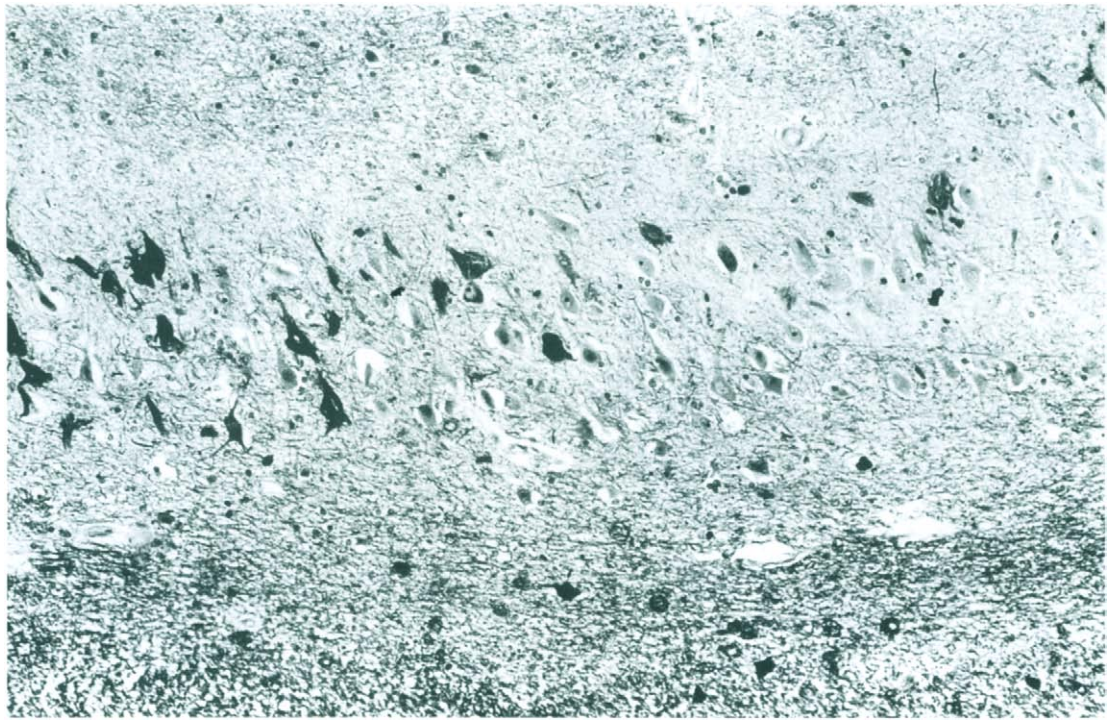


Fig. 197 Alzheimer's disease. Sector H2 of the hippocampus with numerous Alzheimer's neurofibrillary tangles. Bielschowsky stain, ×350. (Courtesy of R. M. Torack, St. Louis, Missouri.)

system. In AD Sommers' sector of Ammon's horn, the glomeruli of the second layer, the entorhinal cortex, and the amygdala are severely affected. Other commonly involved areas are the posterior part of the cingulate gyrus, the posterobasal parts or the temporal lobe, and the adjacent occipital cortex (Hardy *et al.*, 1986). These areas also suffer the most severe neuronal loss. NFTs may also be present in the diencephalon, particularly the nucleus tuberis, the mamilloinfundibular and mamillobasal nuclei, and the serotoninergic raphe neurons (Halliday *et al.*, 1992).

Braak and Braak (1991) proposed a staging of the progression of Alzheimer-type changes based on the number and distribution of NFTs and argyrophilic dendrites, the so-called "neuropil threads." In stages I and II these changes are found only in the transentorhinal cortex and in stages III and IV they also occur in the limbic cortex, while in stages V and VI the isocortex is widely involved. Dementia is usually present in cases of stages V and VI. In contrast, Vermersch *et al.* (1992) found that, despite a relatively identical disease duration with apparently global involvement of the cerebral cortex, the distribution of neurofibrillary degeneration varied significantly across cortical areas and displayed a striking heterogeneity of patterns. In AD no NFTs are found in the Purkinje cells, the lateral geniculate body, or the spinal and sympathetic ganglia. The giant pyrami-

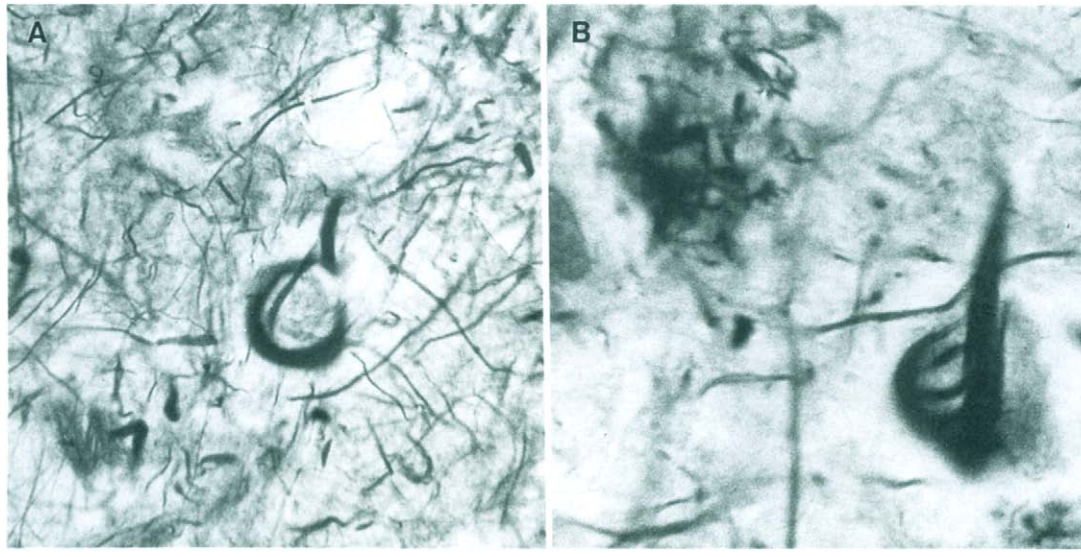


Fig. 198 Alzheimer's neurofibrillary tangles (A) in the basal ganglia and (B) in the cerebral cortex. von Braunmühl stain, ×750.

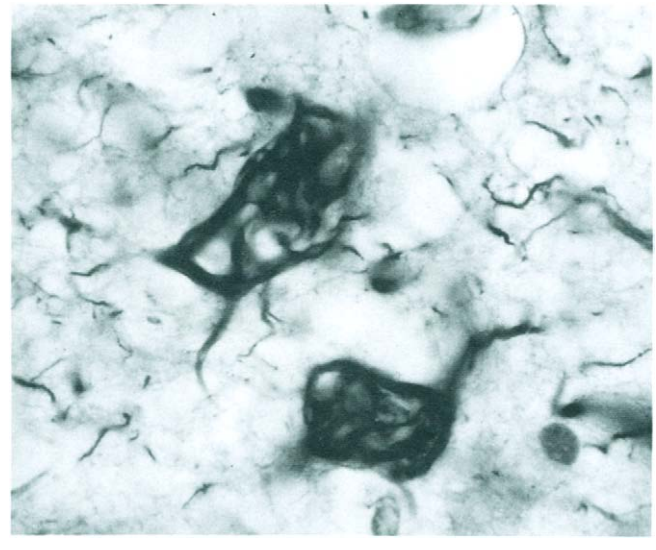


Fig. 199 Ball-shaped (globoid) neurofibrillary tangles. von Braunmühl stain, ×750.

dal cells of Betz and the anterior horn cells of the spinal cord are also largely spared. However, tangle-bearing neurons in motor nuclei of the anterior horn and laminae V and VI of the dorsal horn have been reported (Nölken *et al.*, 1992). Nasal epithelium from patients with AD showed increased reactivity to neurofilament antibodies; abnormal neuronal structures and extensive accumulations of neurites were also observed (Talamo *et al.*, 1989).

Ultrastructurally, the NFTs consist of bundles of paired filaments twisted around each other as a double helix ("paired helical filaments"; Kidd, 1963) (Fig. 201). These paired helical filaments differ from any cytoskeletal element hitherto described in the nervous system. They are also present in the neuritic processes involved in SP formation. Each filament is 10–13 nm thick, the length of each spiral being 80 nm (Kidd, 1963; Terry, 1963). Straight filaments, 10 nm in diameter, may be interspersed between the paired helical ones. Tangles consisting almost exclusively of straight filaments were described by Selkoe (1989).

Histochemical investigations have shown the presence of glycoprotein or glycolipid components in the NFTs (Mann *et al.*, 1988). Immunohistochemically, they share epi-

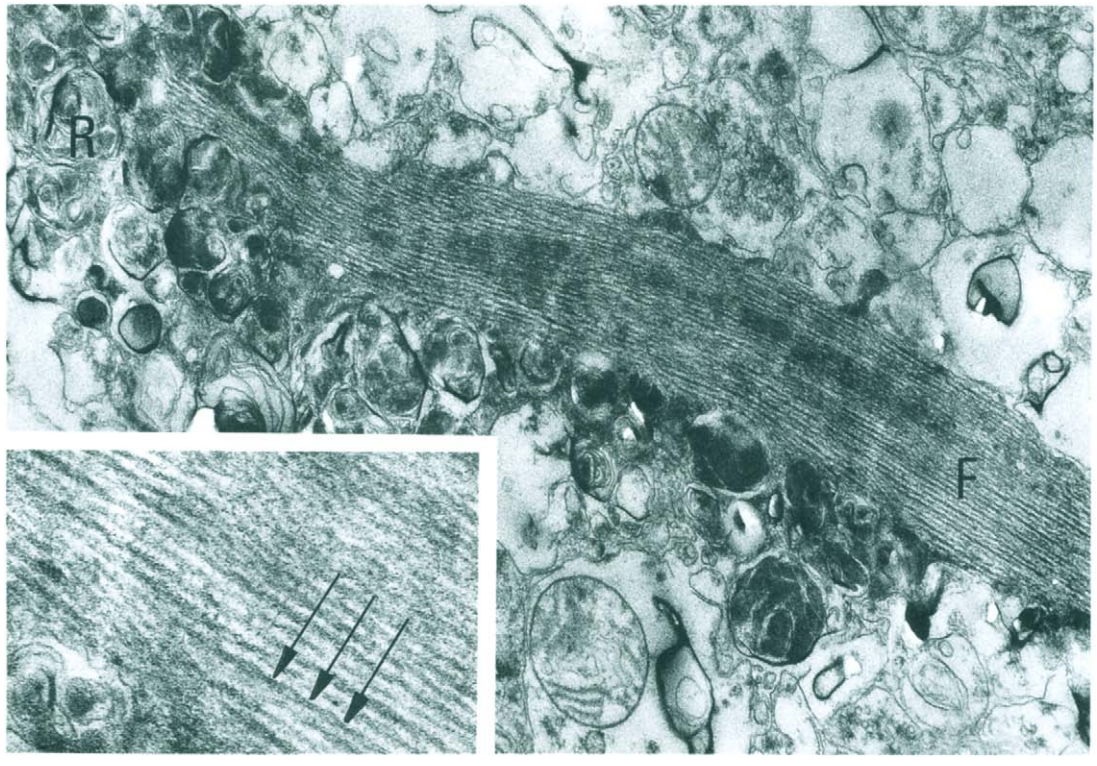


Fig. 201 An Alzheimer's neurofibrillary change in a dendrite, ×18,000. (Inset) Constrictions (arrows) in paired helical filaments, ×36,000.

topes with several cytoskeletal elements and a tubulin-associated unit (Cork *et al.*, 1988; Grundke-Iqbal *et al.*, 1986). NFTs also contain fragments of the β-amyloid precursor protein (APP) (Masters and Beyreuther, 1986). These fragments of APP obtained from NFTs seem to be heterogeneous in structure. Immunohistochemical reactions do not allow quantitative estimations; while the paired helical filaments undoubtedly contain epitopes of normal cytoskeletal elements, no conclusion is possible as to whether these or other proteins are the principal component of the NFTs.

The identity of the composition of the NFTs with normal cytoskeletal elements has been postulated by many authors, who considered the τ-protein to be the main constituent of these tangles (Grundke-Iqbal *et al.*, 1986). The τ-protein is a highly heterogeneous microtubule-associated protein with a molecular mass of 50,000–64,000 Da that serves as a potent promoter of tubulin assembly *in vitro* and is encoded by a single gene (Neve *et al.*, 1986) located on the long arm of chromosome 17. In human brain tissue the normal τ-protein is highly enriched in neurons, as has been observed by both immunocytochemical studies and *in situ* hybridization (Kosik *et al.*, 1989), as well as in some subsets of glial cells (Kosik, 1993; Riederer and Innocenti, 1991). Its complexity arises from the expression of alternatively spliced isoforms (Delacourte *et al.*, 1990; Dickson, 1992) as well as from phosphorylation at multiple sites. Grundke-Iqbal *et al.* (1986) demonstrated that τ in AD is abnormally phosphorylated when converted into the subunits of paired helical filaments.

Cammarata *et al.* (1990) indicated that epitopes of cytoskeletal proteins are hidden by the β-pleated conformation of SP and NFT components. Treatment of tissue sections with formic acid discloses neurofilament epitopes in paired helical filaments and results in a twofold increase of the number of τ-reactive neuropil threads and plaque-related neurites.

The monoclonal antibody Alz50, which detects a group of 65- to 70-kDa proteins (designated A68) at much higher levels in AD than in normal brain tissue (Wolozin *et al.*, 1986), has also been shown to react with τ (Nukina *et al.*, 1988). It has been suggested that the A68 proteins in AD cortex are, in fact, abnormally phosphorylated forms of τ, thus accounting for their slower electrophoretic migration compared to normal τ (50–60 kDa). Immunostaining with τ antibodies allows the recognition of a very early stage of tangle formation, which precedes the morphological appearance of argyrophilic fibrillary inclusions.

The monoclonal antibody AT8 recognizes two Ser–Pro motifs of abnormally phosphorylated τ-protein (Biernat *et al.*, 1992). AT8 labels have been described not only in tangle-bearing nerve cells, but also in neurons in a "pretangle" stage (Braak *et al.*, 1993). Bondareff *et al.* (1994) postulated that different stages of neurofibrillary degeneration can be understood as a sequential stripping of paired helical filaments in which the loss of amino-terminal epitopes, followed by a loss of phosphorylated epitopes, results in the appearance of dispersed extracellular tangles containing paired helical filament core epitopes.

Subcellular fractionation of concentrated NFTs produces a characteristic protein with a molecular mass of 50 kDa (Selkoe *et al.*, 1987), which may be related to a disturbance of axoplasmic transport.

In AD approximately 60% of the NFTs that were stained with an antipaired helical filament serum can also be identified by using ubiquitin antibodies (Leigh *et al.*, 1989). In addition, these antibodies label SPs and dystrophic neurites (Bancher *et al.*, 1991). Ubiquitin epitopes are linked to the neurofibrillary changes in the perikaryon and to neuritic changes of SPs where they do not colocalize with β-amyloid immunoreactivity (He *et al.*, 1993).

Despite being a major NFT constituent, studies have suggested that ubiquitination is a late phenomenon in tangle biogenesis, being preceded by the accumulation of hyperphosphorylated τ-protein. As mentioned, antiubiquitin immunostaining does not identify all tangles in cases of AD (Brion *et al.*, 1989), and in most cases identifies fewer tangles than silver impregnation or anti-τ protein staining (Lantos *et al.*, 1992; Lowe *et al.*, 1993). Since ubiquitin is usually not conjugated to the cytoskeletal proteins from which the NFTs are derived, its accumulation is probably related to the process of neuronal degeneration rather than to the formation of NFTs. In addition to increased aluminum concentrations (Dedman *et al.*, 1992), iron levels have been demonstrated to be significantly higher in NFTs (Good *et al.*, 1992).

Senile Plaques SPs are demonstrated by using silver impregnation techniques (Fig. 202), which highlight the argyrophilic degenerating neurites within and surrounding plaques. Hedreen and Price (1988) maintained that the method revealing the highest number of neuritic plaques is the quick silver method. Other methods demonstrating both diffuse and classic SPs are the silver–copper method, the method of Campbell *et al.* (1987), and immunocytochemistry for amyloid β-protein (Aβ), the main component of plaque amyloid. Additional stains to demonstrate plaque amyloid include PAS, fluorescence with thioflavine S, and birefringence with green dichroism with Congo red viewed under polarized light (Fig. 203). Neuritic plaques containing a central amyloid core are known as classical plaques, while those without a core are called primitive. The latter only consist

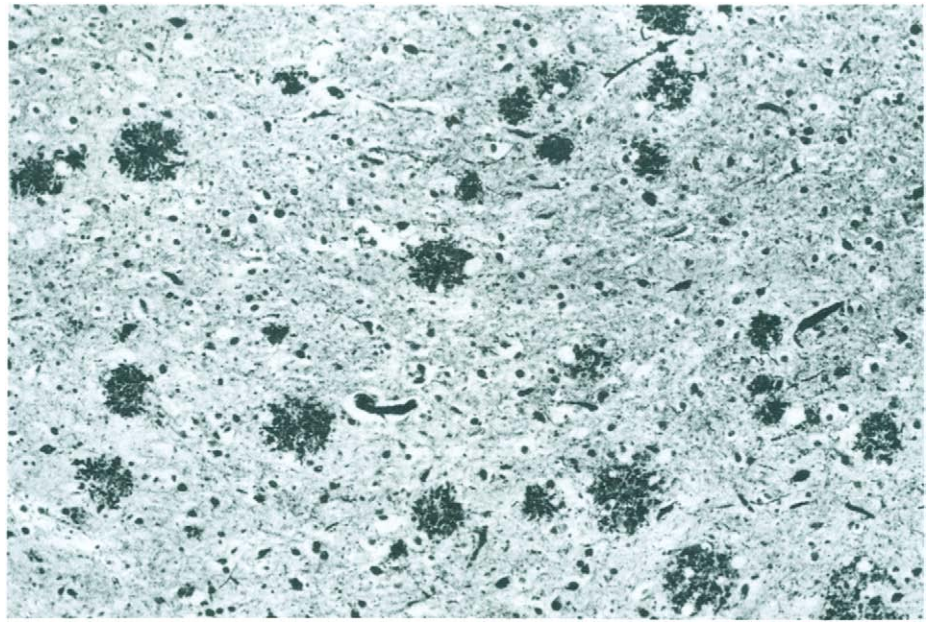


Fig. 202 Alzheimer's disease. Neurons senile plaques in cerebral cortex, von Braunmühl, ×100.

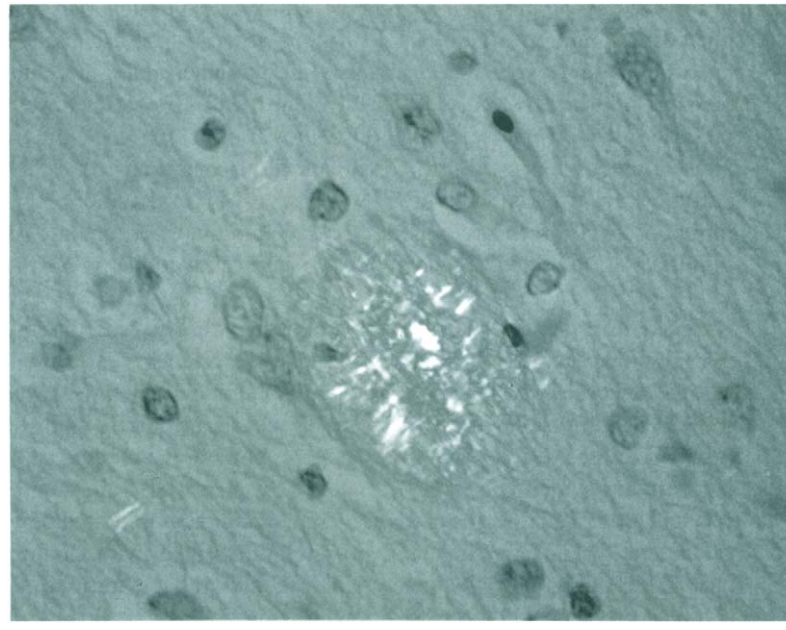


Fig. 203 Alzheimer's disease. Senile plaque showing birefringence and green dichroism in polarized light. Congo red, ×500.

of a condensation of fibrils, while the classical plaques contain a dense, homogeneous, congophilic core (Fig. 204A,B, see color plate). Plaques are 20–200 μm in diameter and are composed of amyloid, degenerating as well as sprouting neuronal processes, reactive astrocytes, and microglia. Primitive plaques contain degenerate cell processes and aggregates of membranous and pleomorphic residual bodies (Fig. 204A, see color plate). Classical plaques contain accumulations of amyloid fibrils both in their central cores and interspersed between other peripheral structures (Fig. 204B, see color plate). The core consists of radially arranged fibrils emerging from the center. The individual fibrils form hollow tubes, consisting of helically wound filaments, in which each spiral is built up of five globular subunits (Miyakawa *et al.*, 1986). The periphery of the plaque consists of dendrites and axons of neurons. Iron accumulates around and within SPs (Connor *et al.*, 1992), while they appear to contain no aluminum (Chafi *et al.*, 1991).

SPs are found predominantly in the cerebral cortex. In early studies there were no significant quantitative differences in their distribution between the frontal, temporal, and occipital cortices or the cingulate gyrus. The hippocampus and the amygdala are consistently affected and SPs may also be found in the basal ganglia, thalamus, and hypothalamus. Numerous SPs as well as neuropil threads were found throughout the various subdivisions of the pulvinar (Kuljis, 1994). Cerebellar SPs were considered by some to be rare in AD and were observed only in atypical cases (Vakili and Muller, 1987); later studies

have demonstrated that they are frequently present in the molecular layer, although they are sparse (Wisniewski *et al.*, 1989; Mann *et al.*, 1990; Suenaga *et al.*, 1990).

Plaques in the white matter show little cellular reaction and are devoid of the neuritic component (Rudelli *et al.*, 1984).

Antibodies against Aβ detect not only neuritic plaques with or without well-defined amyloid cores but also "diffuse" or "preamyloid" plaques that contain few, if any, surrounding dystrophic neurites or activated glia. Such amorphous deposits were not detected by the classical amyloid stains, presumably because the individual molecules of protein are either not folded into a β-pleated configuration or are only loosely aligned so that Congo red cannot detect them (Mann *et al.*, 1990). They are found in the cerebral cortex, cerebellum (Joachim *et al.*, 1989), diencephalon (Ikeda *et al.*, 1989), striatum (Braak and Braak, 1990a), and hypothalamus (Standaert *et al.*, 1991). In some familial cases they are especially abundant in the pallidum (Iseki *et al.*, 1990). Electron microscopy of diffuse plaques revealed only a few degenerating neurites without apparent fibrillary amyloid; in more advanced structures small degenerating neurites were often seen with apparent amyloid fibrils (Yamaguchi *et al.*, 1991).

Diffuse, primitive, and classical types of Aβ deposits may occur in clusters that vary in dimension from 200 to 6400 μm (Armstrong *et al.*, 1993). Isolation and sequencing of Aβ from plaque and blood vessel amyloid of AD and Down syndrome brains led to the identification of the much larger APP. The monomeres of Aβ, which coalesce to form extracellular amyloid, consist of 40–45 amino acids and have a molecular mass of approximately 4 kDa. These are peptide fragments of APP, of which three isoforms (of 695, 751, and 770 amino acids) are predominant in the brain.

The distribution of Aβ-reactive plaques resembles that of the NFTs. Occasional cases show accumulation in the frontal rather than temporal cortex. Mainly sulcal deposition of Aβ corresponds with the preponderance of classic plaques in the sulci (McKenzie *et al.*, 1992).

Coria *et al.* (1988) and Rozemuller *et al.* (1989) have described apo E immunoreactivity in amyloid deposits of cortical plaques of AD and CJD. In addition, Kalaria *et al.* (1991) found that serum amyloid P immunoreactivity is present in neurons showing neurofibrillary pathology as well as in the extracellular remnants of degenerated neurons.

A variety of neurotransmitters and neurotransmitter-associated enzymes can be demonstrated in the neuronal processes surrounding the SPs, including acetylcholine and substance P. Their distribution corresponds to the normal topography of the transmitters in the cerebral cortex; thus, there is no specific "innervation" of the SPs. Dystrophic neurites also immunoreact with antibodies against growth-related molecules, including epidermal growth factor receptor (Birecree *et al.*, 1988), synaptic and axonal proteins, and cytoskeletal proteins (Masilah *et al.*, 1994). The presence of growth-associated protein (GAP43) indicates that some of these neurites are sprouting.

The role of different plaque types in the pathogenesis of AD and their clinical significance remain controversial. Many authors have reported that diffuse plaques are predominant in nondemented elderly individuals, whereas neuritic plaques are more characteristic of AD (Dickson *et al.*, 1988); nevertheless, diffuse plaques are also the most common plaque type encountered in AD (Joachim *et al.*, 1989). Many of the so-called "diffuse plaques" in AD brains represent tangetially sectioned SPs. There is evi-

dence that diffuse plaques may be an early stage in the development of SPs; in Down syndrome patients, who regularly develop the full histopathology of AD by age 50, diffuse plaques were found ubiquitously in those who died at an earlier age (Mann *et al.*, 1989).

Neuropil Threads Neuropil threads, or "curly fibers," are filamentous structures scattered throughout the neuropil and may occur independently of SPs or NFTs (Braak and Braak, 1988), although they tend to be more numerous where tangles are present. Neuropil threads occur in allocortical and isocortical regions with a variable distribution and density in different cortical areas and layers, with cortical lamina C being most severely affected. It has been suggested that the accumulation of neuropil threads in cortical plaque-containing areas may depend on the amount of plaque amyloid in addition to NFTs (Probst *et al.*, 1989). However, others have found no relationship between neuropil threads and plaque amyloid (Hauw *et al.*, 1990). Ultrastructural studies of neuropil threads have shown them to be composed of paired helical filaments and straight filaments (Yamaguchi *et al.*, 1990; Perry *et al.*, 1991). They stain positively with anti-τ and antiubiquitin antibodies.

Neuronal Loss Neuronal loss (Fig. 205) affects particularly the superficial layers of the cortex and accounts, on average, for 36% of the neuronal population. The surviving neurons show an abnormally small nucleolus and a reduction in cytoplasmic RNA (Mann *et al.*, 1985). Comparative studies of chromatin show a decrease in the amount of euchromatin with a corresponding increase in heterochromatin in neurons and glial cells.

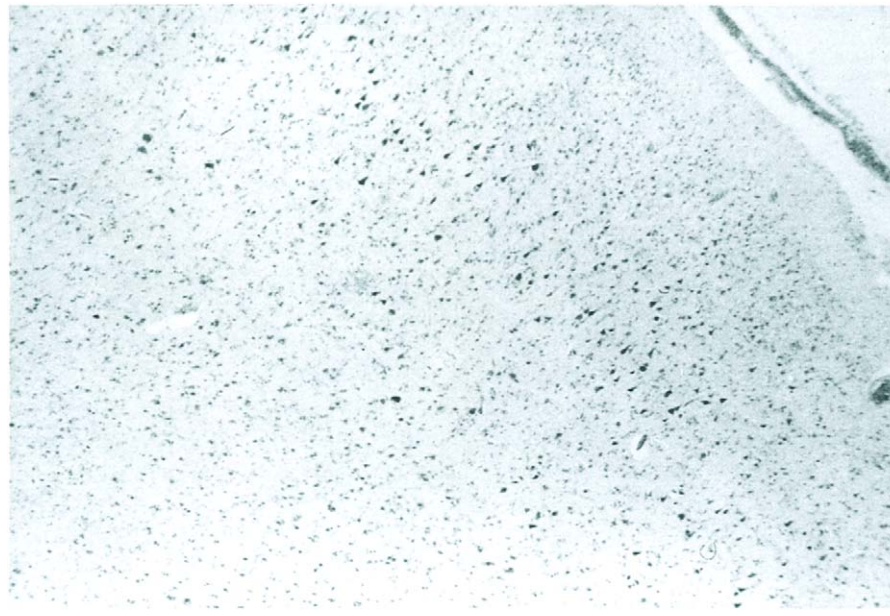


Fig. 205 Alzheimer's disease. A diffuse neuronal loss in the parieto-occipital cortex. Nissl stain, ×80.

This can be interpreted as an expression of reduced transcription capacity (Cervós-Navarro, 1984). Parvalbumin-immunoreactive neurons in the neocortex show resistance to degeneration in AD, suggesting that the pathological process in AD affects specific neuronal subtypes with particular morphological and molecular characteristics (Hof *et al.*, 1991).

In type AD2 the lesions are more widespread. The adrenergic neurons of the locus coeruleus may be reduced in 80% of the normal population (Chan-Palay, 1989). Whitehouse *et al.* (1982) pointed out that the cholinergic neurons of the nucleus basalis of Meynert showed selective severe degenerative changes in AD. McGeer *et al.* (1984) confirmed that the loss of cholinergic cells in AD considerably exceeds that observed in the normal aging process (Lowes-Hummel *et al.*, 1988). The degree of decrease in the number of large neurons in the neostriatum is similar to that in the nucleus basalis (Oyanagi *et al.*, 1989a); both cell populations are considered to be cholinergic and to express the only NGF receptors found in the brain. The loss of large neurons may be even more marked in the nucleus accumbens (Oyanagi *et al.*, 1991b). The dendrites of the cortical pyramidal cells show a considerable loss of branching in Golgi preparations (Fig. 206). These dendritic abnormalities have been observed in cortical pyramidal as well as non-pyramidal neurons (Ferrer *et al.*, 1990). The dendrites of Purkinje cells are affected to a lesser degree.

Neurotransmitters In the field of neurotransmitters, depression of cholinergic activity is the most striking feature. The reduction in choline acetyltransferase is twice that to be expected from neuronal loss in the cortex. The presynaptic cholinergic terminals are particularly affected (Wood *et al.*, 1983). Projection neurons producing monoamine transmitters and cortical neurons producing glutamate, GABA, somatostatin, neuropeptide Y, corticotropin-releasing factor, substance P, and other neuromodulators are also affected. A reduction in neurotransmitter activity has also been well established in the dopaminergic, noradrenergic, and serotoninergic systems (D'Amato *et al.*, 1987). There is no unequivocal correlation, however, between the degree of dementia and the abnormalities of the monoaminergic transmitter system. Reductions in muscarinic receptors in the hippocampus and GABA receptors in the caudate nucleus have been found (Cowburn *et al.*, 1987).

Granulovacuolar Degeneration A constant but rather nonspecific finding in AD is the presence of GVD in pyramidal cells of the hippocampus, first described by Simchowicz (1911). This change is easily seen in preparations stained with H&E, as well as in silver impregnations (Fig. 207). The majority of centrally located granules are immunoreactive for ubiquitin (Okamoto, 1991). They are not congophilic, however. GVD is most commonly found in sector C1 of the hippocampus and the subiculum, but may also occur in C2 and the endorhinal cortex. Occasionally, NFTs and GVD occur in the same cell (Tomonaga *et al.*, 1975).

Electron microscopy has contributed little to the understanding of granulovacuolar degeneration. The vacuoles are membrane bound (Hirano *et al.*, 1968a). Their central core consists of amorphous, granular, osmiophilic material. These granules have been considered to be an age-related type of autophagosome (Okamoto *et al.*, 1991).

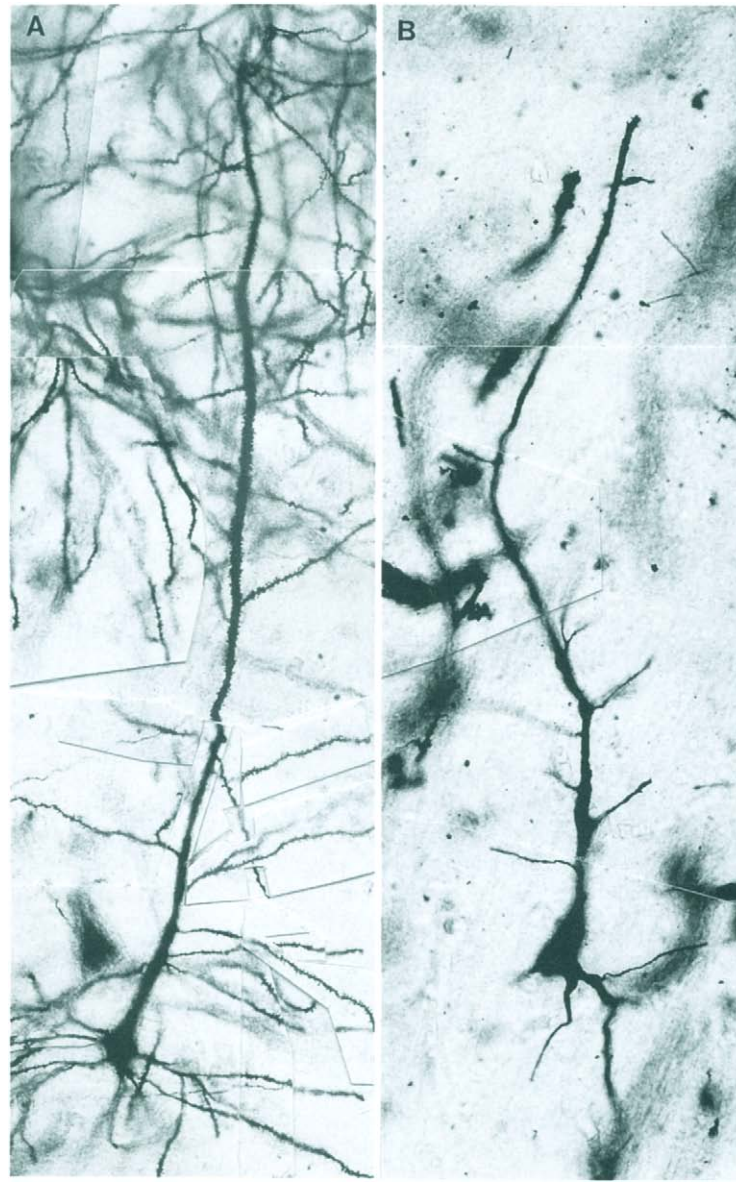


Fig. 206 Pyramidal cells in the cerebral cortex. (A) A normal control. (B) Alzheimer's disease showing striking abnormalities in the dendritic branches. Golgi impregnation, ×500.

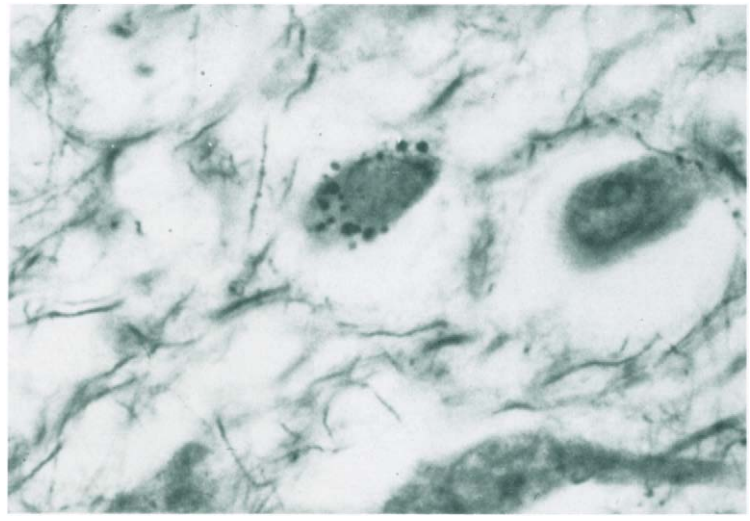


Fig. 207 Alzheimer's disease. Granulovacuolar degeneration of the neuronal cytoplasm. von Braunmühl stain, ×500.

Glial Changes In AD, reactive astrocytes are conspicuous in the orbitofrontal cortex and in the hippocampus, particularly around blood vessels. Forty-eight percent of the examined vessels showed perivascular gliosis, compared to 17% in age-matched controls (Mancardi *et al.*, 1983). Glial reaction is prominent around the NFTs, particularly when they occur extracellularly (Yamaguchi *et al.*, 1991). MAO-B activity is expressed at higher levels in fibrillary astrocytes in or around SPs, suggesting that these cells metabolize exogenous amines occurring in the SPs (Nakamura *et al.*, 1990). In some cases Wegiel and Wisniewski (1994) found prominent Rosenthal fibers and corpora amylacea. The gene for GFAP is overexpressed in AD; GFAP mRNA and GFAP protein are increased in AD patients compared to controls (Sajdel-Sulkowska *et al.*, 1988; Clark *et al.*, 1989). S100-immunoreactive glia are also increased in AD (Jorgensen *et al.*, 1990). Transferrin expression is stimulated in astrocytes in the white matter of the AD brain (Connor *et al.*, 1992). Cortical astrocytes express heat shock protein at high levels (Renkawek *et al.*, 1994).

Microglia seem to play an important role in the processing (Fig. 208) and subsequent deposition of Aβ and in plaque formation (Wisniewski *et al.*, 1992; Schumacher *et al.*, 1994). αB-crystallin, a member of the small heat shock protein family, is expressed in astrocytes and microglia, mainly in areas of SPs and NFTs (Renkawek *et al.*, 1994).

Several alterations of microglia have been described in AD (Rogers *et al.*, 1988; Dickson *et al.*, 1993). The striking increase in activated microglia could be a response to neuronal degeneration in this disease (Carpenter *et al.*, 1993). Alternatively, an explanation of activated microglia may be offered by the close relationship of activated microglia to

SPs, as reported by a number of investigators (Haga *et al.*, 1989; Itagaki *et al.*, 1989; Perlmutter *et al.*, 1990). Vandenabeele and Fiers (1991) postulated that amyloidogenesis results from an interleukin-1/6–mediated acute phase reaction. Reactive microglial cells are cerebral representatives of the immune system's monocytes and macrophages that contribute to inflammatory responses. McGeer and Rogers (1993) found an abnormally low number of microglial cells in AD patients with coexistent rheumatoid arthritis, who had been taking antiinflammatory drugs over long periods.

Increased major histocompatibility complex (MHC) class II glycoprotein expression on microglial cells has been observed in the AD brain (Styren *et al.*, 1990; Tooyama *et al.*, 1990; Perlmutter *et al.*, 1992). In AD retinas this has been demonstrated even in the absence of lymphocytic infiltrates, suggesting that the pathogenesis of retinal changes in AD may be distinct from that occurring in the brain (Liew *et al.*, 1994).

Amyloid Angiopathy In the majority of cases of AD, amyloid deposits are also found in the blood vessels (Fig. 209). The deposition of amyloid begins in the outer layers of the muscular coat of the media of longer and smaller arteries. Fragments of APP coalesce in the neighborhood of pericytic, myocytic, and astrocytic basement membranes to form typical amyloid fibrils. This tendency of amyloid to precipitate on the basement membranes is a feature of all human amyloidoses.

The relationships between amyloid angiopathy and NFTs, on the one hand, and amyloid angiopathy and SPs, on the other, have often been discussed. Some authors found histochemical differences between the amyloid in vessels and SPs. Some of these may be explained by the fact that serum amyloid protein with a molecular mass of 35 kDa does not cross the blood–brain barrier to be incorporated into the plaques. Wisniewski *et al.* (1992) demonstrated that in the cerebral cortex, pericytes and perivascular microglial cells are producers of amyloid fibrils of blood vessel walls. These authors distinguished semicircular or circular thickening of vascular walls containing amorphous material and amyloid fibrils, tuberous amyloid deposits (Fig. 210), and amyloid "stars" composed of predominantly radial arrangements of bundles of amyloid fibrils (Fig. 211). It appears that mononuclear cells of the walls of the vessels, some of which contain amyloid, migrate to the neuropil to transform to microglia, and may get involved in amyloid fibril formation and the development of classical and primitive plaques. In the leptomeningeal vessels Aβ deposits in the media of arteries and arterioles seem to originate from smooth muscle cells (Wisniewski and Wegiel, 1994).

Miscellaneous A large number of reported changes in AD should probably be considered as epiphenomena. *Leukoaraiosis* may be present in primary degenerative SDAT but does not seem to occur more frequently in AD patients than in elderly controls. The pathogenesis of leukoaraiosis in AD is likely to be multifactorial and may include cerebral atrophy, amyloid angiopathy, and in some cases hypertensive arteriolosclerosis (Verny *et al.*, 1991). *Corpora amylacea* in AD brains seem to occur more frequently and may display higher variability in their immunoreactivity to several antibodies (Singhrao *et al.*, 1993). Fischer *et al.* (1990) found a reduction in the net *vascular density* specific to the basal forebrain region and increased kinking and looping of vessels in the hippocampus of AD brains. Mancardi *et al.* (1980) showed a significant difference between patients

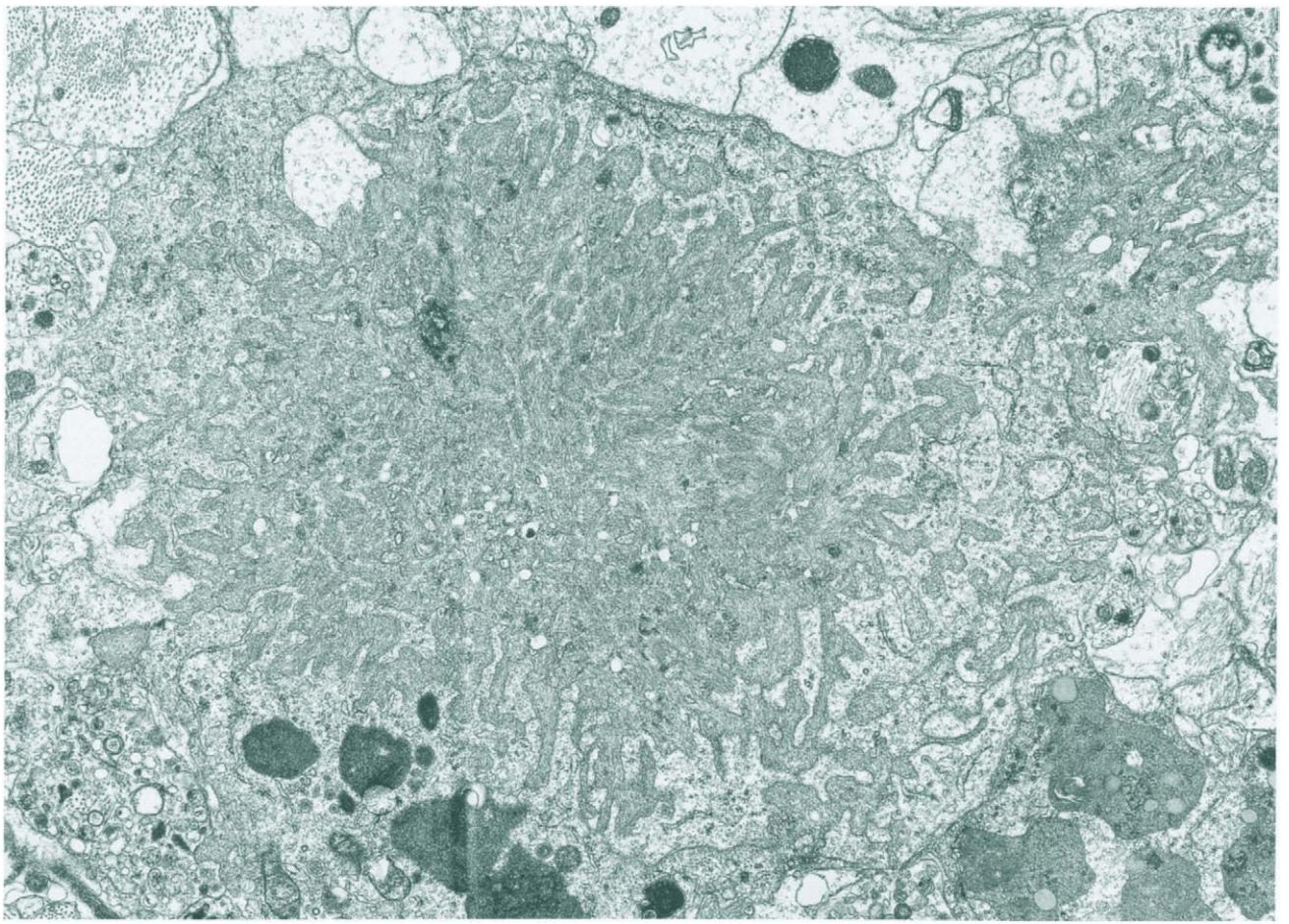


Fig. 208 An amyloid "star" almost completely isolated from the surrounding neuropil by microglia in the cerebral cortex of a patient with Alzheimer's disease. The cytoplasm of microglia is relatively rich in rough endoplasmic reticulum. Deep fingerlike channels formed by microglial membranes and smooth endoplasmic reticulum are filled with parallel-running bundles of amyloid fibers. Densely packed amyloid bundles are in the center of the amyloid star. Very little contact occurs between the astrocytic processes and the amyloid star, ×11,200. (Reproduced from Wisniewski *et al.*, 1990.)

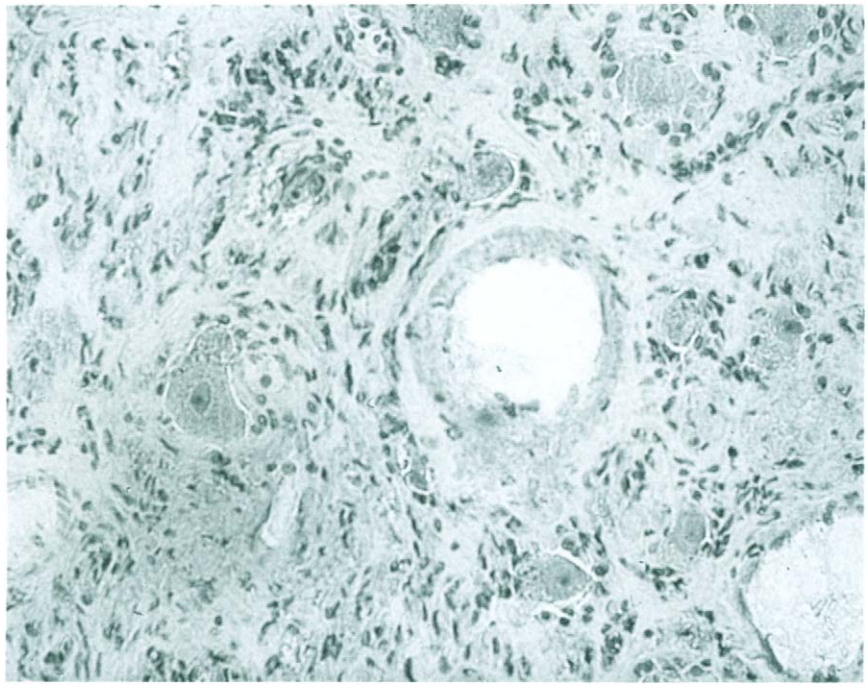


Fig. 209 Alzheimer's disease. Amyloid deposits. Congo red stain, ×220.

with AD and controls with regard to width and surface area of the basement membranes of cerebral capillaries and venules. Electron microscopy reveals fusion of amyloid fibrils with the basement membrane as well as alterations of basement membranes in the absence of amyloid accumulation. Perlmutter *et al.* (1994) suggested that the physicochemical process of amyloid formation, rather than amyloid deposition, may be responsible for basement membrane pathology. *Hirano bodies* are found predominantly in the CA sector of the hippocampus of the normal brain. Frequently, in AD they are displaced to the stratum pyramidale from their usual position in the stratum lacunosum. These bodies contain epitopes related to microfilaments, neurofilaments, and microtubules (Muñoz *et al.*, 1993).

Acetylcholinesterase and *cholinesterase* were found to associate with straight filaments in NFTs, neuropil threads, and dystrophic neurites (Moran *et al.*, 1994). Calbindin D-28k immunoreactivity is reduced in the cerebral cortex of AD patients, particularly in the plexus of the molecular layer and the vertical bundles of the cellular layers (Ferrer *et al.*, 1993b). Baum *et al.* (1992) found that an antiserum against *casein kinase* II stained NFTs intensely. Purified paired helical filaments, however, did not contain casein kinase II, suggesting that this enzyme is extraneously deposited onto the NFTs. Saito *et al.* (1993) found that calcium-activated neutral proteinases, which are considered to be key enzymes of calcium-induced neuronal degeneration, are elevated threefold in the prefrontal cortex in patients with AD. However, they were also significantly elevated, but to a lesser degree, in brain regions with mild AD pathology where there was no overt neuronal degen-

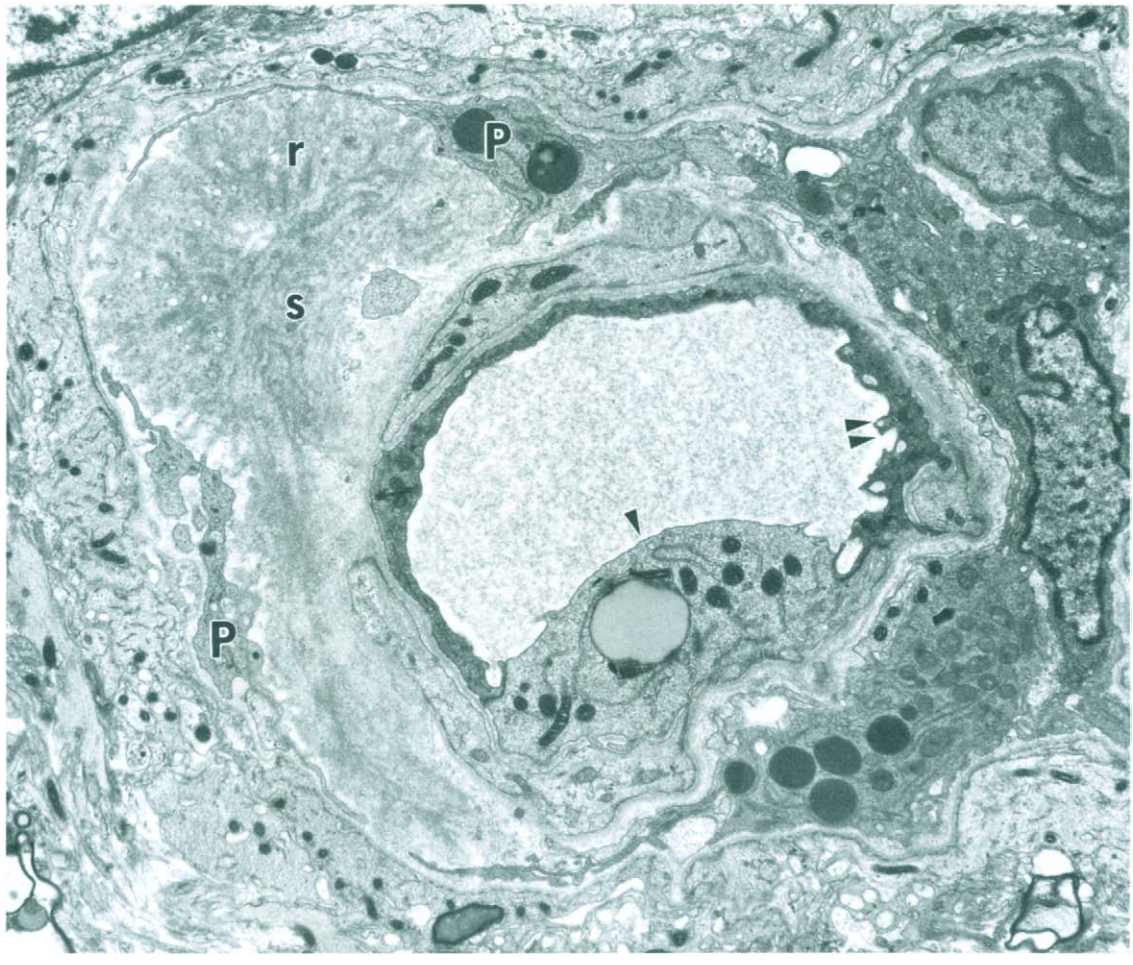
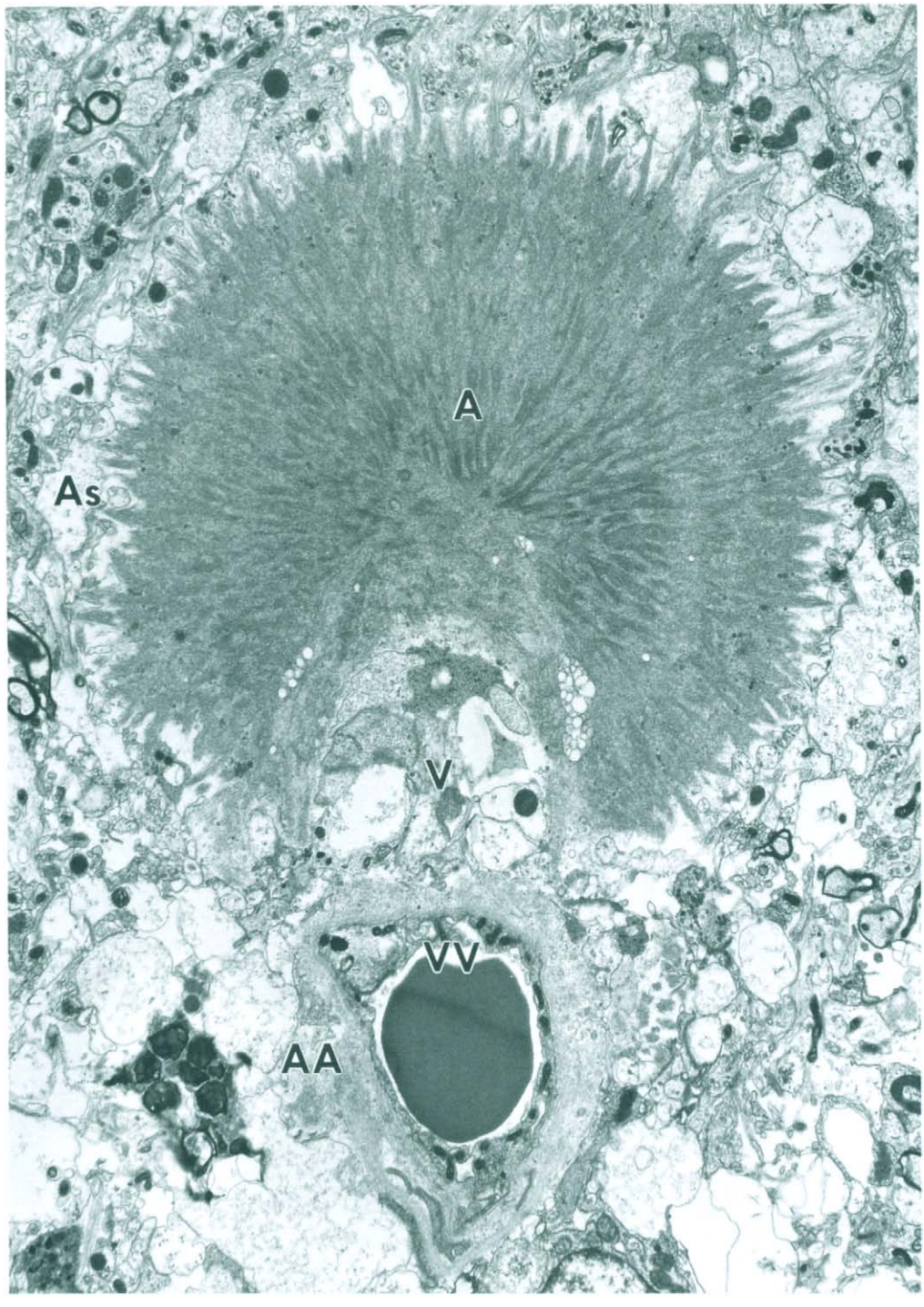


Fig. 210 A tuberous amyloid deposit covered by perivascular cell processes (P). Bundles of amyloid fibrils arranged in striatal (s) and radial (r) fashion are embedded in amorphous material. Normal (arrowhead) and dark (double arrowhead) endothelial cells, ×7656. (Reproduced from Wisniewski *et al.*, 1990.)

eration. Kalaria *et al.* (1993) found increased levels of *antithrombin III* and assumed that this protein may also play a role in the pathogenesis of cerebral amyloidosis. Abnormalities of *membrane phospholipids* have been reported (Farooqui *et al.*, 1988). The activity of phosphofructokinase, a glycolytic enzyme, is reduced to 10% of normal levels (Sima *et al.*, 1987). Abnormalities of cell membrane proteins also occur in nonneural cells (e.g., erythrocytes). Antibodies to GM_1 *gangliosides* have been repeatedly demonstrated in the serum of patients with AD (Chapman *et al.*, 1988). Nakamura *et al.* (1994) demonstrated an abnormal distribution of clathrin in AD, where it constitutes coated vesicles.

Polyglucosan bodies are frequently seen in AD (Fig. 212). They differ from those in age-matched controls (Gertz *et al.*, 1985) by their much higher number and more variable


A
As
V
VV
AA

immunoreactivity, suggesting that they may derive from several sources, including both neuronal and glial cell lines, presumably as a result of the degenerative disease process.

In the motor cortex the *transferrin*-to-iron ratio increases with normal aging, but it decreases dramatically in AD. In the entire cerebral cortex ferritin decreases with normal aging; this decrease is exacerbated in AD, except in the occipital cortex.

Pathogenesis The greatest source of controversy about the pathogenesis of AD derives from attempts to integrate the observed morphological and biochemical changes into a causal, or at least temporal, sequence of pathogenetic events.

The role of NFTs in the pathogenesis of dementia appears limited; NFTs also occur in degenerating neurons in other diseases (e.g., progressive supranuclear palsy) and may be absent in elderly patients with otherwise typical AD. In several classical studies it was found that the loss of memory and cognitive functions correlates well with the number of NFTs and SPs (Wilcock and Esiri, 1982). The density of SPs and NFTs revealed by anti-τ immunocytochemistry also correlated with the severity of the intellectual dysfunction (Delaere *et al.*, 1989). Both NFTs and SPs are found in limited number in normal aging brains. In older patients with Down syndrome, they may be even more abundant than in typical AD, sometimes without being associated with deterioration of the patient's mental status. A generalized disturbance of protein synthesis in AD expresses itself as a reduction in the size of the nucleolus. However, morphometric studies comparing tangle-bearing neurons with neighboring unaffected ones (Gertz *et al.*, 1989) revealed no differences in the size of cells, nuclei, or nucleoli.

The finding of APP mutations as the presumed cause of early-onset familial AD in several families has focused much attention on the role of APP and its metabolism in the pathogenesis of AD. Neurotoxic effects of APP peptides have underlined the potential key role of APP. However, in contrast to Down syndrome, the gene dose for APP in AD is not altered (Podlinsky *et al.*, 1987), and there is no specifically altered expression of one APP mRNA in AD. APPs are metabolized in alternative pathways. As a membrane protein approximately 30% of APP is cleaved just outside the membrane-spanning region within the Aβ peptide; the remaining APPs are reinternalized and metabolized in lysosomes, where potentially amyloidogenic intact Aβ fragments are apparently generated. Whether a misbalanced APP catabolism is the cause of AD or whether Aβ accumulation is only an epiphenomenon of the disease is still a foremost issue in AD research. Neurons treated *in vitro* with APP fragments exhibit the morphological and biochemical characteristics of apoptosis, including membrane blebbing, compaction of nuclear chromatin, and internucleosomal DNA fragmentation (Loo *et al.*, 1993), and the neurotoxic activity of synthetic Aβ peptides in vitro is associated with their fibrillogenic capacity. However, *in vivo* studies on Aβ neurotoxicity have not proved conclusive (Forioni, 1993). Correla-

Fig. 211 A perivascular amyloid star (A) attached to the obliterated vessel (V). The second vascular profile (VV) shows only minimal amyloid fibril infiltration (AA). There is a characteristic radial arrangement of bundles of amyloid fibrils in the star. There is also striatal distribution of amyloid fibrils in the place where these fibrils infiltrate the basal lamina. Also shown is a mantle of astrocytic processes around the star (As), ×9000. (Reproduced from Wisniewski *et al.*, 1990.)

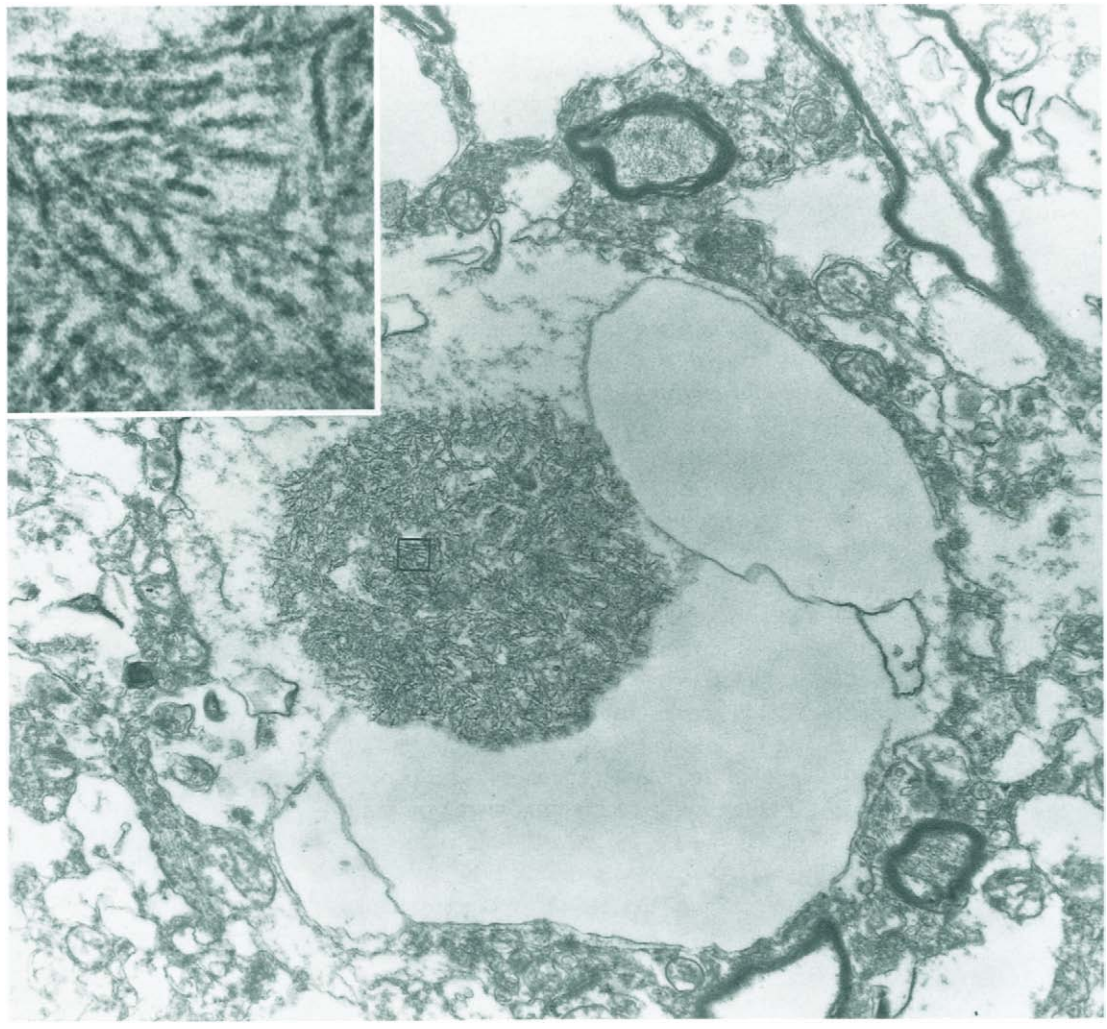


Fig. 212 Alzheimer's disease. A polyglucosan body with amylopectin-like fibrils, ×11,900 (inset ×22,100).

tive and single-case studies have shown that large diffuse Aβ deposits do not necessarily induce an intellectual impairment (Delaere *et al.*, 1991).

Although deficits in hippocampal and cortical choline acetyltransferase levels and shrinkage and loss of cholinergic projection neurons in the basal forebrain should contribute to the progressive memory impairment associated with the disease, there is no evidence that a loss of cholinergic neurons is the triggering factor for dementia. Masliah (1994) suggests that some abnormal neurites in the plaque are sprouting axons that even-

tually degenerate. An inflammatory reaction appears to be associated with SPs (Blass, 1993; Selkoe, 1993), which could induce a series of neuropathological events leading to amyloidogenesis and neuronal death. Still, there remains the crucial question as to the specific causative factor initiating the pathogenic process in the brains of AD patients; an opening of the blood–brain barrier in patients with AD has been disputed (McRae and Dahlström, 1992).

The possibility of a slow viral infection has also been considered, possibly being supported by the combination of a genetic predisposition and the decline of immunological competence with advancing age. However, despite numerous attempts, no experimental transmission of AD has ever been successful. The finding of aluminum accumulation in neurons bearing NFTs has led to the hypothesis that AD may be caused by aluminum toxicity, but the evidence for this is inconclusive. The nature and consequence of the selective accumulation of iron and aluminum, both of which are highly reactive and potentially toxic metals, are unknown.

Fibrillary tangles composed of an abnormally phosphorylated form of the microtubule-associated τ-protein may bind metal ions, thus causing a blockage of τ binding sites, which may catalyze the abnormal accumulation of τ within the neuronal perikarya. However, the only human neurological condition known to be caused by parenteral administration of aluminum is dialysis encephalopathy, observed particularly in areas where the aluminum content of the local water is high. This condition is reversible and does not exhibit the morphological features of AD. On the other hand, aluminum can produce a wide range of lesions in experimental animals (Erasmus *et al.*, 1993). Neurofibrillary degeneration has been induced in rabbits by intravenous or intracerebral injection of soluble aluminum compounds, such as aluminum maltol (Katsetos *et al.*, 1990; Langui *et al.*, 1990), although the tangles produced consist of straight, not paired, helical filaments. It has been shown that the 200-kDa neurofilament protein binds aluminum stoichiometrically. This observation led to two views: one, that the presence of aluminum in the brain may bind the protein and catalyze aggregation into tangles; the other, that wherever there is an accumulation of neurofilaments, aluminum will adhere to them nonspecifically. Thus, the increased content of this metal appears to be either an epiphenomenon or, at best, a contributory factor in the pathogenesis of AD.

It has also been suggested that head injury may precipitate or aggravate the development of AD. The evidence is anecdotal and difficult to evaluate. The effects of repeated head trauma, such as that which occurs in boxers, has been quite well documented. In autopsy studies of the brains of retired boxers with progressive mental deterioration, lesions of AD were found. In a detailed study of 15 cases, Corsellis *et al.* (1973) found numerous NFTs, but no SPs. In reviewing the same material using immunohistochemical methods, Roberts *et al.* (1990) demonstrated numerous diffuse plaques reacting with an antibody against Aβ. The appearance of these plaques was identical to that of the diffuse plaques of AD (Ikeda *et al.*, 1989).

Molecular Genetics The genetics of AD is complex, but over recent years it is being better understood. Several gene loci on chromosomes 21, 19, and 14 are involved (Clark and Goate, 1993; Owen *et al.*, 1994). To date, approximately 100 large multigeneration families with inherited AD have been reported. A clear distinction must be made between

familial AD following a mendelian pattern of inheritance and the predominant sporadic form of late-onset AD.

In view of the invariable appearance of Alzheimer-type pathology in middle-aged patients with Down syndrome (trisomy 21), particular attention has been focused on the *APP* gene located on this chromosome (St. George-Hyslop *et al.*, 1987). A point mutation at codon 717 causing a single amino acid substitution close to the carboxy terminus of the Aβ peptide was the earliest mutation to be found in some families (Goate *et al.*, 1991; Chartier-Harlin *et al.*, 1991). Mutations at two further sites of APP, at codons 670/671 and 692/693, are associated with early-onset disease (Crawford *et al.*, 1992). Families with APP mutations typically show a disease onset around 50 years of age. Despite much publicity, few more than a dozen families with APP mutations have been documented, and it is believed that APP mutations occur in less than 10% of the cases of early-onset familial AD and less than 0.5% of all AD cases.

Genetic analysis of a large number of AD families has clearly demonstrated that the disease is heterogeneous. In other families genetic linkage has been demonstrated for a locus on the long arm of chromosome 14 (Schellenberg *et al.*, 1992). The onset of disease in familial AD linked to this chromosome is somewhat earlier than in those associated with chromosome 21. In the pedigree reported by Haltia *et al.* (1994), the mean age at onset of symptoms was 36 years. This disease follows a severe subacute course; the frequent presence of myoclonus and seizures may resemble CJD clinically. Other families with disease of early onset are not linked to the known sites for early-onset AD on chromosome 21 or 14; these include well-documented families of Volga–German ancestry.

The evidence of genetic factors in late-onset AD is less clear-cut. The cumulative evidence suggests that while familial AD of early onset is due to simple mendelian inheritance, the pathogenesis of the common late-onset disease seems to be multifactorial, due to environmental influences acting on a genetic background. There is a large body of evidence suggesting an increased risk of dementia in first-degree relatives of patients affected by AD. This may run as high as 40% by the age of 85–90 years (Owen *et al.*, 1994). Moreover, studies of concordance in twins, albeit not entirely conclusive, point to genetic factors (Breitner *et al.*, 1993). Segregation analysis suggested the presence of a major gene with age-dependent penetrance (Farrer *et al.*, 1991). Evidence for linkage to the proximal long arm of chromosome 19 in some late-onset families (Clark and Goate, 1993) has led to the discovery of the apo E as an important factor influencing the individual risk and the age of disease onset in AD cases. Apo E has for some time been known to be colocalized with plaques in cerebral and systemic amyloidoses and with NFTs in AD; the molecule had been considered an unspecific "escort" of amyloids. It occurs in the three isoforms apo E2, apo E3, and apo E4. In homozygotes for the Apo *E4* allele, the lifetime risk of developing AD is over 90% by the age of 80 (Scott, 1993; Corder *et al.*, 1993), whereas absence of apo *E4* seems to protect the patient from AD; the risk for apo E2 homozygotes is the lowest, at 20%, and in E3 homozygotes the risk is approximately 45%. The difference between the two isoforms apo E3 and apo E4 consists only of an exchange of one amino acid; this small molecular difference is sufficient to delay onset of the disease by 15 years. On the other hand, several apo E4 homozygotes have been documented to reach old age without develop-

ing dementia, and approximately 40% of the cases of AD do not possess this allele, so that it appears neither necessary nor sufficient to cause the disease.

Interestingly, the apo *E4* allele does not influence the clinical expression of familial early-onset AD associated with APP codon 692 or 693 mutations (Haan *et al.*, 1994). The discovery of a high incidence of the *E4* allele in late-onset AD, both familial and sporadic, compared with normal controls, underlines the importance of genetic factors in predisposing persons to AD (Strittmatter *et al.*, 1993; Saunders *et al.*, 1993; Scott, 1993; Poirier *et al.*, 1993; Corder *et al.*, 1993; Owen *et al.*, 1994).

Variants of Alzheimer's Disease

Terry *et al.* (1987) described AD without neocortical tangles. SPs were abundant and tangles were present in the hippocampal formation. This pattern was found in 30% of the 60 cases of SDAT over the age of 74. In a subsequent study Probst *et al.* (1989) showed that in the absence of neocortical tangles, the neurites of plaques do not contain paired helical filaments or τ-protein, as demonstrated by immunohistochemical methods.

Ulrich *et al.* (1992) described 10 cases with abundant NFTs, localized predominantly to the hippocampus, the entorhinal cortex, and the amygdala, but devoid of plaques. In reviewing the literature the authors found only three previously reported similar cases. Another unusual neuropathological subset of AD was reported by Hansen *et al.* (1989), who found five cases of concomitant AD and diffuse Lewy body disease with coexistent spongiform change in the neuropil. Several authors have described the coexistence of Alzheimer-type pathology and cortical Lewy bodies in demented individuals. Many of these cases fulfill the histopathological criteria of AD, but in others the number of SPs is insufficient to warrant a diagnosis of AD, and occasionally there is dementia in the absence of Alzheimer-type changes when there are only numerous cortical Lewy bodies. Cases of coincidental AD with numerous cortical Lewy bodies have been classified as the *Lewy body variant of AD*. These patients often present with clinical features of parkinsonism, such as hypomimia, resting tremor, bradykinesia, mild neck rigidity, and slowing of rapidly alternating movements. Typically, they do not improve with levodopa therapy.

Braak and Braak (1989) described, in many cases with dementia, argyrophilic grains loosely scattered throughout the neuropil and coiled bodes of silver-stained filaments mainly located within the white matter close to the cortical gray matter. The changes appear to be associated with Parkinson's disease and AD. However, some cases showed exclusively argyrophilic grains and coiled bodies and were considered the morphological substrate of a form of adult-onset dementia.

Mizutani *et al.* (1990) reported seven cases of SDAT with unusual clinicopathological findings. The mental disturbance started after the age of 65 in all patients. The main clinical feature was a marked personality change, in addition to a disturbance of cognitive function. These patients showed a neuronal loss in laminar pattern, with gliosis confined to the CA1 region of the hippocampus, the area of the hippocampal gyrus (entorhinal cortex), and the medial occipitotemporal cortex. The subcortical white matter showed more fibrillary gliosis than loss of myelin. Both Alzheimer's NFTs and SPs were fewer than in SDAT.

Fibrillary Degeneration and Senile Plaques in Animals SPs are found in aging monkeys (Uno and Walker, 1993), dogs, and other mammalian species (Cork *et al.*, 1988). Abnormal cytofilaments have been seen in aging rats and monkeys (Walker *et al.*, 1990). The pattern of distribution in aged primates appears to differ from that found in humans with AD (Heilborner and Kemper, 1990). NFTs resembling those of human AD occur more infrequently and have been described in only a few species of large bears (Strothjohann *et al.*, 1993).

The use of transgenic mice has not yet proved successful. None of the animal models currently reported has faithfully reproduced the pathological changes or the clinical symptoms associated with AD (Aguzzi *et al.*, 1994).

Pick's Disease (Pick-Type Atrophy; Presenile Frontotemporal Atrophy)

This disease was first described by Pick (1892) as a special form of cerebral atrophy. The light microscopic appearances were reported by Alzheimer (1911). Pick's disease and AD have much in common and have even been found to occur simultaneously in the same individual (Smith and Lantos, 1983; Hof *et al.*, 1994). Moreover, sharing of specific antigens by degenerating neurons in Pick's disease and AD has been shown (Love *et al.*, 1988). This may reflect a metabolic defect common to the formation of these two types of intraneuronal inclusions (Love *et al.*, 1988). Combinations of Pick's disease with amyotrophic lateral sclerosis and other degenerative diseases occur occasionally (Arima *et al.*, 1992).

Clinical Picture The condition is usually sporadic and appears only occasionally in siblings. It is more common in women. The age at onset ranges between 40 and 60 years, although cases occurring as early as 25 years or as late as 70 years have been recorded. The prominent features are various changes of character and personality with preservation of memory. It is important to elicit the earliest symptoms in the patient's history as they often have a characteristic slant. These consist of a disturbance of the faculties embedded in everyday activities, domestic or professional. Emotional disturbances are also prominent, as well as periods of increased irritability, restlessness, and loss of inhibition. The atrophy of the frontal and anterior temporal lobes, often seen on CT, is neither pathognomonic nor constant. The average duration of the illness is 7 years, although it may range from a few months to 17 years (Jakob, 1979). The average clinical duration of Pick's disease with onset before 39 years of age was about $4\frac{1}{2}$ years (Hori *et al.*, 1983). In cases with generalized cortical and subcortical involvement, the disease appeared about two decades earlier than in the classical cases. Dominant inheritance of a principal gene with polygenic modification has been postulated in the rare familial cases.

Neuropathology *Gross appearances.* The brain shows a usually sharply defined cortical atrophy limited to certain areas of predilection (Fig. 213). It is rarely confined to one

lobe, but appears in combinations, the frontotemporal lobe being the most common. In the frontal lobe the opercular part and the orbital cortex with the gyrus rectus are often the most severely affected. Total atrophy of the frontal lobe, encroaching on the precentral gyrus, is rare, with atrophy limited to the frontal convexity being rarer still. Atrophy of the temporal lobe (Fig. 214) is usually most pronounced at the pole and at the basal surface, but can extend onto the lateral or basal aspects of the occipital lobe. Involvement of the lower parts of the parietal lobe is not uncommon. In the basal ganglia the striking feature is atrophy of the caudate nucleus, which need not correspond in severity with the cortical lesions. The putamen, pallidum, and substantia nigra may be involved and total destruction of the caudate has also been reported. Muñoz-Garcia and Ludwin (1984) separated a classical type with predominantly cortical atrophy and a second type (generalized) with involvement of the subcortical structures.

Light microscopy. The atrophic areas show a remarkably constant pattern. The distribution of lesions in the common frontotemporobasal atrophy is very precise. Allocortical regions are systematically affected, with frontotemporal accentuation. The periarchicortical cingulate gyrus and the anteroventral part of the insula form the limit of the lesion. In the basal regions the brunt of the lesions falls on the base of the temporal lobe; the posterior orbital cortex, including the paleocortical gyrus subcallosus; the prepyriform and endorhinal regions; the amygdaloid nucleus; and the stria terminalis. Ammon's horn is often

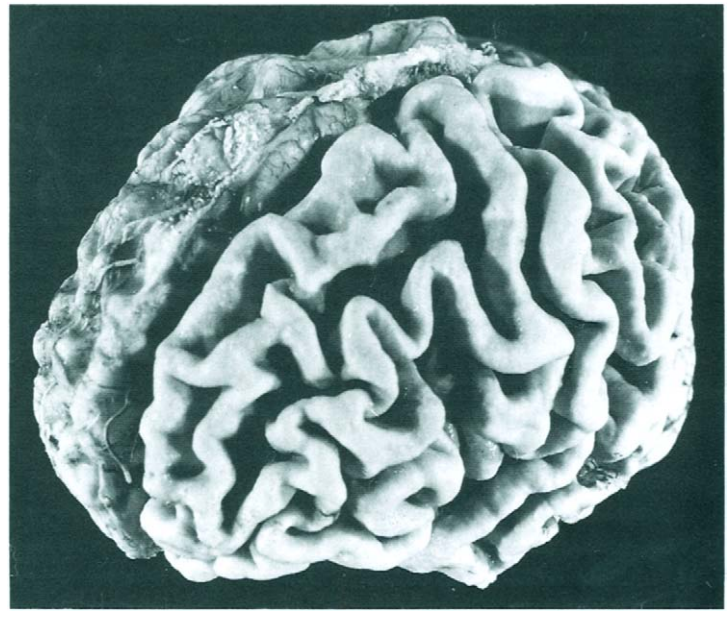


Fig. 213 Pick's disease. The left cerebral hemisphere, showing massive atrophy of the convolutions in the frontal lobes.

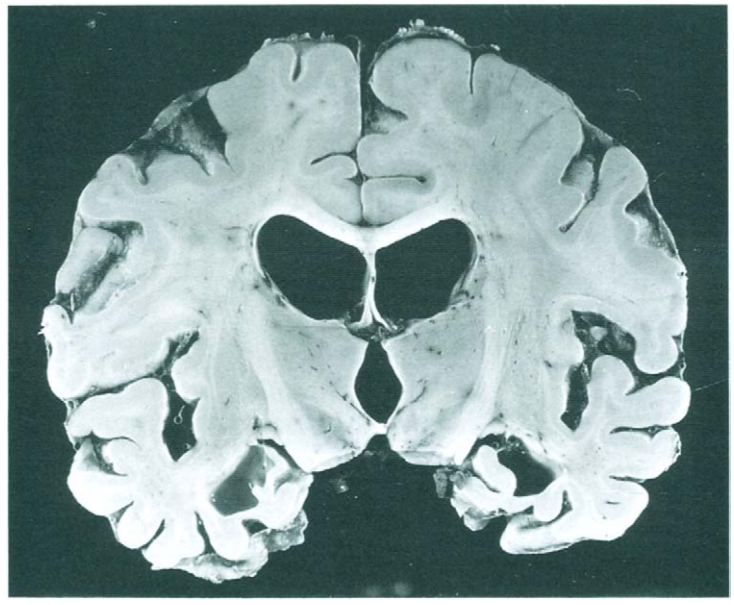


Fig. 214 Pick's disease. Dilatation of the lateral ventricles. The cortical atrophy is pronounced in the temporal lobes.

spared, but may be involved early. Within the affected areas the neuronal loss has a laminar distribution. In lesser degrees of atrophy, it may be present even in the absence of macroscopic changes. The order of laminar involvement has been questioned but has been accepted by the majority of the authors. Layer IIIa is the first to undergo atrophy. As layer IIIc is relatively resistant, the subsequent order is IIIb–II–IIIc, followed by V and VI, layer IV remaining intact longest.

The atrophy of the molecular layer affects primarily the association systems. This has been suspected on clinical grounds. An almost total loss of dendritic spines of the pyramidal cells was observed by Wechsler *et al.* (1982).

Neuronal loss in the nucleus basalis has been seen by some authors (Uhl *et al.*, 1983a), but not by others (Clark *et al.*, 1986). Involvement of the thalamic nuclei and the anterior horns of the spinal cord has been recorded. Cell loss in the caudate nucleus was also reported by Hori *et al.* (1983) in an atypical case that cannot, with certainty, be classified as Pick's disease.

Spherical argyrophilic bodies, so-called *Pick bodies* (PBs), may be found in the neuronal perikarya (Fig. 215). They are found most densely in the amygdaloid, hippocampus, innominate substance, posterior cingulate gyrus and insula, inferior parietal lobule, and posterior inferior temporal gyrus. In the frontotemporal neocortex they are preferentially distributed in layers II and VI (Hof *et al.*, 1994), less densely in the anterior frontotemporal gyri, occipital gyri, caudatum, hypothalamus, claustrum, putamen, pallidum, and olfactory

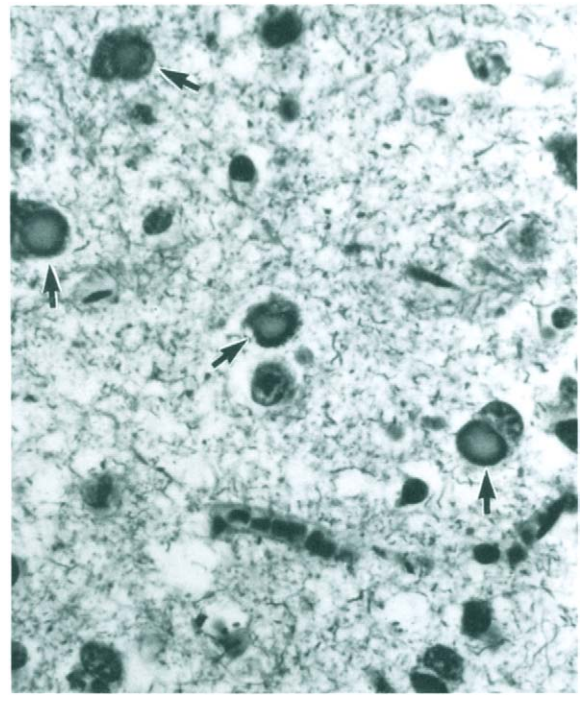


Fig. 215 Pick's disease. Ammon's horn, showing spherical argyrophilic inclusions (Pick bodies; arrows) in the neurons. Bielschowsky stain, ×300.

bulbs and tubercles. The tectum and central gray of the midbrain, red nuclei, substantia nigra, locus coeruleus (Forno *et al.*, 1989), superior central nuclei, tegmental reticular nuclei, pontine nuclei, dorsal vagal nuclei, and arcuate nuclei are also severely affected. They are sparse in the pre- and postcentral gyri and the superior parietal lobule, and the calcar and the cerebellum are mostly spared (Yoshimura, 1989). Diffuse nonargyrophilic inclusions may involve the perikaryon and extend into the apical dendrite. Neurofilament antigens are present in PBs as well as antigenic determinants of Alzheimer's NFTs. PBs are not always present, nor are they entirely pathognomonic, and have been described in a wide range of conditions, different from Pick's disease (Clark *et al.*, 1986; Pietrini *et al.*, 1993). Neuronal inclusions once thought to be specific for certain disorders may reflect a form of cytoskeletal disorganization, which is not entirely restricted to a specific disease entity (Gibb *et al.*, 1989; Lippa *et al.*, 1990). Arima *et al.* (1992) described a presenile dementia with PBs in the atrophied cerebral cortex and red nucleus, and progressive supranuclear palsy tangles in the basal ganglia, subthalamic nucleus, and substantia nigra. Hirano bodies are also found occasionally. In the cases with subcortical involvement (Muñoz-Garcia and Ludwin, 1984), the cytoplasmic inclusions contained RNA and stained poorly with silver and antibodies against neurofilaments and microtubules.

The *Pick cells* resemble, morphologically and immunohistochemically, the chromatolytic cells of axonal reaction (Dickson *et al.*, 1986). Distended Pick cells need not contain argyrophilic inclusions (Fig. 216). Their presence cannot be correlated either with definite areas or with the course of the disease. They may appear in regions free of atrophy, and can be seen in cases with rapid disease progression or with a protracted course.

Filamentous structures related to the neuropil threads in AD (see p. 456) are scattered throughout the neocortex, but in lesser numbers than in AD (Davis *et al.*, 1992). Sinha *et al.* (1993) identified, using the fluorescent cyanin stain Di-I combined with confocal microscopy in the focal sense, neuritic aggregates, 50–200 μm in diameter, that were scattered throughout all of the cortical layers. They were not associated with amyloid deposits, astrocytic processes, or capillaries. In the intervening neuropil there were fewer neurites compared to the situation in controls. The authors postulated that this neuritic pattern may reflect the loss of specific subpopulations of cortical neurons and the proliferation of neurites of the remaining neurons.

Ultrastructurally, similar appearances are found in PBs and Pick cells. Straight and paired helical filaments, tubules, lipofuscin, and remnants of endoplasmic reticulum are found in both, with considerable variation from cell to cell (Muñoz-Garcia and Ludwin, 1984; Clark *et al.*, 1986). In PBs Yoshimura (1989) disclosed two component fibrils: smooth-surfaced, straight, tubular filaments with a diameter of 15 ± nm and no periodic constrictions, and long-period (160-nm) constricted fibrils. Glial inclusions were

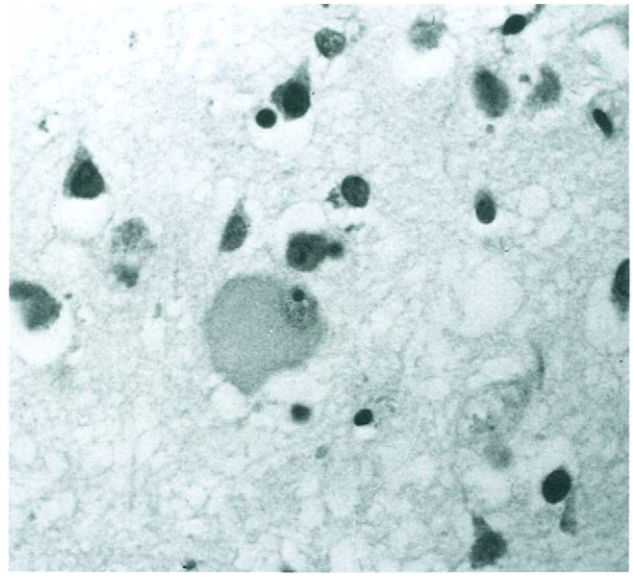


Fig. 216 Pick's disease. A Pick cell with a swollen cytoplasm and peripheral nucleus. Nissl stain, ×300.

detected in the white matter (Ishizu *et al.*, 1994). These were immunoreactive for antiphosphorylated τ antibody and argyrophilic with the Gallyas method. Ultrastructurally, these inclusions were composed of three forms of filaments: 13- to 15-nm straight filaments on roughly parallel arrangement with many granular components (three cases), loosely wavy filaments with periodic constriction from 11 to 22 nm at every 170- to 300-nm interval (one case), and randomly arranged 11- to 25-nm filaments. There are cases that show only simple atrophy without swollen cells, with or without PBs. They account for about 30% of the cases of otherwise typical lobar atrophy (Constantinidis *et al.*, 1974). For these authors an absence of typical cells does not justify the exclusion of these cases from classification as Pick's disease. A firm diagnostic criterion has been considered to be the sequential laminar atrophy of the cortex with characteristic topographic distribution. By adhering to this criterion, Pick's disease can be separated from "primary subcortical gliosis" (Neumann, 1949; Neumann and Cohn, 1967) or from "presenile glial dystrophy" (Seitelberger, 1968). However, there are difficulties in clear-cut differentiation from the "lobar atrophy without Pick bodies."

Pathogenesis In the rare cases with familiary appearance, autosomal-dominant inheritance has been postulated.

The most detailed neuropathological spectrum of patients presenting clinically with Pick's disease was provided by the subclassification of Constantinidis *et al.* (1974). It was based on the distribution of the atrophy and the presence or absence of PBs. Their group A had both Pick cells and PBs in the limbic system, with or without temporal atrophy. Group B had predominantly frontal atrophy with only Pick cells or PBs and was subdivided into group C1, with atrophy of the temporal pole, and group C2, with frontal, temporal, cingular, orbital, and insular atrophy, as well as involvement of the basal ganglia and the thalamus. PBs, like Lewy bodies and the granulovacuolar inclusions of AD, remain rarely as extracellular "ghosts" after destruction of their parent neurons, even in cases in which PBs are numerous. Thus, their absence at autopsy cannot be interpreted as definitive evidence of their absence at some earlier time. However, histological, immunohistochemical, and electron microscopic evidence of extracellular PBs has been found in the granular cell layer and, rarely, in the pyramidal cell layer of the hippocampus by Izumiyama *et al.* (1994). They did not react with anti-τ and antiubiquitin antibodies, suggesting that the PB is discharged into the neuropil after destruction of the neuron, losing its immunoreactivity to certain antibodies during this process.

Pick's disease is included among the "progressive cerebrospinal system atrophies" because of the selective and fairly stereotyped topography of the lesions. Aside from some hereditary factors, nothing can explain the progressive atrophic process. A loss of muscarinic receptors has been reported in the affected areas. An increased excretion of zinc in the patient's urine and an impairment of zinc transport by plasma proteins have also been mentioned.

An accumulation of phosphorylated neurofilaments in the cytoplasm of nerve cells has been revealed in numerous pathological conditions, including Parkinson's disease (Dickson *et al.*, 1986). These abnormalities of the cytoskeleton could support the existence of an alteration in the axonal flow (Pietrini *et al.*, 1993).

Lobar Atrophy without Pick Bodies (Dementia of the Frontal Lobe Type; Lobar Atrophy; Frontal Lobe Degeneration of the Non-Alzheimer Type; Dementia Lacking Distinctive Histological Features; Variants of Pick's Disease)

Cases of frontotemporal degeneration without distinctive histology are being increasingly reported in the neurology literature (Knopman *et al.*, 1990; Hulette and Crain, 1992). As a rule, the patients present with a clinical picture suggestive of progressive selective damage to frontal regions of the brain without pathological or chemical hallmarks of AD. There is a great deal of overlap between these cases and cases variously reported as "lobar atrophy," "frontal lobe degeneration of non-Alzheimer type" (Brun, 1987), "dementia lacking distinctive histologic features" (Knopman *et al.*, 1990), "variants of Pick's disease" (Muñoz-Garcia and Ludwin, 1984), "Pick's disease without Pick's bodies" corresponding to group C in the classification of Constantinidis and Tissot (1974), etc. Although Filley *et al.* (1994) proposed that subgroups should be categorized both by microscopic features and by gross patterns of atrophy, for the time being we describe the different reported cases altogether.

Clinical Picture As a rule, the patients were under age 70 years at the onset of symptoms. In several patients the illness was quite rapid from onset to death within 5 years. Most patients had disease durations of 6–9 years. Later they experienced cognitive impairment, memory failure and rigidity, masked facies, gait disturbance, dysarthria, and dysphagia. In several patients the dysphagia and dysarthria were of rather rapid onset and progressed quite quickly to total inability to swallow and anarthria (Knopman *et al.*, 1990). The relevance of EEG findings in distinguishing AD from non-AD was stressed by Neary *et al.* (1986). The predominant features included a change in character and social conduct with loss of social awareness, disinhibition, forgetfulness, and distractibility.

Neuropathology *Gross appearances.* By gross examinations the cerebral hemispheres are only mildly to moderately atrophic. Only the frontal lobes show gyral narrowing.

Light microscopy. All cases showed degeneration of the cerebral cortex, which was most severe in the frontal and parietal cortices, less severe in the temporal cortex, and generally absent in the occipital cortex.

The degeneration is characterized by vacuolation of the second cortical layer (Brun, 1987), with prominent astrocytosis in the deep layers and diffuse degeneration and astrocytosis in the most severe cases (Hauw *et al.*, 1994). The hippocampal formation in many cases is severely degenerated; in the other cases the changes are milder. The subiculum and CA1 regions showed the most severe cell loss and astrocytosis (Knopman *et al.*, 1990). Several of the patients had prominent cell loss and astrocytic proliferation in the medial thalamus, the striatum, or both. The substantia nigra was severely degenerated in most cases, with both medial and more lateral segments involved. The full extent of the disease process can be appreciated first on microscopic investigation. Pick cells with inclusions are not found, and only occasional neurons resembling inflated cells or rather degenerated, pale, chromatolytic neurons were described. The disease distribution involves,

in all cases, the frontal lobe convexities and, in a few cases, prominent changes also in the basal frontal cortex. Diffuse deposits of β-protein occur only in areas of the cortex where functional neurons are still present and are absent where neuronal decimation has taken place (Mann *et al.*, 1992).

The temporal lobes show cortical changes in their anterior half, but in some cases they were only minimally affected (Brun, 1987). A slight white matter gliosis with an accompanying slight reduction of myelin has been reported (Englund and Brun, 1987).

Corticodentatonigral Degeneration with Neuronal Achromasia (Corticobasal Degeneration)

This syndrome was described by Rebeiz *et al.* (1967, 1968) in three patients. Additional cases were reported, and subsequent authors (Gibb *et al.*, 1989; Sawle *et al.*, 1991; Muhiddin *et al.*, 1994) have adopted the term *corticobasal degeneration* in preference to that suggested by the original investigators. Despite some pathological similarities to Pick's disease, we suggest that the distribution of nerve cell loss and the corticobasal inclusion are unique to corticobasal degeneration (Gibb *et al.*, 1989). However, Paulus and Selim (1990) reported a transitional case with pathological features of corticonigral degeneration, progressive supranuclear palsy, progressive subcortical gliosis, and Pick's disease.

Clinical Picture The first symptoms appear toward the end of the sixth or in the seventh decade. Slowing and coarsening of movements mainly of the legs, but sometimes involving the arms, are accompanied by extrapyramidal abnormal movements, usually beginning on the left side and becoming generalized. These closely resemble those of progressive supranuclear palsy (see p. 604) and consist of focal dystonia and myoclonus in one arm, often associated with the "alien hand" symptoms (Lippa *et al.*, 1990). Cerebellar signs are usually mild. Intellectual faculties remain intact, even in cases with progressive aphasia (Lippa *et al.*, 1991). Death occurs 6–8 years after the onset of symptoms. MRI scans show cortical atrophy, most prominent in the parasylvian region, and ventricular enlargement (Lippa *et al.*, 1990). The asymmetry of symptoms and signs is often striking. Brain imaging may demonstrate greater abnormalities contralateral to the more affected side (Riley *et al.*, 1990). Positron emission tomography reveals a unique pattern of regional cortical oxygen hypometabolism and abnormalities of striatal fluorodopa uptake (Sawle *et al.*, 1991).

Neuropathology *Gross appearances.* A moderate frontoparietal cortical atrophy, sometimes more severe in the precentral gyrus with dilatation of the precentral sulcus, is seen (Mori *et al.*, 1994). However, the severe, focal, "knife-edged" cortical atrophy characteristic of Pick's disease is lacking. An asymmetrical accentuation may be present. The temporal lobes are unaffected.

In the pallidum the severe loss of neurons may be equal in the lateral and medial segments. A mild loss of neurons in the putamen, dorsomedial nucleus of the thalamus, and cerebral cortex and a moderate loss of neurons with a spongy change in the second and third layers may be present in the severely damaged areas. The substantia nigra shows a severe loss of neurons, a few spheroids, and some extraneuronal pigments.

Light microscopy. A characteristic feature is the presence of swollen neurons resistant to most stains (achromasia). These are seen in the cerebral cortex, amygdala, basal ganglia, thalamus, various nuclei of the brain stem, and dentate nucleus. With the Bielschowsky silver stain the swollen neurons exhibit variable argyrophilia, without PBs or NFTs. They closely resemble Pick cells, and are sometimes referred to as such (Gibb *et al.*, 1989). Argyrophilic PBs, however, are not found. In the pigmented nuclei of the substantia nigra and the locus coeruleus, the pattern is somewhat different and consists of weakly basophilic hyaline inclusions displacing the neuromelanin granules. In one case Mori *et al.* (1994) found NFTs in the brain stem and the dentate nucleus that were indistinguishable from those seen in progressive supranuclear palsy. Abnormal neurons showed intense immunocytochemical staining for abnormal τ antigen within the perikaryon, which sometimes extended into proximal neuritic processes without NFTs (Wakabayashi *et al.*, 1994). Neuronal loss and gliosis are apparent in all affected areas (Gibb *et al.*, 1989; Riley *et al.*, 1990). On ultrastructural examination the cytoplasm of the swollen neurons was seen to contain numerous straight or slightly curved, often criss-crossing, paired helical filaments (Mori *et al.*, 1994), which were interspersed among vesicular profiles, granular material, mitochondria, and lipofuscin bodies.

Progressive Aphasia and Aphasic Dementia

Mesulam (1982) reported on six patients with a slowly progressive aphasia. Four of these never developed any cognitive deficit, while two became demented 7 years after the onset of aphasia. CT showed focal perisylvian atrophy in the left frontotemporal region; EEG exhibited slowing of rhythm in the same area. A cortical biopsy was inconclusive. Autopsy in two patients discussed by Kirschner *et al.* (1987) showed focal status spongiosus affecting particularly lamina II of the left inferior frontal gyrus; in one patient the temporal lobe was similarly affected. An additional group of three patients was reported by Poeck and Luzzati (1988). The aphasia began in the presenium, and mild cognitive changes developed over the course of the disease, which lasted 4–5 years.

In a large study of asmmetrical cortical degeneration presenting with a variety of clinical syndromes, 12 patients presented with aphasia (Caselli and Jack, 1992). No information on pathological findings is available in the aphasic group, but a cortical biopsy in a patient with a different clinical presentation showed status spongiosus of the superficial cortical layers of the frontal cortex.

Kobayashi *et al.* (1990) reported the case of a 64-year-old woman in whom an initial aphasia disturbance was followed by mutism, progressive dementia, parkinsonism, and muscular atrophy. At autopsy localized cortical atrophy was present in the pars triangularis and the pars opercularis of the inferior frontal gyrus, as well as the supramarginal and angular gyri of the inferior parietal lobule and the posterior halves of the middle and inferior temporal gyri, predominantly on the left. Other lesions included a crossed cerebellar atrophy with shrinkage of the right middle cerebellar peduncle, degeneration of the substantia nigra, and gliosis of the amygdaloid complex and the inferior olives. This case shows some resemblance to the next group, which consists of seven cases reported by Caselli *et al.* (1993). These patients presented with rapidly progressive aphasic dementia followed by the development of motor neuron disease. Autopsies were carried out on three patients, all of whom showed extensive frontotemporal status spongiosus, and in two this was accompanied by ac-

centuation of the atrophy in the left perisylvian region. There was a mild loss of neurons in the substantia nigra, a loss of hypoglossal neurons in two cases, and a loss of anterior horn cells in all three. These cases appear to represent a variant of "motor neuron disease with dementia" (Horoupian *et al.*, 1984; Neary *et al.*, 1990), which, in turn, falls into the broader group of "dementia lacking distinct features" (Knopman *et al.*, 1990).

Primary Limbic Lobe Gliosis: Familial and Sporadic Cases

Sima *et al.* (1994) reported seven cases that showed progressive dementia, aggressive behavior, and Klüver–Bucy syndrome. Three cases belonged to an Irish kindred in whom three additional cases have been confirmed at autopsy, and the other four cases appear to have been sporadic. The cases were diagnosed clinically as AD. The patient's age at onset of disease varied from 55 to 77 years, and the disease duration ranged from 3 to 15 years. The pathology was characterized by marked gliosis and a milder degree of neuronal loss of the entorhinal cortex, presubiculum, anterior cingulate cortex, insular cortex, prepyriform cortex, amygdala, and nucleus accumbens. The hippocampus was spared, except for mild neuronal loss and gliosis of CA4. Also, the parasubicular area was relatively spared, whereas the perforant pathway of the hippocampal formation was rarefied and gliotic. Neuritic plaques, NFTs, Lewy bodies, or PBs were not identified. Although there were variations in the severity of the pathology between cases, the characteristic and repetitive anatomical distribution of the lesions suggests a distinct entity, resulting in deafferentation of the hippocampal formation. The familial cases showed a milder pathological involvement than the sporadic cases. Molecular genetic studies of the familial cases have revealed linkage to chromosome 17, and *Moynahan syndrome* has been suggested as the name for the familial form.

Alper's Disease (Alper's Syndrome; Progressive Cortical Poliodystrophy; Diffuse Progressive Cerebral Poliodystrophy; Diffuse Cortical Sclerosis; Spongy Glioneuronal Dystrophy of Childhood)

Alper (1931) described a peculiar degeneration of the cerebral gray matter in children, manifesting itself in the form of epileptic seizures. A similar case had been previously reported by Freedom (1927). The disease was defined as a diffuse cerebral cortical atrophy, even though the basal ganglia and the cerebellum may also be involved. Christensen and Krabbe (1949) introduced the term *poliodystrophy*. Several authors expressed doubts as to whether this condition constitutes a single entity (Bicknese *et al.*, 1992). Certainly, ulegyrias and focal softenings with hemiatrophy should not be included in the concept of Alper's disease (Larroche, 1984).

Clinical Picture The disease manifests itself in infancy, sometimes after a few weeks or months of apparently normal development. The first symptoms consist of seizures, followed by spastic pareses and mental retardation. Deafness and blindness with optic atrophy and myoclonic jerks are observed occasionally. Boyd *et al.* (1986) described characteristic changes on the EEG. Unilateral accentuation of the neurological symptoms has

been noted. Death occurs after a few months or 1–2 years. Most patients present with involvement of the liver with hepatomegaly, abnormal transaminase values, and, occasionally, cirrhosis (Narkewicz *et al.*, 1991). Some authors (Huttenlocher *et al.*, 1976; Bicknese *et al.*, 1992) reported a subgroup of children with progressive hepatocerebral disease, many of whom had affected relatives.

Ford *et al.* (1951) separated a group of patients in whom symptoms appeared between the ages of 4 and 6 years. They presented with progressive dementia, choreoathetoid movements, and increasing spasticity with hemiplegia. The duration of the illness was 15 years or more. High levels of lactate were found in the serum and the CSF. Greenhouse and Neubürger (1964) included here a group of nine patients who, in adolescence or adulthood, developed fever and epileptic seizures and died a few weeks after the onset of symptoms.

Pathology *Gross appearances.* Atrophy of the liver as well as hepatomegaly can be found.

Light microscopy. The liver showed centrilobular necrosis with diffuse leukocytic infiltration, hemorrhages, and lipid storage (Van Der Linde and Walter, 1984). Massive hepatocyte dropout and a proliferation of bile ductular elements have been reported in many cases (Narkewicz *et al.*, 1991). A defect in cytochrome a_3 was found in skeletal muscle by enzyme histochemistry (Prick *et al.*, 1983).

Electron microscopy. Mitochondrial abnormalities were found in cardiac and skeletal muscle (Sengers *et al.*, 1984).

Neuropathology *Gross appearances.* The leptomeninges are thickened and the underlying cerebral cortex is atrophic with narrow gyri. In some cases a focal granular atrophy of the cortex was seen. Coronal sections reveal a brown discoloration and a soft consistency of the cortex with a striking predilection for the striate cortex (Harding, 1990). Occasionally, small cystic necroses may be seen, sometimes encroaching on the white matter. The white matter may also be atrophic and the ventricles may appear dilated.

Light microscopy. Neuronal loss of various extent and severity is apparent in the cortex (Van Der Linde and Walter, 1984). However; De Coo *et al.* (1991) found, in quantitative neuromorphological analysis of the cortex, normal values, except for poor dendritic arborization of the inner layers. The changes are particularly severe in the depths of the sulci (Fig. 217). A prominent status spongiosus is present with a laminar distribution, affecting mainly layers III and V (Fig. 218). In some cases this takes the form of a fine microcystic change (Fig. 219). The cortical damage may show unilateral accentuation, or may even be confined to one hemisphere. The remaining neurons often show pyknotic nuclei and a shrunken basophilic cytoplasm. Brightly eosinophilic necrotic neurons may also be present, particularly in Ammon's horn (Van Der Linde and Walter, 1984). All areas may be affected, but the calcarine cortex is usually most severely affected.

Neuronal changes are also found in the striatum, thalamus, subthalamic nucleus, substantia nigra, and pontine gray. Very rarely, the lesions are associated with status marmoratus. A loss or degeneration of Purkinje cells is seen in the cerebellum (Fig. 220). Scattered neuronal loss is also found in the dentate nucleus. Astrocytic and capillary proliferation may be prominent. Reactive astrocytes appear early in the gray matter and the subcortical white matter. They often have large nuclei and prominent nucleoli. Evidence of active

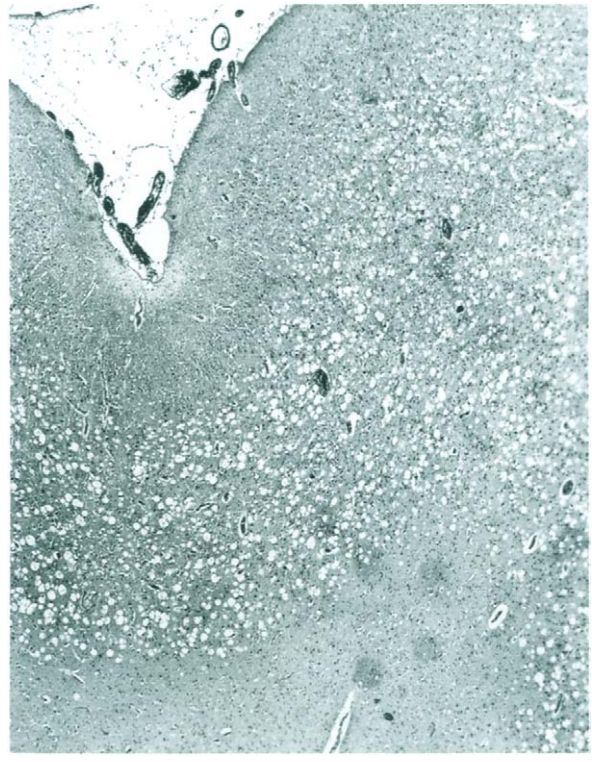


Fig. 217 Alpers' disease. Status spongiosus of the parietal cortex. Nissl stain, ×40.

breakdown may be seen during short periods. Under the atrophic cerebral and cerebellar cortices the white matter shows a variable degree of loss of axons and myelin sheaths.

Electron microscopy. Giant mitochondria (Dekaban and Norman, 1958) or mitochondria with dense matrix have been described based on cortical biopsies. These findings have not been confirmed by other observers, however.

Pathogenesis The occurrence of this disease in twins and in occasional familial clusters suggests a genetic predisposition. Prenatal, perinatal, and postnatal factors, such as anoxia, mechanical injury, or infection, can often be elicited in the patient's history. Also, the unilateral occurrence of lesions suggests the operation of exogenous factors, mainly of a hypoxic nature (Greenhouse and Neubürger, 1964; Barodawala and Dastur, 1986). Nevertheless, a genetic abnormality has been postulated to account for familial cases. The normal early development in many infantile cases and almost all juvenile cases militates against a prenatal or perinatal etiology. It has been suggested that a genetic predisposition may be rendered manifest by an intercurrent infection. The frequent involvement of the liver and the histological similarity of the cortical changes to those of CJD were also believed to point to a viral etiology.

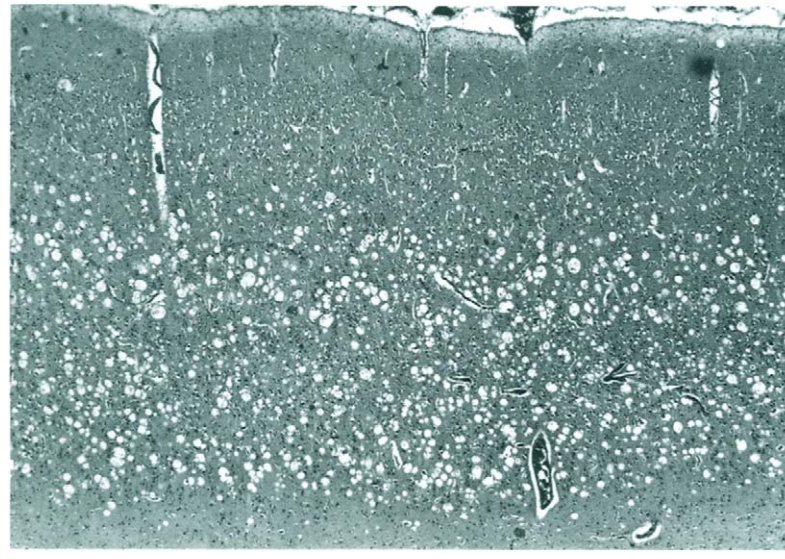


Fig. 218 Same case shown in Fig. 217. Pseudolaminar distribution of status spongiosus with a predilection for cortical layers III and V. Nissl stain, ×60.

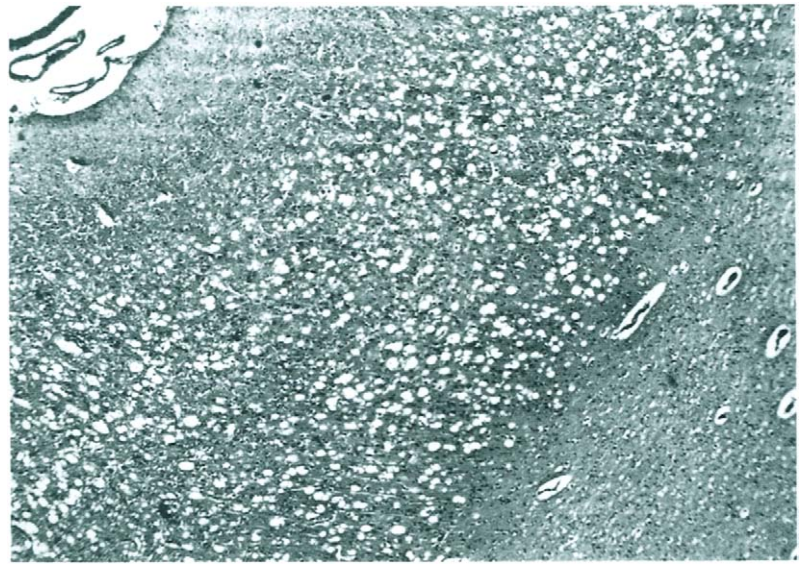


Fig. 219 Same case shown in Fig. 217. The microcystic character of the status spongiosus is clearly seen in the depth of a sulcus. Nissl stain, ×70.

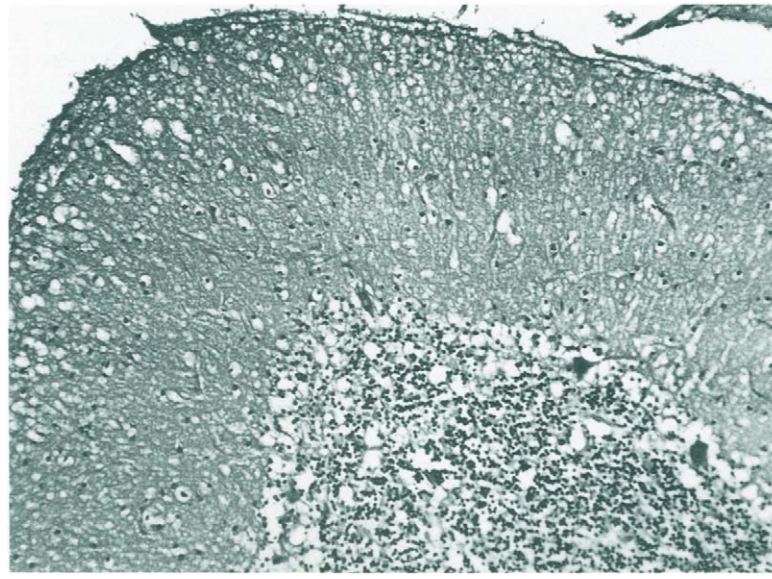


Fig. 220 Same case shown in Fig. 217. The cerebellum, showing a severe loss of Purkinje cells. The remaining cells are shrunken. Nissl stain, ×70.

Microcephaly and Progressive Degeneration of the Cerebral Cortex

Skullerud *et al.* (1973) isolated within the context of Alper's disease a group of patients with a familial incidence of microcephaly and cortical degeneration, in whom prenatal or perinatal anoxia could be excluded. The case reported by Patt *et al.* (1993), with Alper's disease with onset in early infancy, microcephaly, and micrognathia, should also be included in this subset.

The neuropathological findings were confined to severe atrophy of the cerebral cortex. Minor neuronal losses in the pons and in the anterior horn of the spinal cord were considered to be secondary phenomena. The cerebellum, basal ganglia, and Ammon's horn were unaffected. Hypomyelinization and mild astrocytic gliosis can be present (Patt *et al.*, 1993).

The microcephaly suggested a prenatal onset of the disease process.

Diffuse Lewy Body Disease (Lewy Body Dementia; Lewy Body Variant of Alzheimer's Dementia)

Diffuse Lewy body disease is an increasingly recognized form of primary degenerative dementia that shares histopathological features with Parkinson's disease and often with AD.

Since the first description of this syndrome (Okazaki *et al.*, 1961), several publications have appeared, largely from Japanese authors, but including European patients. The oc-

currence of an organic dementia in patients with juvenile parkinsonism (Yoshimura, 1983) as well as in patients in late stages of classical Parkinson's disease (Boller *et al.*, 1980) renders difficult the separation of generalized Lewy body disease from paralysis agitans with dementia (see p. 557).

Clinical Picture Early-onset cases often have clinically apparent extrapyramidal features, while cognitive deficits usually overshadow motor deficits in late-onset cases (Byrne *et al.*, 1989; Crystal *et al.*, 1990; Ince *et al.*, 1991; Mark *et al.*, 1992).

Patients in their sixth decade or later suffer, with few exceptions, from parkinsonism and progressive dementia, which usually precedes the onset of parkinsonian symptoms. One fifth of the Japanese patients had no parkinsonism (Kosaka, 1993). Autonomic disturbances may be present in some patients.

Neuropathology *Gross appearances.* Moderate cerebral atrophy is present in all cases. A frontal accentuation of the atrophy is a common feature (Forstl *et al.*, 1993).

Light microscopy. Numerous single or multiple Lewy bodies are present in the cytoplasm of cortical neurons. These are eosinophilic and may be surrounded by a pale halo, but this is uncommon in the cerebral cortex. The cortical areas of predilection are the frontal and temporal lobes, the cingulate gyrus and insula, and, rarely, the hippocampus (Yoshimura, 1983). It has been suggested that this distribution correlates with mesolimbic dopaminergic projections (DeKeyser *et al.*, 1990). These bodies are found most commonly in the pyramidal cells of the fifth and sixth layers (Kosaka and Mehraein, 1978). Lewy bodies are also found in the basal ganglia, diencephalon, substantia nigra, locus coeruleus, spinal cord, and sympathetic ganglia (Kosaka *et al.*, 1984). An exclusively cortical form of Lewy body disease with sparing of the pigmented brain stem nuclei has been reported (Masliah *et al.*, 1990). Other patterns of localization have been documented (Pollanen *et al.*, 1993). In otherwise typical Parkinson's disease some cortical Lewy bodies, usually limited to the limbic and insular cortices, can be detected with careful inspection (Hughes *et al.*, 1992). However, their number and distribution are more restricted than in diffuse Lewy body disease (Dickson *et al.*, 1994).

Within the substantia nigra neuronal loss and Lewy body formation tend to be greatest in the ventrolateral region in patients with prominent motor manifestations (Gibb and Lees, 1991) and medial in patients with cognitive manifestations (Rinne *et al.*, 1989). Neuritic abnormalities have rarely been reported (Reyes *et al.*, 1993; Sugiyama *et al.*, 1993). In an atypical case of antiubiquitin, immunostaining revealed abundant dystrophic neurites, torpedolike axons, and abnormal neuritic processes in the molecular layer of the dentate gyrus, pyramidal cell layer in CA1, subiculum, deep layer of the neocortex, claustrum, caudate, putamen, and globus pallidus. Relatively mild neuritic alterations were observed in the nucleus basalis of Meynert and locus coeruleus (Reyes *et al.*, 1993). Dickson *et al.* (1994) found that, in addition to being ubiquitin positive, both cortical Lewy bodies and dystrophic neurites in the CA2/CA3 region of the hippocampus were positive with neurofilament monoclonal antibody (RM032). Lewy body inclusions are immunoreactive for ubiquitin (Bancher *et al.*, 1989) and all three neurofilament proteins (Hill *et al.*, 1991; Schmidt *et al.*, 1991), but not τ-proteins.

Neuronal loss is slight. CAA is a common feature in generalized Lewy body disease (Wu and Dickson, 1990).

SPs can be present throughout the cerebral cortex, particularly in the occipital lobes. Alzheimer's NFTs are also found, mainly in the temporal lobes. However, in many cases Lewy bodies have an exclusive cortical distribution in the absence of Alzheimer-like changes (Armstrong *et al.*, 1991; Dickson *et al.*, 1987; Dickson *et al.*, 1989; Hansen *et al.*, 1990; Itoh *et al.*, 1982).

Immunohistochemically, the cortical Lewy bodies do not differ from the mesencephalic ones. They are immunolabeled with antibodies against ubiquitin, neurofilaments, and gelosin (Wisniewski *et al.*, 1991) and are negative with antipaired helical filaments and Alz50 (Kuzuhara *et al.*, 1988; Love *et al.*, 1988; Schmidt *et al.*, 1991). Dopamine and homovanillic acid are severely depleted in the basal ganglia of cases of Lewy body-variant AD, but were not significantly altered in pure AD cases (Langlais *et al.*, 1993).

Ultrastructurally, the inclusions in the cerebral cortex contained intermediate-sized filaments with variable amounts of granular material and other organelles, whereas the brain stem inclusions consisted of an electron-dense core and an outer area with radially oriented filaments (Fukuda *et al.*, 1993).

Werner Syndrome (Progeria Adultorum)

Werner (1904) first described a syndrome shared by four siblings: "cataracts in combination with scleroderma." Oppenheimer and Kugel (1934) presented a case to which they gave the eponymous designation *Werner syndrome*. Some 150 cases have since been reported. This syndrome differs from classical progeria (Hutchinson–Gilford syndrome), which manifests itself in early childhood and is not associated with neurological symptoms (Stables and Morley, 1994).

Clinical Picture The principal features of the syndrome are premature graying of the hair, baldness, arteriosclerosis, senile changes in the skin, cataracts, diabetes mellitus, and hypogonadism.

Both patients with dementia (Abe *et al.*, 1993) and neurologically and intellectually normal ones (Haustein *et al.*, 1989) have been described. Occasionally, psychotic syndromes and minor neurological abnormalities, such as loss of reflexes and paresthesias, have been reported. Abe *et al.* (1993) reported spastic parapareses and polyneuropathy in a 33-year-old woman in which the disease manifested itself at the end of the second decade.

The mode of inheritance is autosomal recessive. The life expectation is variable. The average age of the patient at death is 47 years.

Pathology Changes are present in the skin, bones, and muscles. The arteries show atherosclerosis. Fibroblasts and lymphocytes from the peripheral blood show evidence of increased chromosomal instability with reciprocal translocations, deletions, and inversions, which led to the term *variegated translocation mosaicism* (Thweatt and Goldstein, 1993).

Neuropathology *Gross appearances.* A variable degree of cerebral atrophy (Fig. 221)

expresses itself in a considerable reduction of brain weight. The cerebellum may be slightly atrophic. The cerebral arteries are atherosclerotic and ectatic.

Light microscopy. Diffuse neuronal loss, particularly prominent in laminae II and III of the cerebral cortex (Fig. 222), is accompanied by astrocytic and microglial proliferation. Moderate to severe lipofuscinosis is found in the neurons of the cerebral cortex, dentate nucleus, and inferior olives. Aside from sclerosis and tortuosity of the arterioles in the cortex, hypothalamus, and white matter (Fig. 223), numerous small infarcts may be present (Fig. 224). Vascular changes are also present in the cerebellum and the spinal cord, with a loss of neurons in the anterior and posterior horns and the intermediolateral nucleus.

Pathogenesis This disease is caused by a recessive mutation that has been mapped to the chromosome 8p11.1–21.1 region (Yu-Ce *et al.*, 1994). Examination of the genotypes of the affected children suggests the order of the mapped loci to be 8pter–D8S135–D8S87–HRG–WT251–WRN–ANK1–PLAT–8cen (Thomas *et al.*, 1993). Normal human fibroblasts achieve approximately 60 population doublings in culture, while Werner syndrome cells usually achieve only approximately 20 population doublings. This suggests that the Werner syndrome gene is a "counting" gene controlling the

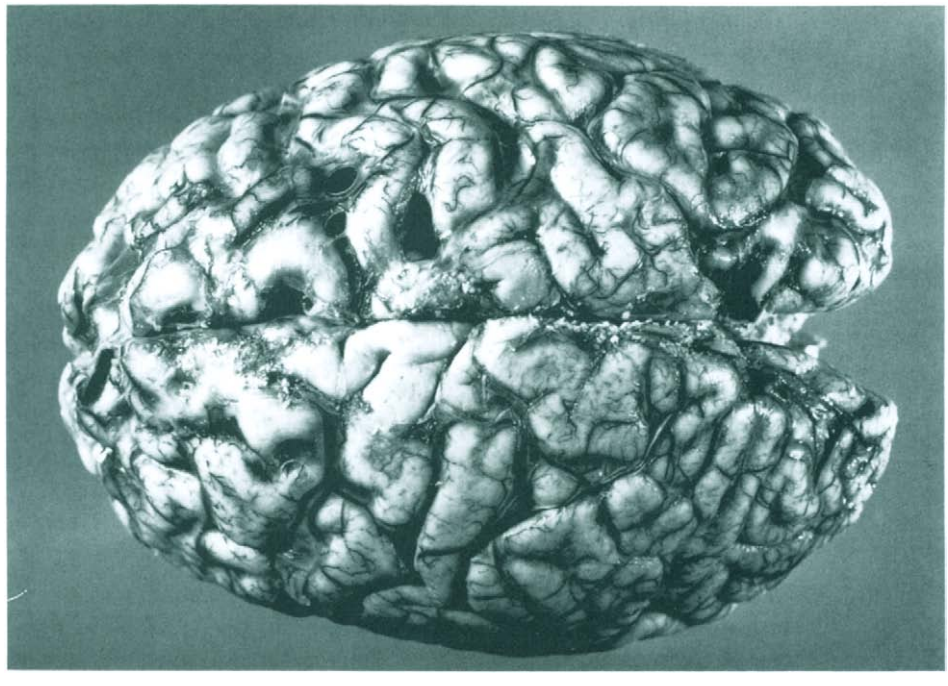


Fig. 221 Werner syndrome. Cortical atrophy of the frontal and parietal lobes, accentuated on the right. (Reproduced from Haustein *et al.*, 1989.)

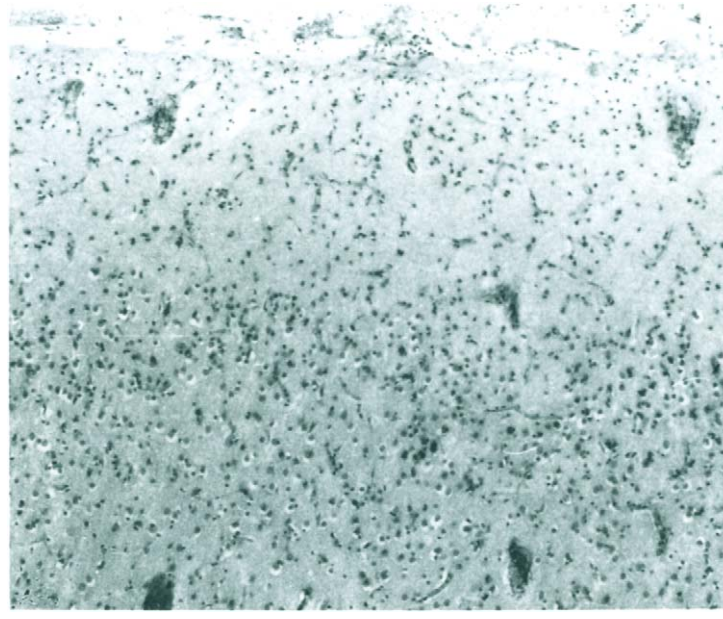


Fig. 222 Same case shown in Fig. 221. A diffuse loss of ganglion cells in laminae II and III of the cerebral cortex. Hematoxylin–eosin stain, ×60.

number of times that human cells are able to divide before terminal differentiation (Faragher *et al.*, 1993).

Several overexpressed gene sequences isolated from a Werner syndrome fibroblast have been shown to possess the capacity to inhibit DNA synthesis and disrupt many normal biochemical processes. Because a similar constellation of genes is overexpressed in Werner syndrome and senescent normal fibroblasts, these data suggest the existence of a common molecular genetic pathway for replicative senescence in both types of cells (Thweatt and Goldstein, 1993).

Sudanophilic Leukodystrophies (Orthochromatic Leukodystrophies; Schilder's Disease; Simple Degenerative Diffuse Sclerosis—Hallervorden; Dysmyelinating Leukodystrophies—Poser)

The comprehensive term *sudanophilic leukodystrophies* embraces a group of biochemically and genetically diverse conditions, the common feature of which is demyelination with accumulation of lipids ("neutral fats"), staining strongly with Sudan dyes (scarlet red, Sudan III, Sudan IV, and oil red O) as well as with basic aniline dyes. This form of myelin breakdown is not confined to metabolic dystrophies, but occurs in myelinoclastic

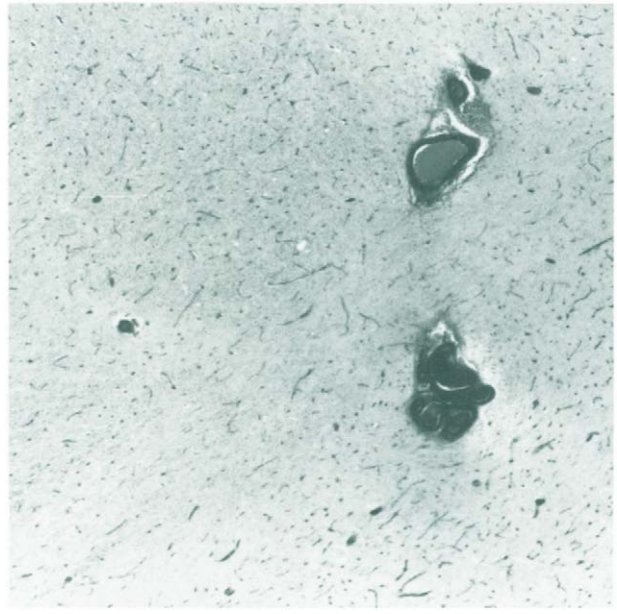


Fig. 223 Same case shown in Fig. 221. Arteriosclerosis of an arteriole in the white matter with tortuosity and glomerular formation. Periodic acid–Schiff stain, ×40.

processes in inflammatory diseases, wallerian degeneration, infarcts, traumatic lesions, and chronic compression.

It is fairly easy to differentiate the myelinoclastic demyelinations from leukodystrophies, using the criteria of inflammatory infiltrates and the asymmetrical distribution of lesions. Once this group was excluded, opinions still differed as to whether a case should or should not be classified as orthochromatic leukodystrophy. Adrenoleukodystrophy, formerly included among the orthochromatic leukodystrophies, is now considered a separate metabolic disorder with a characteristic mode of inheritance, clinical and morphological features, and presumptive enzymopathy (see p. 346). When this group is excluded, some cases remain in the category of orthochromatic leukodystrophies. The clear identification of adrenoleukodystrophy and the attempt to separate Pelizaeus–Merzbacher disease date back only to the 1970s. Since then, very few cases of pure sudanophilic leukodystrophy have been reported, although a breakdown to neutral lipids has been noted in a variety of different syndromes.

This rarity of recent neuropathological studies, combined with the difficulty in evaluating earlier cases, precludes a satisfactory classification, all the more so in that very few cases show a definite genetic pattern.

Various classifications followed that reflected the current state of knowledge concerning the mechanisms of demyelination. Some of these classifications are outdated, while others have better withstood the test of time.

Following Ulrich's (1971) suggestion, we propose classification of the simple or-

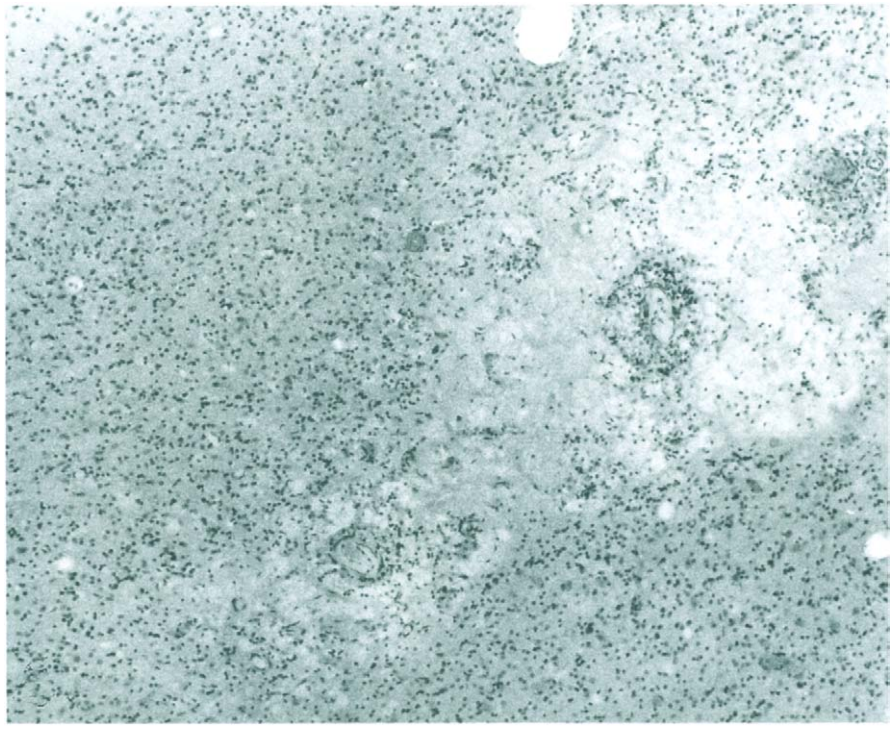


Fig. 224 Same case shown in Fig. 221. A small infarct in the subcortical white matter. Hematoxylin–eosin stain, ×125.

thochromatic leukodystrophies by age groups, and deal separately with the well-defined Pelizaeus–Merzbacher disease, in which molecular genetics events are better known, and with complex syndromes in which sudanophilic leukodystrophy appears combined with other characteristic features.

Congenital Form

The majority of reported congenital cases appear to belong to the Pelizaeus–Merzbacher group. Some authors leave open the question of whether their cases represent a simple suadnophilic leukodystrophy or Pelizaeus–Merzbacher disease. As in the congenital form of Pelizaeus–Merzbacher disease, the characteristic islands of myelin are lacking; the only differential criterion that remains is the intensity of sudanophilic breakdown, or lack of it. Even this may be influenced by the length of survival of the individual patients. Cases defined as transitional may be interpreted as congenital cases with a protracted course.

Clinical Picture Symptoms appear immediately after birth in the form of seizures (Ulrich, 1971; Yokoi *et al.*, 1985) or abnormal head movements. In severe cases the in-

fants are hypotonic and show little or no evidence of psychomotor development. These patients die within days, weeks, or months. Most cases, however, run a protracted course with regression of early development, progressive mental retardation, and quadriplegia. Some of these patients may survive into the second decade.

Neuropathology *Gross appearances.* The brain may be atrophic. On coronal sections the gray and the white matter are barely distinguishable from each other.

Light microscopy. The white matter is largely unmyelinated. The demyelination can encroach on the U-fibers. The myelinization of long tracts may be partially preserved (Ulrich, 1971). The cerebellum is equally demyelinated; some preservation of the myelin sheaths may be seen in the dentate nucleus and the flocculus. Myelinization of the inferior olives and of the cranial and spinal nerve roots is normal, as a rule. The demyelinated areas are studded with numerous fat granule cells, which stain intensely with Sudan dyes. In the myelinated areas fat granule cells are confined to the perivascular spaces. The axons are generally preserved. Moderate to severe fibrillary gliosis is present in all demyelinated areas. No metachromatic breakdown products are seen.

Electron microscopy. Pleomorphic inclusions were found in the cytoplasm of unspecified phagocytic cells (Renier *et al.*, 1981) in addition to vacuolation of the oligodendroglia.

Infantile and Juvenile Forms

Orthochromatic leukodystrophy is rare between the ages of 6 months and 5 years. Most patients in the earlier literature in whom the diseases began between the ages of 5 and 15 years suffered from adrenoleukodystrophy. Ulrich (1971) included all female patients and all those in whom there was no clinical or pathological evidence of adrenal involvement in the group of simple orthochromatic leukodystrophies. Meanwhile, it has become apparent that women may develop adrenoleukodystrophy (see p. 352) and that clinical evidence of a lack of adrenal disease may be unreliable. The whole group, therefore, is open to doubt.

Clinical Picture The onset of symptoms ranges from the age of 2 years to that of 13 years. The course of the disease may be as short as a few months or as long as 10 years or more. Disturbances of coordination are frequently the first symptom. Parapareses, horizontal nystagmus, and choreoathetoid movements may follow. A decline in scholastic performance may be an early symptom in older children. Tonic seizures are not uncommon. As the disease progresses dementia develops, and also spastic quadriplegia, with contractures, blindness, deafness, and bulbar symptoms. Almost all patients die in a state of decerebrate rigidity.

This relatively nonspecific picture of diffuse demyelination can be differentiated from van Bogaert's subacute sclerosing leukoencephalitis (subacute sclerosing panencephalitis) only by the absence of characteristic EEG changes.

Neuropathology *Gross appearances.* Mild cerebral atrophy may be present, sometimes with an occipital accentuation. Norman *et al.* (1962, 1967) found an associated macrogyria in two siblings. Upon sectioning the brain, one finds moderate atrophy of the white matter and dilatation of the lateral ventricles. Hypertrophy of the brain due to ex-

pansion of the white matter has occasionally been reported. Both the cerebral and the cerebellar white matter may be firm and tough or, in some cases, soft and gelatinous. It is always grayish, either focally or diffusely.

Light microscopy. Demyelination may be either diffuse or multifocal, consisting of well-defined and circumscribed lesions. In the latter situation the condition cannot be differentiated from Pelizaeus–Merzbacher disease with any degree of certainty. The focal lesions are distributed over both hemispheres and are joined by a totally demyelinated corpus callosum (Ulrich, 1971). Milder degrees of demyelination may also occur and may manifest themselves only by a pallor of myelin.

An accumulation of strongly sudanophilic fat granule cells is found in all cases. In less severe cases most of the lipid droplets are found in astrocytes. In some cases with severe disintegration of the myelin sheaths, reactive astrocytes were the only phagocytic cells. As a rule, however, phagocytosis is carried out by macrophages that may contain PAS-positive granules as well as lipid droplets. The axons are generally well preserved in areas of demyelination, but may show swellings and other degenerative changes, and may even be destroyed in old lesions from which the products of myelin breakdown have been completely removed. Fibrillary gliosis is prominent in areas of demyelination and may encroach on neighboring, still myelinated, zones. The inflammatory reaction is usually slight and may consist of a few lymphoplasmacytic perivascular infiltrates and occasional glial nodules. The neurons are generally unaffected. Some neuronal loss in the cortex and the brain stem may be seen in patients with severe seizures.

Electron microscopy. Lipid droplets are present in the macrophages and the astrocytes.

Adult Form

Cases have been allocated to this group that were undoubtedly examples of adrenoleukodystrophy. Other patients are included in this group for whom enzymological and biochemical data are inadequate, if available at all. The available clinical and morphological data are insufficient to exclude multiple sclerosis in some cases. The neuropathological findings are equally variable. Some cases are very difficult to classify, particularly those with cyst formation and those with a tigroid pattern of demyelination, interpreted as transition forms to Pelizaeus–Merzbacher disease (Diezel *et al.*, 1965; Rizzuto *et al.*, 1979). The clinical picture is highly variable. The age at onset of the disease ranges from the second to the sixth decades; the duration, from a few months to several years. Mental changes were the first manifestation in many cases.

Neuropathology *Gross appearances.* Marked brain atrophy is present with dilated ventricles. The white matter had a brown discoloration.

Light microscopy. In the demyelinated areas abundant pigmented cells were found containing PAS- and iron-positive, autofluorescent, sudanophilic granules. Immunohistochemistry revealed positive reaction with CD 68 and MAC 387 antibodies to macrophage antigen. Using neurofilament subunit immunocytochemistry, Ferrer *et al.* (1993a) demonstrated widespread axonal degeneration in the cerebral white matter. Calbindin D-28k immunocytochemistry, which selectively recognizes Purkinje cells and their axons, also showed widespread axonal degeneration in the cerebellar white matter.

Electron microscopy. Deposition of electron-dense material, consisting of multilamellar structures or fingerprint profiles, was found (Lang *et al.*, 1993).

Pathogenesis Cases described in the literature as orthochromatic leukodystrophy form a heterogeneous group with a presumably different etiology even within the same age class. An increase in the hexosamine fraction in the white matter was found in about one quarter of the cases. This occurs in metachromatic leukodystrophy and other storage diseases, however, and throws no light on the etiology or pathogenesis of orthochromatic leukodystrophy.

The results of biochemical investigations by various authors are also divergent. They point to disturbances in myelin anabolism and catabolism without explaining the pathogenetic mechanism.

Pelizaeus–Merzbacher Disease

Pelizaeus (1899) examined clinically three generations of a family affected by a hereditary cerebral condition with an early onset and a protracted chronic course. Merzbacher (1910) added observations on several additional members of the same family and published the first anatomopathological examination of one of the patients, who died at the age of 20 years. The clinical diagnosis of Pelizaeus–Merzbacher disease requires a family history, a slowly progressive course, and an appropriate neurological symptomatology. The disease is confirmed when neuropathological examination reveals extensive demyelination with preserved islands of intact myelin. The morphological substrate of the disease, however, falls into at least three patterns:

1. Almost complete demyelination
2. The classical form, with extensive demyelination and well-defined islands of preserved myelin
3. The blotchy blurred pattern, with ill-defined margins of demyelination seen in cases of late onset

On clinical and genetic grounds one can distinguish three forms of the disease: the classical form, with infantile or late infantile onset, inherited as a sex-linked recessive; a congenital form, also probably sex linked; and an adult form, with apparently dominant inheritance. Sporadic transitional forms between the congenital and classical types have also been discussed. Seitelberger (1970) included all cases with tigroid demyelination, including Cockayne's syndrome (see p. 501), in the overall concept of Pelizaeus–Merzbacher disease. Other authors pleaded for a restriction of the eponym to the classical form of the disease (Diezel *et al.*, 1965; Martin *et al.*, 1971).

Congenital Form (Seitelberger Type)

Seitelberger (1954) described a congenital form of Pelizaeus–Merzbacher disease. Other cases of this rare condition have also been reported, sometimes as examples of congenital orthochromatic leukodystrophy (see p. 489) (Norman *et al.*, 1962; Renier *et al.*,

1981; Satoh *et al.*, 1986). A few earlier cases probably belong to this group. Transitional forms between the congenital and classical types have also been described.

Clinical Picture Nystagmus and a total lack of motor development are observed soon after birth. The infants are hypotonic and hardly react to sensory stimuli. Spasticity supervenes in the later stages. Speech does not develop or remains rudimentary. Renier *et al.* (1981) emphasized congenital stridor as a characteristic feature. MRI showed a total alteration of the supratentorial white matter, not sparing the U-fibers, and the infratentorial white matter (Gallucci *et al.*, 1994a). These severely retarded children die after a few years, usually in the first decade (Scheffer *et al.*, 1991), but may survive into the second decade. An early demise has been reported occasionally (Niesenbaum *et al.*, 1965).

Neuropathology *Gross appearances.* Slight atrophy of the cerebellum may be present, particularly in the vermis. Marked cerebellar atrophy has been described occasionally. Upon sectioning the brain, the white matter appears grayish brown and poorly demarcated from the cortex. The corpus callosum is atrophic.

Light microscopy. Myelin stains reveal almost a total absence of myelin sheaths. A partial preservation of the internal capsule with total demyelination of the centrum ovale, corpus callosum, and external and extreme capsules has been described. The axis cylinders are well preserved in both the gray and the white matter. A gliosis of variable intensity is present throughout the white matter. The number of glial cells, particularly oligodendrocytes, is reduced. Fat stains are generally negative and reveal no evidence of active myelin breakdown. A few perivascular lipid-laden macrophages have been seen in some cases (Woelki *et al.*, 1990). A few remaining myelin sheaths may be present in the cerebellar white matter and in the spinal cord. They are very thin and lie mainly in the neighborhood of blood vessels. Neurons are generally preserved in the cortex and the subcortical gray nuclei. Some reduction in the number of Purkinje cells has been observed occasionally. Total atrophy of the cerebellar cortex was present in rare cases.

Electron microscopy. The white matter appears totally devoid of myelin and consists of neuronal processes and astrocytic elements with tightly packed glial filaments. The appearances are similar in the spinal cord, but some thinly myelinated fibers may be seen occasionally. Aside from myelin aplasia, Kolkmann *et al.* (1971) found abnormal mitochondria resembling those seen in Canavan's disease (see p. 527).

Infantile and Late Infantile Forms (Classical Form of Orthochromatic Leukodystrophy of the Pelizaeus–Merzbacher Type)

This form of the disease is characterized by an early onset in childhood and a protracted clinical course. Aside from the cases of Pelizaeus and Merzbacher, several other cases have been reported with typical family histories and characteristic morphological appearances. Although the inheritance is X-linked recessive, occasional cases have been described in girls (Baumrind *et al.*, 1990).

Clinical Picture Slowing of physical and mental development with a loss of already acquired faculties may be observed as early as the first year. Nystagmus and wobbly head

movements appear soon afterward. Disturbances of vision and spastic parapareses with pyramidal signs develop in later years. Skeletal anomalies may occur and some patients are microcephalic. The slow, sometimes stepwise, progression of the disease ends with dementia, which is not necessarily severe, and leads to death between the ages of 15 and 25 years.

Neuropathology A review of the literature reveals some significant differences among cases.

Gross appearances. The brain is atrophic, as a rule. Occasionally, the tigroid demyelination may be appreciable to the naked eye. Severe cerebellar atrophy has been repeatedly recorded (Ulrich, 1971).

Light microscopy. The characteristic demyelination is present predominantly in the central parts of the cerebral and the cerebellar white matter (Fig. 225), but also in the brain stem (Fig. 226) and the spinal cord. The demyelination usually spares the U-fibers, but may affect the myelinated fibers in the cerebral cortex (Yokoi and Ishii 1959; Lüthy and Bischoff, 1961). Patches with remarkably well-preserved myelin sheaths may be seen in the demyelinated areas. These are not always related to blood vessels, and may also be seen in the cortex. In some circumscribed areas the demyelination may be complete Diezel and Huth, 1963). Damage to the axons may be slight or moderate (Poser, 1968). A striking feature is the absence of active breakdown, particularly of the fat granule cells (Konishi and Kamoshita, 1975). Cases with typical islands of preserved myelin and abundant fat granule cells (Diezel and Huth, 1963) are interpreted as transitional between Pelizaeus–Merzbacher disease and simple orthochromatic leukodystrophy. Fibrillary gliosis accompanies the loss of myelin. The number of oligodendrocytes is reduced, while that of astrocytes is increased. Peripheral nerves are unaffected, as a rule. Occasionally, the Purkinje cells in the cerebellum were reduced in number and abnormally positioned (Baumrind *et al.*, 1990). Cruz-Sanchez *et al.* (1989b) reported on a patient who presented with a clinical syndrome compatible with leukodystrophy and in whom neuropathological features of both Pelizaeus–Merzbacher disease and subacute necrotizing encephalopathy were apparent.

Electron microscopy. The remaining myelin sheaths show no definite abnormalities. Oligodendrocytes are hypertrophic, with large nuclei and prominent nucleoli. Their cytoplasm contains abundant mitochondria, ribosomes, and endoplasmic reticulum, as well as a Golgi apparatus and microtubules. Almost all oligodendrocytes contain intracytoplasmic inclusions, up to 1 μm in diameter, consisting of a central vacuole surrounded by concentric lamellae. The vacuoles may contain granules resembling ribosomes. The lamellae may form up to 20 layers with a periodicity of 8 nm.

Adult Form (Cases of Late Onset; Löwenberg–Hill Type)

Löwenberg and Hill (1933) described a patient whose disease began in adulthood and whose morphological appearances resembled those of Pelizaeus–Merzbacher disease. Subsequently, four other members of the family were similarly affected (Camp and Löwenberg, 1941). Certain clinical and morphological peculiarities have caused some authors to raise doubts about placing these cases in the Pelizaeus–Merzbacher group (Peiffer and Zerbin-Rüdin, 1963).

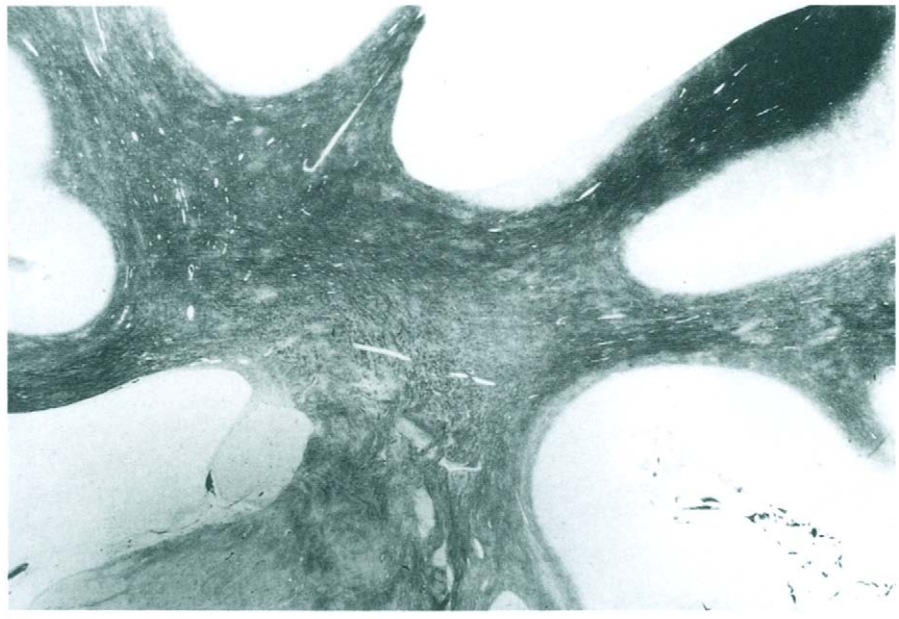


Fig. 225 Late infantile form of Pelizaeus–Merzbacher disease. Spotty demyelination of the centrum semiovale. Heidenhain–Wölcke stain.

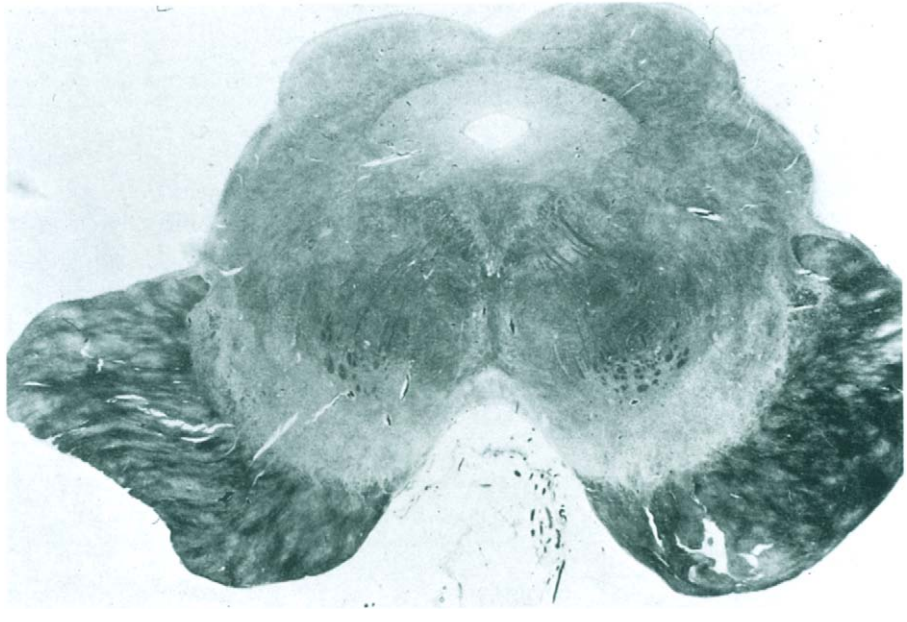


Fig. 226 Same case shown in Fig. 225. Demyelination is apparent in the cerebral peduncles. Heidenhain–Wölcke stain.

Clinical Picture The disease begins around the age of 40 years with progressive paraparesis, muscular wasting, and urinary and fecal incontinence (Bruyn *et al.*, 1985). Seizures and mental decline develop later. Decerebrate rigidity marks the terminal stage.

Neuropathology *Gross appearances.* The brain is moderately atrophic. Coronal sections reveal a glassy gray discoloration of the white matter with sunken patches resembling sago grains in the central parts. The U-fibers are preserved. The cerebellar white matter is of an elastic rubbery consistency, with circumscribed areas of glassy gray discoloration.

Light microscopy. The demyelinated area extends from the frontal to the occipital lobes. The arcuate fibers are generally preserved, but an ill-defined demyelination may encroach on the cortex in the floors of the sulci. In the central parts of the white matter, ill-defined irregularly shaped foci of partial demyelination are found in juxtaposition with totally demyelinated areas. Rarefaction of the tissue may amount to a status spongiosus or even larger defects. Well-preserved patches of myelin may be found around larger intracerebral blood vessels, yet the typical tigroid appearance is rarely seen. The cerebellar white matter is uniformly pale. The axis cylinders are damaged and rarefied in the areas of severe demyelination. Axonal swellings are abundant, as are fragments of broken-down axons. Neurons are well preserved. Those of the third and fifth cortical layers contain abundant lipid. Fat stains show lipid in the neurons and fat droplets in the microglial cells. Fat granule cells are rarely seen in areas of demyelination, and almost exclusively around blood vessels. In stains for glial fibers, a marked discrepancy becomes apparent between the severe demyelination and the sparse fibrillary gliosis. Cells resembling Alzheimer's type II glia may be present. Diezel *et al.* (1965) found a rarefaction of the granule cells and abnormalities in the Purkinje cells in one of their cases.

Electron microscopy. An accumulation of fingerprint bodies was found in the satellite cells and the interfascicular oligodendroglia of the white matter (Bruyn *et al.*, 1985).

Pathogenesis The disease is attributed to a primary severe defect in myelinization of the otherwise normal axons. The reduced number of oligodendrocytes and the absence of breakdown products are indicators against a degradation of preexisting myelin sheaths. Diezel *et al.* (1965) assumed prenatal damage preventing normal myelinization. Schneck *et al.* (1971) attributed the defective myelinization to faulty maturation of the oligodendroglia. Bruyn *et al.* (1985) postulated a lysosomal disease of the oligodendrocytes.

The question of whether the congenital, classical, and adult forms can be subsumed in one entity cannot be answered at present. Some authors considered it probable that the three forms were genetically heterogeneous, but could not exclude the possibility of a phenotypically divergent expression of the same genotype. The intermediate cases rest on purely morphological criteria and cannot be used to support one or the other view. Sequence analysis revealed a single C-to-T transition in exon IV, which leads, in amino acid 155, to a T-to-I substitution within a hydrophobic intramembrane domain (Weimbs *et al.*, 1990). This mutation leads to disruption of myelinogenesis. Pham-Dinh *et al.* (1991)

identified a V-to-F point mutation in a putative extracellular loop of myelin proteolipid. Kurosawa *et al.* (1993) identified an insertion event in exon VII of the proteolipid protein (*PLP*) gene, and Iwaki *et al.* (1993) recognized a G-to-T transition in exon V. PLP is an integral membrane protein of CNS myelin. A transversion in nucleotide pair 35 (Pratt *et al.*, 1993) and an insertion/deletion (Pham-Dinh *et al.*, 1993) of exon 4 of PLP has been found. The disease has also been mapped to Xq21–q22 as an allelic disorder (Saugier-Veber *et al.*, 1994).

Hypomyelinization in Animals Two mouse mutants (*quaking* and *jimpy*) show a defect in the synthesis and deposition of myelin (Sidman *et al.*, 1964), which resembles that presumed to occur in Pelizaeus–Merzbacher disease. Sapirstein (1982) already attributed the hypomyelinization to a defective expression of the oligodendroglial plasma membrane proteins. Mutations of the X chromosome-linked *PLP* gene cause glial cell death and myelin deficiency in *jimpy* mice and canine *shaking* pups (Trofatter *et al.*, 1989; Nadon *et al.*, 1990). In other neurological mutants by transgenic complementation an increase of the *PLP* gene dosage with only twofold transcriptional overexpression results in a severe hypomyelinization and astrocytosis. Schneider *et al.* (1992) found that the mouse mutant *rumpshaker*, defined by the I-to-T amino acid substitution at residue 186 in a membrane-embedded domain of PLP, although myelin deficient, has morphologically normal oligodendrocytes. They suggested that PLP has a vital function in glial cell development, distinct from its later role in myelin assembly. This may explain the clinical spectrum of Pelizaeus–Merzbacher disease. Gow *et al.* (1994) postulated that the pathobiology observed in *PLP* mutants may result from oligodendrocyte cell death caused by the accumulation of misfolded protein in the endoplasmic reticulum. Failure of PLP to reach the cell surface of oligodendrocytes, rather than the inability of the mutant protein to perform some crucial function at the cell surface, may be responsible for the diseases caused by many *PLP* mutations.

Complex Syndromes with Orthochromatic Leukodystrophy

Leukodystrophy with sudanophilic breakdown occurs in a variety of unrelated conditions, associated with other lesions in the CNS or the peripheral nervous system, as well as in the skin. These are rare diseases, and their etiology and pathogenesis are unknown. Cockayne's syndrome is sometimes included in this group (Peiffer, 1984).

Orthochromatic Leukodystrophy with Meningeal Angiomatosis

Divry and van Bogaert (1946) described this syndrome in two siblings. Additional cases of this type were reported by Bignami *et al.* (1966). The case of Iglesias *et al.* (1981) with angiofibrosis of the brain stem does not belong to this group.

Clinical Picture All affected patients have been male. Two pairs of brothers were among the reported cases. The patients of Divry and van Bogaert (1946) were young

adults; all others were children, in some of whom the disease started in infancy. In the adult cases an abnormal blood flow through the skin was apparent in some segments. Mental changes were prominent in all cases and psychomotor retardation was found in children. Epileptic seizures occurred almost regularly; contractures and incontinence were common in the terminal stages. These children died before the age of 2 years after a 6- to 12-month duration of the illness. In adolescents and adults the course was protracted, and death occurred only after several years.

Pathology Fatty infiltration of the liver is found in the majority of the cases. Sudanophil lipid was present in the renal tubules in the somewhat atypical case reported by Martin *et al.* (1968).

Neuropathology Grossly dilated, mostly venous, telangiectatic vessels are present throughout the leptomeninges of the cerebrum and the cerebellum. The dura is also thickened, highly vascular, and congested. The angiomatosis is more pronounced in the occipital region. Both total and selective necroses may be present in the cerebral cortex, globus pallidus, and thalamus. Demyelination can be seen in the white matter of the cerebrum and the cerebellum, but in some cases it is confined to the cerebrum. It is not clearly demarcated, spares the U-fibers, and is associated with sudanophilic breakdown products, generally phagocytosed by glial cells. In the case reported by Divry and van Bogaert (1946), the tinctorial properties of the lipid were unusual in that it stained orange with the red Sudan dyes. In a case documented by Martin *et al.* (1968), the peripheral nerves were also involved. The demyelination was independent of cortical necroses and occurred also in the corpus callosum and in distant areas of the white matter. It was accompanied by an isomorphic gliosis.

Dermatoleukodystrophy with Neuroaxonal Spheroids

This syndrome was first described by Matsuyama *et al.* (1978). Autopsy of four cases was reported by Axelsson *et al.* (1984) as evidence of "hereditary diffuse leukoencephalopathy with spheroids" in a Swedish family with 71 members of four generations. One case discussed by Minagawa (1980) corresponds to the infantile form with early onset. Two cases of adult leukodystrophy described by Oda *et al.* (1983) can be included in this group.

Clinical Picture The children with this condition had thickened wrinkled skin since birth. In the cases with early onset after 6 months of normal development, a progressive neurological disorder appeared, with psychomotor retardation. In the other cases age at onset varied between 8 and 60 years. The patients presented amnestic data of various combinations of psychiatric symptoms with depression, anxiety, aggression, and severe dementia. The neurological symptoms were impaired balance with retropulsion, hyperkinesia, and epilepsy. Gastrointestinal disorders, arthritis, and gynecological problems were also present in many members of the family.

Approximately one third of the patients died within 3 years of the onset of symptoms; one third, after about 10 years; and one third, after more than 30 years. The reasons for

this variation remain unclear, but the course is evidently more fulminant in patients with an early onset of psychiatric and neurological symptoms.

Pathology The cause of death in both cases of Oda *et al.* was bronchopneumonia and pulmonary edema. The skin showed epidermal hyperplasia with hyperkeratosis, as well as hypercellularity and connective tissue overgrowth in the dermis.

Neuropathology *Gross appearances.* The brains were moderately to severely atrophic. The consistency of the white matter appeared firm upon sectioning the brain.

The white matter of the centrum semiovale and the temporal lobes showed a grayish brown discoloration extending into the proximal parts of the gyral white matter but leaving the subcortical U-fibers unaffected. The internal capsules displayed considerable shrinkage and a pale brownish discoloration. Grayish discoloration was noticed in the pyramidal tracts of the medulla.

Atrophic changes were found, particularly in the anterior parts of the brain, and there was diffuse degeneration of the myelin and the axons in the same areas. The most prominent and characteristic features detected by light microscopy were peculiar axonal changes (i.e., neuroaxonal spheroids) in the extensively destroyed cerebral white matter of all autopsy cases.

Light microscopy. A diffuse but irregularly distributed loss of myelin sheaths with relatively preserved U-fibers (Axelsson *et al.*, 1984) was accompanied by fibrillary gliosis. Numerous sudanophil lipid-laden macrophages were found in the deeper parts of the centrum semiovale, internal capsule, pyramidal tracts, globus pallidus, thalamus, and cerebellar white matter. Numerous axonal swellings of variable diameter up to several micrometers were present. The spheroid bodies stained with varying intensity in H&E, luxol fast blue, and cresyl violet, van Gieson, and silver staining. With silver staining they showed dark dense fibrillary material surrounding a centrally located pale zone, but in some areas completely black. Under ultraviolet light these bodies displayed a greenish yellow autofluorescence. The spheroid seemed to be negative for iron, but iron deposits were located intracellularly in the glial cells. Cells identified as oligodendrocytes showed an asymmetrically expanded cytoplasm studded with fine PAS-positive granules.

Electron microscopy. The axonal spheroids consist partly of an osmiophilic matrix and partly of concentric lamellae. The granules in oligodendrocytes were also strongly osmiophilic, while the matrix was not as electron dense as in the spheroids. Similar changes were seen in Schwann cells of the peripheral nerves (Matsuyama *et al.*, 1978).

Sudanophilic Leukodystrophy with Microcephaly and Calcification

This is a heterogeneous group. It was first mentioned by Bodechtel (1929) in a family with Pelizaeus–Merzbacher disease. The first morphological description was published by Horanyi-Hechst and Meyer (1939). The group is heterogeneous both in the age at onset and in the distribution of the lesions, but shares some common clinical and morphological features.

Aside from these heterogeneous cases, some of which are difficult to classify, the following syndromes belong to this group: Laubenthal–Hallervorden syndrome (p. 500),

Pena–Shokeir syndrome type II (p. 501), Cockayne's syndrome (p. 501), and neuroaxonal dystrophy with basal ganglia mineralization (Venkatesh *et al.*, 1994). While some authors consider these to be variants of the same entity, they are best considered separately until their nosology is clarified by genetic studies.

Clinical Picture The disease begins in infancy in some cases (Jervis, 1954), but in the late infantile period in most instances (Kufs *et al.*, 1954). The condition is familial. The presenting symptoms in the infantile group are microcephaly, psychomotor retardation, and spasticity, while seizures predominate in the late infantile cases. Choreoathetoid movements (Horanyi-Hechst and Meyer, 1939) or a spastic paraplegia (Norman *et al.*, 1962) may follow. The patients with disease of early onset die before the age of 5 years; those with later onset and a more protracted course, during the second decade.

Pathology In the majority of the cases, the internal organs are normal. Hepatomegaly and a small spleen were recorded by Norman *et al.* (1962).

Neuropathology Gross appearances. The brain is severely atrophic. The atrophy is particularly striking in the brain stem and the cerebellum, with the exception of the vermis. The lateral ventricles are enlarged. A large part of the white matter is gray and soft, feels spongy, and tends to sink under the cut surface.

Light microscopy. Extensive demyelination of variable severity and distribution is present. In younger patients active myelin degradation is prominent, with numerous fat granule cells that stain orange with Sudan dyes and are PAS positive. The longer the clinical course, the less abundant are the fat granule cells. They may be absent in patients who survive into the second decade. Calcifications may appear in the cerebral cortex adjacent to the demyelinated white matter.

Infantile Familial Encephalopathy with Cerebral Calcifications and Leukodystrophy (Laubenthal-Hallervorden Syndrome)

This combination of lesions occurs in three conditions: Laubenthal–Hallervorden syndrome, Pena–Shokeir syndrome type II, and Cockayne's syndrome.

Cases reported as variants of diffuse sclerosis may belong to this group or to that discussed previously. The entity was defined by Laubenthal and Hallervorden (1940). Several additional cases have been reported, which, in spite of individual differences, share a number of clinical and neuropathological features.

Clinical Picture The disease manifests itself sometime soon after birth (Aicardi and Goutieres, 1984; Razavi-Encha *et al.*, 1988), but mainly after some weeks or months, or even in the second year. The children are retarded, dystonic, and spastic. They are generally microcephalic and suffer from epileptic seizures. Bilateral calcifications in the basal ganglia, white matter, and cerebral and cerebellar cortices have been demonstrated radiologically and by CT scan (Aicardi and Goutieres, 1984; Miura *et al.*, 1985; Razavi-Echna *et al.*, 1988). Hypodensity of the white matter can also be seen on CT. Some patients show a persistent lymphocytosis in the CSF (Aicardi and Goutieres, 1984).

Neuropathology *Gross appearances.* The brain is atrophic with a normal convolutional pattern, hypoplasia of the corpus callosum, and hydrocephalus. Occasionally, cerebellar hypoplasia and retrocerebellar arachnoid cysts have been seen (Troost *et al.*, 1984). Upon sectioning the brain, calcium concrements are found in the basal ganglia, thalamus, cerebral and cerebellar white matter, and dentate nucleus.

Light microscopy. A diffuse loss of axons and myelin is seen in the white matter (Laubenthal and Hallervorden, 1940), in some cases associated with a honeycomb rarefaction (Razavi-Echna *et al.*, 1988). The calcifications are perivascular and may occlude the lumen. They are PAS positive. Neuronal loss occurs in areas of dense calcification.

Electron microscopy. The hyperplastic astrocytes show a marked increase in glial filaments (Razavi-Echna *et al.*, 1988).

Pathogenesis Smits *et al.* (1983) emphasized the progressive nature of the disease by drawing attention to the differences in the extent of calcification in siblings of different ages.

Pena–Shokeir Syndrome Type II (Cerebrooculofacial Skeletal Syndrome)

This syndrome, described by Pena and Shokeir (1974b), occurs in children of all races and both sexes, with a slight predilection for Native Americans (Shokeir, 1982). Microcephaly, microphthalmos or anophthalmia, arthrogryposis, osteoporosis, and bony dysplasias are the principal features. The children are retarded and die usually at the age of 3–4 years from intercurrent respiratory infections. Symmetrical calcifications in the basal ganglia and the white matter of the hemispheres are seen on CT scans (Linna *et al.*, 1982).

Neuropathology Poor demarcation between the gray and the white matter and neuronal loss in the cerebrum, cerebellum, and ganglion cell layer of the retina are prominent features. The ventricles are dilated and the atrophy of the white matter resembles a leukodystrophy. Focal calcifications have also been seen.

The interpretation that this syndrome is an early infantile variant of Cockayne's syndrome is not very convincing (Lowry, 1982). Silengo *et al.* (1984) reported a case of the syndrome originally described by Neu *et al.* (1971) and interpreted it as a lethal variant of the cerebrooculofacial syndrome of Pena and Shokeir.

Cockayne's Syndrome (Cockayne–Neill–Dingwall Syndrome; Dwarfism with Retinal Atrophy and Deafness)

This disease was described by Cockayne (1936) in two siblings as dwarfism with retinal atrophy and deafness. Ten years later the same author pointed out the progressive nature of the disease (Cockayne, 1946).

Clinical Picture After normal birth and early development symptoms appear during the second year. These consist of stunted growth, RP, mental retardation, impaired hearing or deafness, deep-set eyes, prognathism, low-set ears, coarse voice, and hypohidrosis of the skin, which is abnormally sensitive to ultraviolet light. Photodermatosis may occa-

sionally appear as the first symptom. An unexplained febrile illness may precede the onset of symptoms in some cases. Late onset in the second decade is rarely observed. The disease frequently affects siblings (Leech *et al.*, 1985). Cerebellar and extrapyramidal symptoms are slowly progressive in most patients. Severe mental retardation is present in all patients. Most patients do not survive beyond the second decade, but survivors well into middle age have been reported (Scott *et al.*, 1993a; Miyanoki *et al.*, 1994).

Thickening of the skull bones and intracranial calcifications are the characteristic radiological features (Takada and Becker, 1986). CT and MRI confirm the generalized atrophy, calcifications, and low density of the white matter (Damaerel *et al.*, 1993). Two genetically different complementation groups, A and B, have been identified, of which B is the more common. Conduction velocity in the peripheral nerves is impaired in 80% of the cases (Smits *et al.*, 1982), but not as severely as in the central motor pathway (Cruz-Sanchez and Anciones, 1991).

Pathology The skin lesions resemble those of xeroderma pigmentosum (Guzetta, 1972), but, in contrast with that condition, skin cancers are uncommon, even in long-term survivors (Scott *et al.*, 1993a). Abnormally small exocrine sweat glands were described by Landing *et al.* (1983) as a characteristic feature of the syndrome.

Neuropathology *Gross appearances.* Thickened leptomeninges are commonly seen. The brain is microcephalic with pronounced cerebellar atrophy (Leech *et al.*, 1985) and dilated ventricles. The white matter appears pinkish gray and of a soft consistency, with focal cystic subcortical softenings. Calcifications are localized in the periventricular white matter and the centrum semiovale as well as in the striatum, pallidum, and dentate nucleus.

Light microscopy. The leptomeninges are fibrotic. The cerebral cortex is atrophic. A spotty demyelination is seen in the white matter, involving the U-fibers (Leech *et al.*, 1985). Sudanophilic lipid is abundant (D'Hoore and Gullotta, 1971). Small areas of preserved myelin, unrelated to the blood vessels, are present in the cerebral cortex, internal capsule, and basal ganglia. Moossy (1967) found excessive lipofuscin in the basal ganglia, thalamus, pons, medulla oblongata, and dentate nucleus. Leech *et al.* (1985) noted binucleate Purkinje cells. The optic nerve is often atrophic and shows an isomorphic gliosis (Gandolfi *et al.*, 1984). The primary atrophy of the spiral ganglion leads to transneuronal degeneration of the ventral cochlear nucleus (Gandolfi *et al.*, 1984).

Both in the cerebrum and in the cerebellum an extensive accumulation is seen of small and large, partially confluent, calcium concrements ("brain stones"), both free and perivascular (Norman and Tingey, 1966; Urich, 1976; Houston *et al.*, 1982). There is no topographic correlation between calcification and demyelination, the former being more extensive.

Alzheimer's NFTs are found in the cerebral cortex (Soffer *et al.*, 1979) and also in the nucleus basalis, locus coeruleus, and substantia nigra (Takada and Becker, 1986), but, in contrast with AD and Down syndrome, no Aβ immunoreactivity could be demonstrated (Woody *et al.*, 1991). Multinucleated astrocytes are seen particularly in the cerebral cortex. The walls of the ventricles show breaches in the ependyma and subependymal gliosis. The choroid plexuses are atrophic (Urich, 1976).

Segmental demyelination was found in the peripheral nerves by several authors (Sasaki *et al.*, 1992), but not by others (Jin *et al.*, 1979).

Electron microscopy. Hypomyelinization was seen in the white matter (Kennedy *et al.*, 1980). The NFTs consist of paired helical filaments (Takada and Becker, 1986). Membrane-bound polymorphic inclusions were found in the Schwann cells (Vos *et al.*, 1983).

Pathogenesis The presence of Alzheimer's NFTs was interpreted as a sign of premature aging of the brain (Takada and Becker, 1986). The nuclear atypias in astrocytes and neurons may be due to an accumulation of damaged and unrepaired DNA fragments (Leech *et al.*, 1985). Early-onset Cockayne's syndrome and chromosomal anomaly (47XXX) in one patient seem to be coincidental (Hayashi *et al.*, 1992).

Skin fibroblasts from patients with Cockayne's syndrome show a diminished ability to form colonies *in vitro* after ultraviolet irradiation. The restitution of the DNA damaged by ultraviolet light is delayed. The probable causes are either a defective DNA polymerase or impaired rejoining of the DNA strands (Schwaiger and Hirsch-Kauffmann, 1986). There is no correlation, however, between the degree of impairment of DNA repair and the severity of neurological involvement (Sugita *et al.*, 1991). The long-surviving patients of Miyauchi *et al.* (1994) with typical Cockayne's syndrome had only slight impairment of DNA repair. The relationship between Cockayne's syndrome and xeroderma pigmentosum remains obscure. They certainly share similar skin lesions, and some cases of Cockayne's syndrome are associated with the complementation groups B and D, and occasionally G, of xeroderma pigmentosum (Vermeulen *et al.*, 1993). Cases with clinical characteristics of xeroderma pigmentosum, but biochemical features of Cockayne's syndrome, have been reported (Greenhaugh *et al.*, 1992; Scott *et al.*, 1993a).

Classical Cockayne's syndrome patients are primarily deficient in the preferential repair of DNA damage in actively transcribed genes, whereas in most xeroderma pigmentosum patients the genetic defect affects both "preferential" and "overall" nucleotide excision repair modalities. Therefore, xeroderma pigmentosum and Cockayne's syndrome are biochemically closely related and may be part of a broader clinical disease spectrum (Vermeulen *et al.*, 1993).

Mutations of the human repair gene *ERCC6*, a presumed DNA (or RNA) helicase, are responsible for the hereditary repair disorder Cockayne's syndrome complementation group B, the most common form of the disease. This gene consists of at least 21 exons, together with the promoter covering a region of 82–90 kb on the genome. The "invariable" GT dinucleotide in the consensus (C,A)AG/GTPuAGT is replaced by the exceptional GC (Troelstra *et al.*, 1993).

Cholesterol Ester Leukodystrophy (Yates)

Yates *et al.* (1982) described a case with severe demyelination and increased cholesterol esters, which they interpreted as a new type of leukodystrophy. The 31-year-old patient developed disorders of gait, homonymous hemianopia, and a left-sided facial paresis with hypesthesia 10 months before death. Four months later he became increasingly lethargic.

Neuropathology *Gross appearances.* The white matter of the centrum semiovale appeared spotty, with adjacent dark and ivory patches. The consistency of the tissue was firm. The white matter of the basal ganglia was similarly affected. Cystic changes were

present in some demyelinated areas. The cerebral and cerebellar cortices were macroscopically unremarkable, as was the cerebellar white matter.

Light microscopy. The confluent foci of demyelination contained numerous reactive astrocytes, with a total loss of oligodendroglia and a partial loss of axons.

Pathogenesis This unique case has been included in the group of sudanophil leukodystrophies because of its clinical, morphological, and biochemical features. A search for other affected members of the family revealed no abnormality (Yates, personal communication).

Pigmented Form of Orthochromatic Leukodystrophy (Late Adult Form of Orthochromatic Leukodystrophy; Leukodystrophy with Pigmented Glial Cells)

The first case of this disease was described by van Bogaert and Nyssen (1936) under the term "late form of familiar progressive leucodystrophy." Additional cases have been reported by Gray *et al.* (1987) and Tunon *et al.* (1988).

The disease manifests itself clinically in adult age. Decline of intellectual faculties, disorientation, and loss of judgment are often the first symptoms. Dysarthria, pyramidal symptoms, and spastic quadriparesis develop subsequently. The clinical course is steadily progressive and leads to death within 3–13 years. Some cases were familial (van Bogaert and Nyssen, 1936; Okeda, 1989; Constantinidis and Wisniewski, 1991), whereas others were sporadic.

An early onset has been rarely reported (Harding *et al.*, 1990; Seiser *et al.*, 1990; Taniike *et al.*, 1992), with progressive psychomotor deterioration starting after birth or during early infancy.

Neuropathology Macroscopically, most cases showed marked or slight atrophy. Coronal sections revealed a bilateral and symmetrical gray–brown discoloration of the hemispheric white matter, more marked in the frontal lobes and in the periventricular regions, where its consistency was firmer than usual. Dilatation of the lateral ventricle, chiefly in the frontal horns, can be observed.

Light microscopy. A bilateral symmetrical demyelination with sparing of the U-fibers is present in the white matter of the cerebral hemispheres. The demyelination is most prominent in the frontal lobes. The brain stem and the cerebellum are minimally involved. Atrophy of the cerebellar cortex is observed occasionally. Aside from scanty macrophages filled with sudanophilic nonmetachromatic lipid, both astrocytes and macrophages contain a brownish pigment staining positively for iron. However, a positive iron reaction is not always present. No inflammatory infiltrates are seen. The pigment granules in the astrocytes are blackish yellow and stain a greenish black color with Nissl's cresyl violet. In the demyelinated areas an isomorphous diffuse gliosis was observed. Oligodendroglia was depleted in these areas, but a relative increase in the number of oligodendrocytes, identified by their reactivity to myelin basic protein antibody, was observed in the less affected subcortical regions as well as in small foci scattered in the deep white matter (Tunon *et al.*, 1988). The case reported by Taniike *et al.* (1992) showed

unique findings of severe neuronal loss and the collection of globoid-like cells in the interface of the gray and the white matter. Gray *et al.* (1987) found changes in the phospholipid fraction with an increase in plasmalogens.

Electron microscopy. Deposition of electron-dense material consisting of multilamellar structures or fingerprint profiles was found (Lang *et al.*, 1993). Electron microscopy of the white matter shows that most macrophages and many astrocytes were filled with membrane-bound cytosomes containing poorly defined electron-dense multilamellar inclusions and massive fingerprint profiles accompanied by various amounts of lipofuscin and lipid droplets. Similar electron-dense inclusions are also present in oligodendrocytes of the white matter.

Membranous Lipodystrophy (Hereditary Polycystic Osteodysplasia with Sclerosing Leukoencephalopathy; Nasu–Hakola Disease)

This is a chronic disease of the bone and the CNS in which the coincidence of involvement of the two systems was overlooked until Nasu *et al.* (1970) established that it formed part of a single nosological entity.

Clinical Picture The disease manifests itself in adolescence or in young adult life, usually in the third decade. The first symptoms are pains in the bones of the limbs and fractures. Neurological symptoms appear only in some cases. Soon after the onset of bony symptoms, or sometimes even before, personality changes and behavioral disorders suggestive of frontal lobe syndrome become apparent, progressing to dementia (Miyazu *et al.*, 1991). Pyramidal and extrapyramidal symptoms develop frequently, and seizures occur in about 50% of the cases. Radiologically, resorption of bone is apparent in long bones and also in carpal and tarsal ones. Shibata *et al.* (1990) found diffuse changes in the cerebral white matter and cerebellar atrophy by CT and MRI. (Preziuso *et al.*, 1992). A T_2-weighted MRI finding of reduced signal intensity in the thalamus and the putamen probably relates to intracranial calcification. The patients die usually 15–20 years after the onset of symptoms. The disease is usually inherited as an autosomal-recessive trait (Deisenhammer *et al.*, 1993).

Pathology *Gross appearances.* Gross wasting of the whole body is accompanied by a severe loss of adipose tissue. The heart shows brown atrophy. The bones are thin and fragile and are filled almost entirely with fatty marrow.

Light microscopy. Membranous structures are seen in the fatty marrow as well as in subcutaneous, mesenteric, and retroperitoneal fat. The membranes are heavily folded and lie between the adipose cells. They are eosinophilic, sudanophilic, and PAS positive. They stain with luxol fast blue and Baker's hematin and are autofluorescent. They are not pathognomonic, however, Fujiwara (1979) found these membranes in the adipose tissue of 50% of the routine autopsy cases. The autofluorescence suggests that they contain oxidized lipids. Lipid staining and the lipase digestion test revealed triglycerides localized in the cystic spaces in the microtubular structures. Lectin histochemical examination

demonstrated that *Maclura pomifera* agglutinin bound strongly to the membrane (Mii *et al.*, 1991).

Electron microscopy. The folded bands consist of complex substructures. Microtubules are arranged at right angles to the inner surface of the membranes, which are filled with an amorphous lightly osmiophilic substance. The outer side of the membranes consists of a network of tubules and vesicles (Tanaka, 1980).

Neuropathology Matsushita *et al.* (1981) divided all neuropathologically examined cases into two groups: one with sudanophilic (Nasu *et al.*, 1970; Tanaka, 1980) and the other with sclerosing leukodystrophy (Koizumi *et al.*, 1980; Minagawa *et al.*, 1985; Yokoi *et al.*, 1989).

Light microscopy. The white cores of the gyri are narrow and the deep white matter is shrunken. In preparations stained for myelin, demyelination is barely appreciable to the naked eye. In cases with sudanophilic breakdown, there are numerous perivascular macrophages filled with sudanophilic lipid. In other cases only isolated sudanophilic granules can be seen in addition to scanty perivascular fat granule cells. The histochemical reactions of the fat granules are those of glycolipid and sphingolipid, without metachromasia. The white matter is highly cellular, the cell population consisting of oligodendrocytes and reactive astrocytes with abundant fibrils. Gliosis is particularly prominent in patients with the sclerosing type of leukodystrophy, in which it exceeds by far the gliosis expected from the degree of myelin loss (Minagawa *et al.*, 1985). The appearances correspond with those described by van Bogaert and De Buscher (1939) as "*dissociation gliomyélinique.*" The destruction of the white matter is most prominent in the deep frontal white matter, where it consists of confluent patches. The axons are also reduced in number and axonal spheroids are seen throughout the white matter. Gray matter involvement has been reported in only a few publications. Minagawa *et al.* (1985) reported lesions of Onufrowicz' nucleus, and Miyazu *et al.* (1991) diagnosed thalamic degeneration. Amano *et al.* (1987) reported a diffuse polio–leukoencephalopathic type.

Electron microscopy. The axonal spheroids consist of aggregations of mitochondria, electron-dense inclusions, and small lamellar bodies (Amano *et al.*, 1987).

Pathogenesis The pathogenesis is unknown, but is believed to be an enzyme defect of the glycolipid metabolism. Oishi *et al.* (1993) found in two patients increased nervonic acid in the serum lipids, and the plasma amino acid analysis showed decreased glutamine.

Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (Hereditary Multi-infarct Dementia; Chronic Familial Vascular Encephalopathy; Familial Binswanger Dementia; Familial Subcortical Dementia with Arteriopathic Leukoencephalopathy)

Clinical and radiological features with pathology of the small arteries of the brain and autosomal-dominant inheritance have been described in many unrelated families in Eu-

rope (Sonninen and Savontaus, 1987; Davous and Fallet-Bianco, 1991; Tournier-Lasserve *et al.*, 1991; Mas *et al.*, 1992; Salvi *et al.*, 1992; Gutierrez-Molina *et al.*, 1994).

Clinical Picture *Hereditary multiinfarct dementia, chronic familial vascular encephalopathy*, or *familial subcortical dementia with arteriopathic leukoencephalopathy* are synonyms for a disorder characterized by recurrent attacks of focal brain deficits starting in midadulthood and often leading to severe motor disability with pseudobulbar palsy and dementia of the subcortical type. The clinical features of the most severely affected members are suggestive of Binswanger's subcortical arteriosclerotic encephalopathy. This picture differs, however, from the classical description of Binswanger dementia by the lack of hypertension, earlier age at onset, and familial aggregation with autosomal-dominant inheritance. CT showed diffuse low-density changes in the cerebral white matter (leukoaraiosis) and low-density lesions in the left lenticular nucleus, internal capsule, and corona radiata. Some members of the affected families were clinically asymptomatic but had abnormal neuroimaging (Mas *et al.*, 1992), MRI showed diffuse white matter abnormalities and focal lesions in the centrum semiovale (A), left thalamus, and external capsule. The diffuse white matter and some focal lesions were hyperintense on both echoes of T_2-weighted sequences, while other focal lesions had a signal identical to that of the CSF on all sequences (cystic lesions).

Neuropathology Necropsy revealed multiple small infarcts that sometimes coalesced into larger areas of infarction in the basal ganglia, thalamus, cerebral white matter, brain stem, and cerebellum (Sonninen and Savontaus, 1987; Davous and Fallet-Bianco, 1991). Myelin loss and pallor of the periventricular white matter, sparing the U-fibers, and gliosis were reported in some cases (Fig. 227) (Davous and Fallet-Bianco, 1991; Gray *et al.*, 1994). The vascular changes were mainly localized to small arteries and arterioles of the central white matter (Fig. 228A), basal ganglia, thalamus, pons, cerebellum, and leptomeninges (Fig. 228B). They consisted of splitting of the elastic lamina (Davous and Fallet-Bianco, 1991), degeneration of the media (Davous and Fallet-Bianco, 1991), severe narrowing or occlusion of the vascular lumen (Davous and Fallet-Bianco, 1991), sclerohyalinosis and thickening of the arterial wall (Davous and Fallet-Bianco, 1991), or proliferation or reduplication of the intima. The media is replaced by an eosinophilic, PAS-positive, Congo red-negative, granular substance (Gray *et al.*, 1994).

Neuroaxonal Dystrophies

Neuroaxonal swellings (spheroids) occur in degenerative and metabolic diseases (Sung *et al.*, 1981), in advanced age (Maccario *et al.*, 1983), in intoxications (Liu *et al.*, 1977), and in trauma and tumors (Reyes *et al.*, 1976). They may be found in the anterior horns of the spinal cord in healthy individuals, occasionally even in infants, and constantly after the age of 20 years (Clark *et al.*, 1984). The concept of *neuroaxonal dystrophy*, which may occur in a variety of diseases of known and unknown etiology, is justified only when the swellings form the principal, or even exclusive, morphological finding, as in the syndrome described by Seitelberger in 1952.

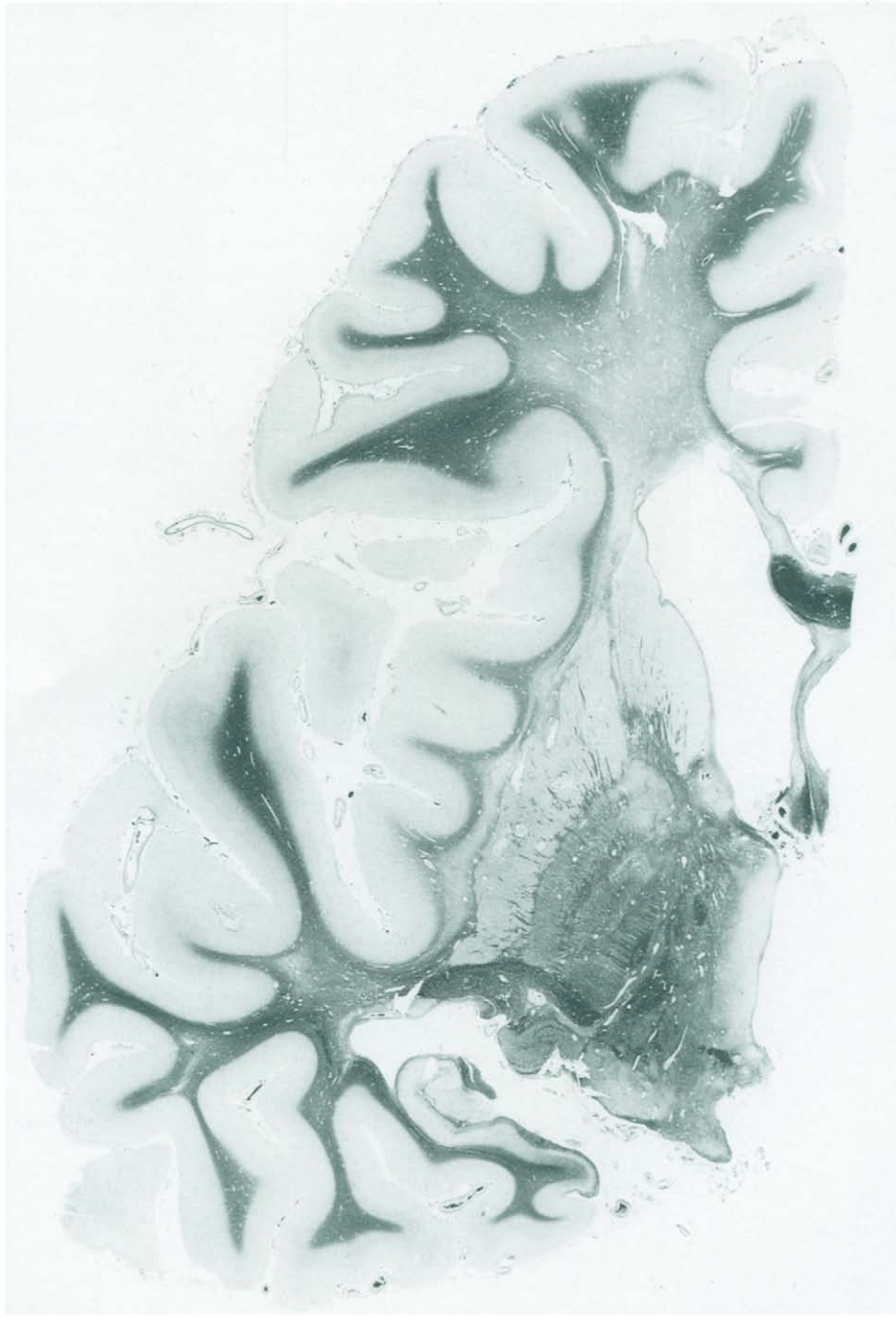


Fig. 227 A coronal section of the left cerebral hemisphere through the lateral geniculate body, demonstrating anteriopathic leukoencephalopathy. There is diffuse myelin pallor of the deep white matter, sparing the unmyelinated fibers and type 1 lacunae in the lateral part of the corpus callosum, internal capsule, and basal ganglia. Paraffin embedding. Wölcke's myelin stain. (Reproduced from Gray *et al.*, 1994.)

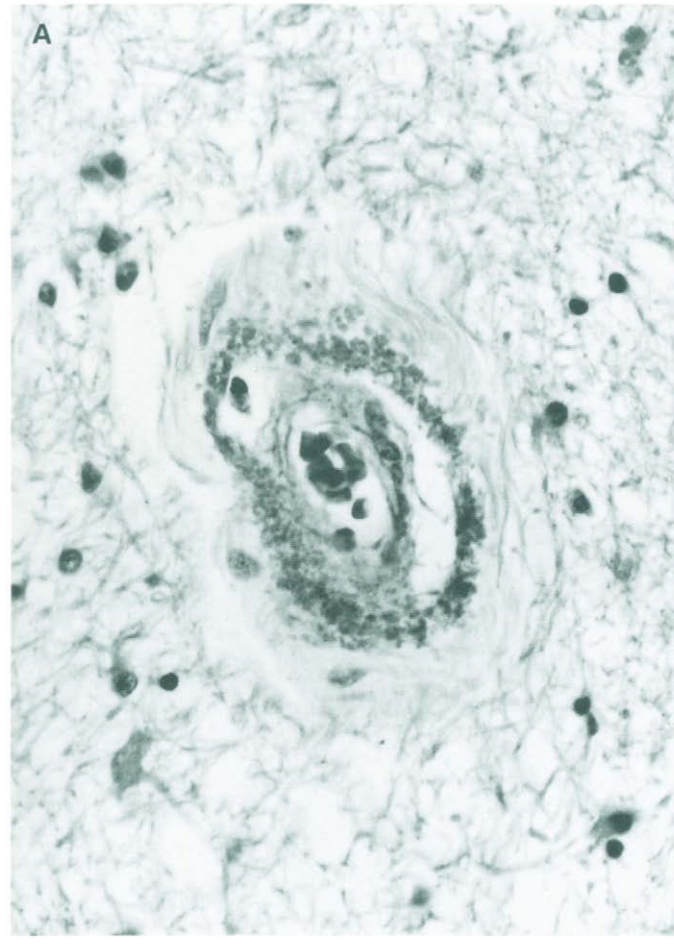


Fig. 228 Nonamyloid nonarteriosclerotic arteriopathy in arterioles of (A) the deep white matter and (B) the leptomeninges. Concentric thickening of the arterial wall with intimal hyperplasia (A), eosinophilic granular deposit in the media around the swollen myocytes, and fibrosis of the adventitia. Hematoxylin–eosin stain, ×250.

Since neuroaxonal swellings are a prominent feature of Hallervorden–Spatz syndrome (see p. 544), this condition was included with others in the group of neuroaxonal dystrophies (Seitelberger, 1986). This group was subdivided by Gilman and Barrett (1973) into three types: the localized form of Hallervorden–Spatz syndrome (type I), the generalized infantile form (type III), and an intermediate generalized form with pallidal pigmentation (type II). A further generalized late infantile/juvenile form without pallidal pigmentation was identified by Rozdilsky *et al.* (1971).

Only the generalized forms are considered here. Those with pallidonigral pigmentation are discussed in conjunction with Hallervorden–Spatz syndrome in the context of degenerative diseases with a predilection for the brain stem.

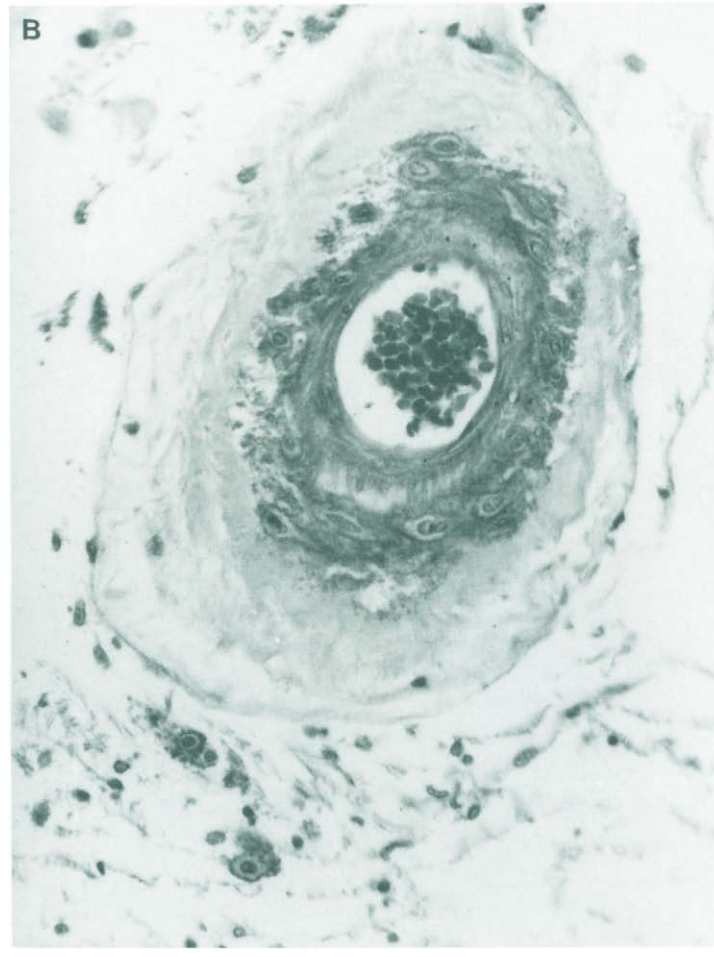


Fig. 228 Continued.

Generalized Infantile Neuroaxonal Dystrophy (Seitelberger's Disease; Type III of Gilman and Barrett)

In 1952 Seitelberger presented the findings in a child (one of uniovular twins) with widespread neuroaxonal swellings, but without pallidonigral pigmentation, and separated this syndrome from Hallervorden–Spatz syndrome. Cowen and Olmstead (1963) added further observations and coined the term *infantile neuroaxonal dystrophy.*

Clinical Picture Muscular hypotonia sets in usually during the first or second year or, rarely, immediately after birth (Venkatesh *et al.*, 1994). Spastic pareses follow, as well as torsion spasms, choreoathetoid movements, myoclonus, and seizures of various types.

Psychomotor retardation is accompanied by visual disturbances progressing to blindness through optic atrophy, paralleled by impaired hearing and progressive dementia. In cases with an early postnatal onset, a diencephalic syndrome was prominent as well as rigidity of all of the extremities (Venkatesh *et al.*, 1994). Associations have been reported linking neurogenic muscular atrophy and Rosenthal fibers with albinism (Wisniewski *et al.*, 1985) and with Behr's disease (Horoupian *et al.*, 1979). Death usually occurs after a 3- to 5-year course or, rarely, a longer (Martin *et al.*, 1972) or shorter one.

Pathology Lipid deposits and aggregations of PAS-positive histiocytes are found occasionally in the liver, spleen, lymph nodes, bone marrow, and kidneys (Cowen and Olmstead, 1963).

Neuropathology *Gross appearances.* Cerebellar atrophy is present in most cases. Optic atrophy is found in about one half of the cases (Klein and Anzil, 1994).

Light microscopy. The most prominent feature is the presence of axonal spheroids (Fig. 229), which exceed in size the neuronal cell bodies. Smaller, wormlike, axonal swellings may also be present. All axonal expansions are found predominantly in the gray matter or, less commonly, in the white matter (Fig. 230). They are generally round, but can also be lobulated or elongated. De Leon and Mitchell (1985) drew attention to the differences in size and shape between the axonal swellings in the gray and the white matter.

The spheroids stain pale blue or gray with thionin or brownish, smoky gray, or blackish gray with van Gieson's solution and contain fine pigment granules in the periphery. In Klüver–Barrera stain they appear pale green, sometimes with a darker core. They are violet–blue in trichrome stains. The spheroids do not stain with cresyl violet, only

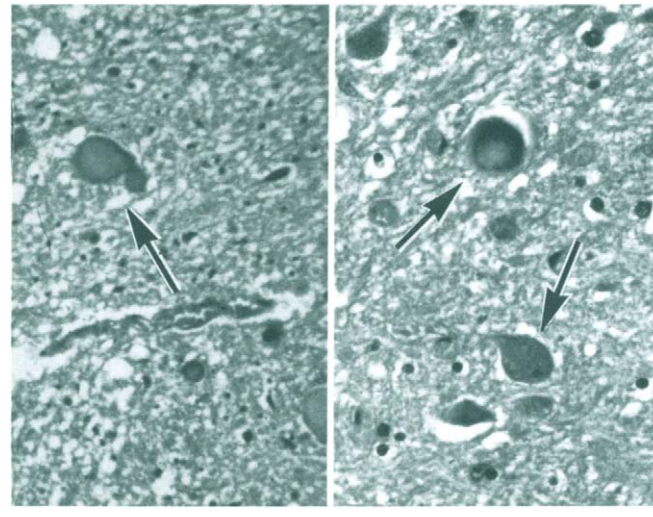


Fig. 229 Infantile neuroaxonal dystrophy. Axonal spheroids (arrows) in the occipital cortex. van Gieson's stain, ×140.

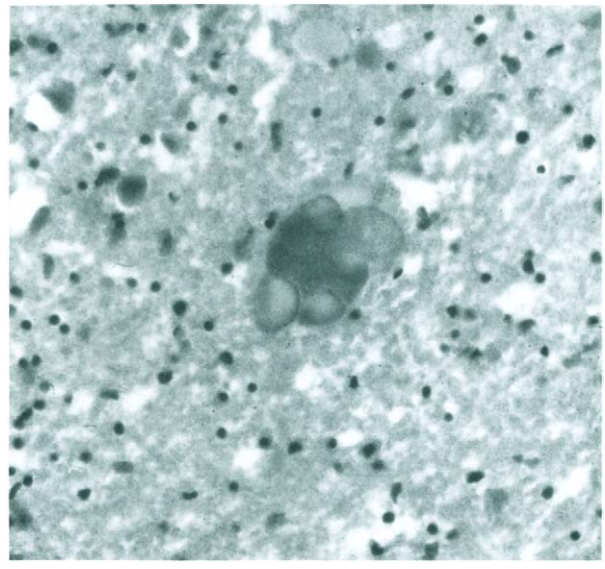


Fig. 230 Same case shown in Fig. 229. A large lobulated axonal swelling in the white matter of the centrum ovale. van Gieson's stain, ×140.

weakly with PAS, but well with alcian blue. They can be demonstrated with Bielschowsky or Bodian silver impregnations.

The basal ganglia and the nuclei of the pons, medulla oblongata, and spinal cord (Fig. 231) are more severely affected than the cerebral cortex (Jellinger, 1973). Occasionally, the hypothalamus, infundibulum, and neurohypophysis may be preferentially involved. In the cases with Behr's disease, axonal swellings were present in the lateral geniculate nucleus and the thalamus. In the cerebellum most swellings are found in the granular layer adjacent to the Purkinje layer.

In the areas in which the swellings are particularly abundant, a spongy rarefaction of the tissue may be present. Slight spongiform changes may also be present in the first three layers of the cerebral cortex. Widespread neuronal loss, with reactive gliosis, marked in globus pallidus and the brain stem, and mineralized neurons in the division of the globus pallidus and the thalamus were found in the neonatal case presented by Venkatesh *et al.* (1994).

Loose glial nodules are frequently seen in the neighborhood of the axonal spheroids. Lipophagocytosis with fat granule cells but without tissue necrosis is frequently seen in the striatum and the pallidum (Jellinger, 1973).

The axonal dystrophy also affects the autonomic ganglia and the peripheral nerves (Fig. 232) (Goebel *et al.*, 1980). System atrophies of the pyramidal, optic, and auditory pathways may be present (Seitelberger, 1952).

Histochemically, the swellings contain protein combined with complex lipids and small quantities of polysaccharides (Cowen and Olmstead, 1963). Enzyme histochemistry has demonstrated an increased activity of nonspecific esterase and NADH-tetrazolium

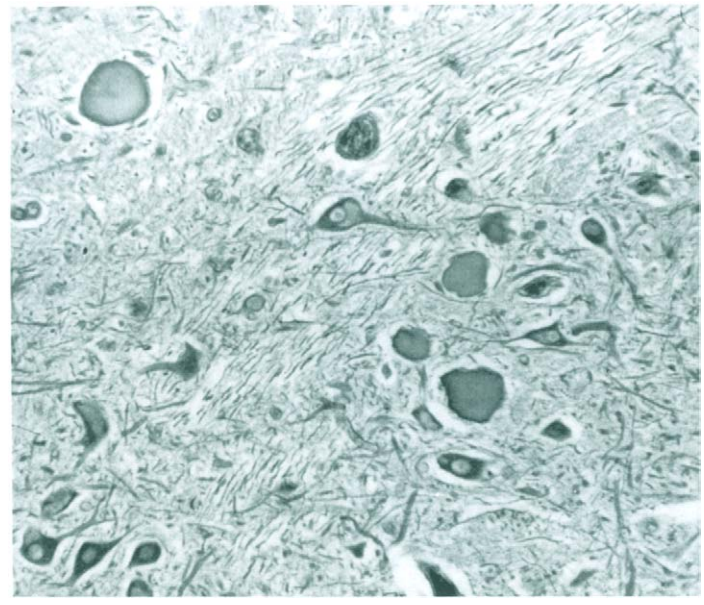


Fig. 231 Same case shown in Fig. 229. Axonal spheroids in the intermediolateral horn of the spinal cord. Kelemen stain, ×140.

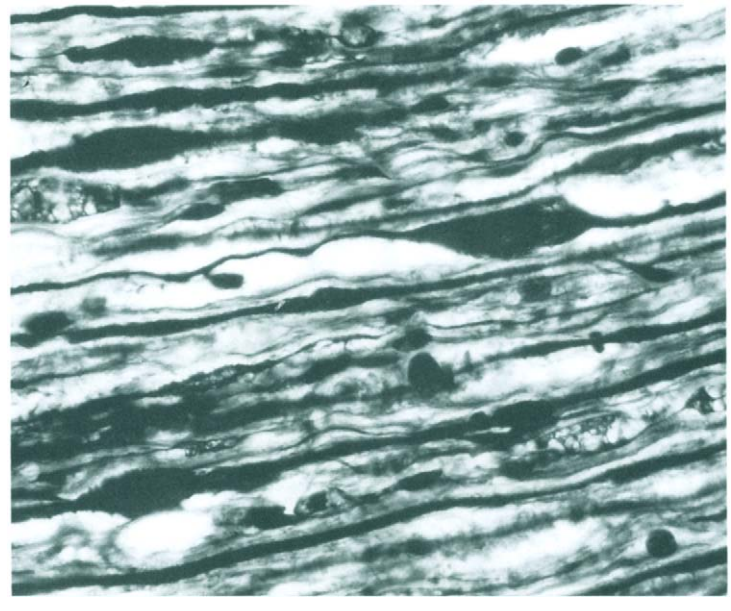


Fig. 232 Same case shown in Fig. 229. Axonal swellings in the anterior root of the spinal nerve. Bielschowsky stain, ×500.

reductase (Elleder and Jirasek, 1983). Biochemical investigations revealed a reduction in the activity of various enzymes of the cholinergic and GABAergic neurotransmission. Immunohistochemically, the axonal swellings of small size react with antibodies against human neurofilaments and ubiquitin. However, swellings larger than 30 μm are negative (Moretto *et al.*, 1993).

Electron microscopy. The dystrophic axons contain condensed neurofilaments, occasionally absent, as well as swollen or deformed mitochondria with interlocking membranes, convoluted tubes of endoplasmic cisterns (Husain, 1986), and multilamellar bodies, granular structures, and electron-dense inclusions. Yagashita and Kimura (1975) also found Hirano bodies and crystalline inclusions. Neurotubules are absent or scanty and are more commonly seen in the cortex. Filamentous structures, on the other hand, are more frequently found in the diencephalon, brain stem, and spinal cord. Clark *et al.* (1984) distinguished the neurofilamentous axonal swellings found in motor neuron diseases and in the normal spinal cord from those seen in neuroaxonal dystrophies.

In the cerebral cortex axonal swellings are found in the synaptic terminals which are enlarged and rounded and contain disorganized tubules, membranous structures, giant mitochondria, and synaptic vesicles. The axonal swellings in the nucleus gracilis of elderly people show a different structure (Yagishita, 1979).

The myelin sheaths surrounding the axonal swellings are thin and may show focal signs of disintegration in places. Numerous spheroids are devoid of myelin sheaths (Martin *et al.*, 1972).

The Schwann cells (Figs. 233 and 234) may show an accumulation of membranotubular profiles and other abnormal organelles. Nerve, skin, conjunctival, and rectal biopsies offer the possibility of making a diagnosis during the patient's life (Goebel *et al.*, 1980; Rosenberg *et al.*, 1985).

Generalized Late Infantile and Juvenile Neuroaxonal Dystrophies

Cases with onset after the age of 3 years have been classified separately as belonging to the late infantile form (Cowen and Olmstead, 1963), even though transitional cases occur between the infantile and the late infantile form, in which symptoms appear toward the end of the second year. Patients with disease onset after the first decade (Jellinger, 1973) are classified as having the juvenile form. They do not differ clinically or morphologically, however, from those with the late infantile form.

Clinical Picture In the majority of the cases, cerebellar symptoms with tremor, ataxia, and myoclonic jerks dominate the early picture. Myoclonus may be absent. Juvenile cases often present with spasticity and incipient dementia. The cerebellar ataxia progresses slowly and is accompanied by increasing dementia, spasticity, and, occasionally, blindness. Psychiatric symptoms may be prominent (Sugiyama *et al.*, 1993). The course of the disease is progressive and the patients die in the second or third decade.

Neuropathology *Gross appearances.* Conspicuous cerebellar atrophy, affecting particularly the vermis, is present with rare exceptions (Rozdilski *et al.*, 1971). In rare cases the cerebrum was also atrophic.

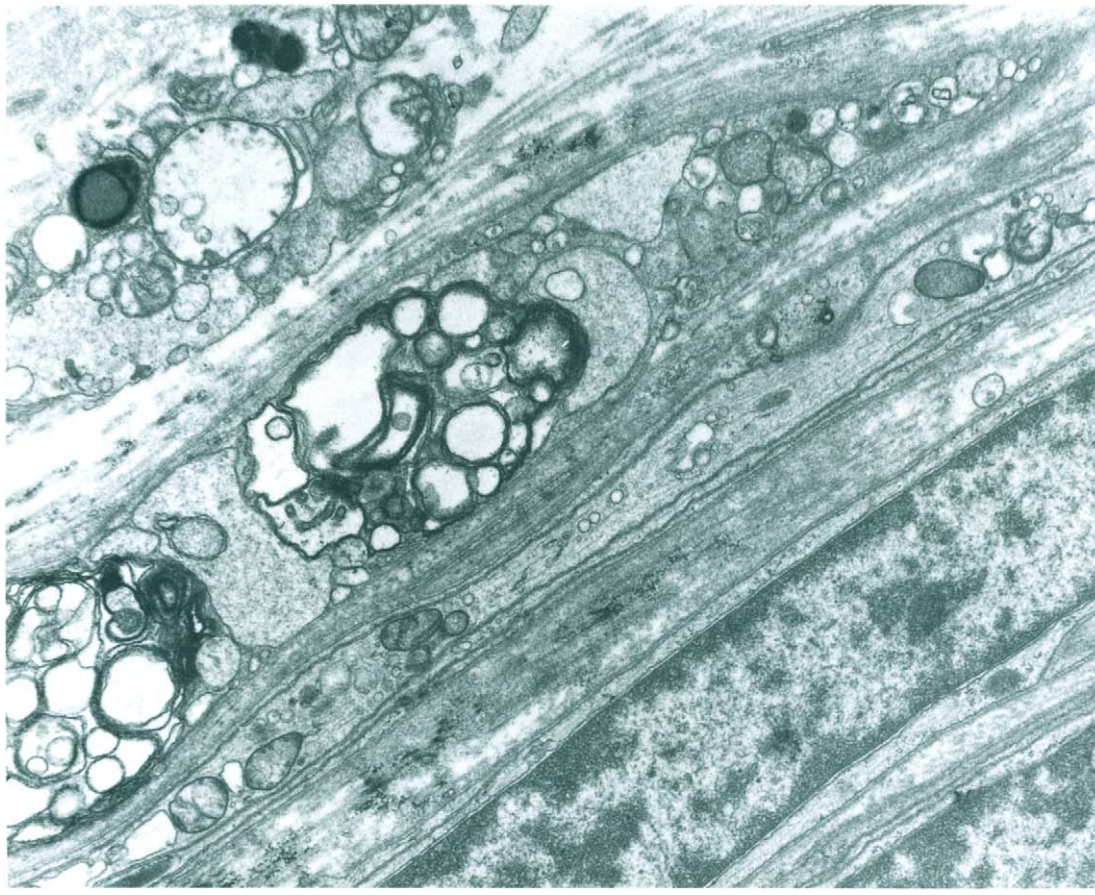


Fig. 233 Infantile neuroaxonal dystrophy. The sural nerve, showing an accumulation of myelin breakdown products in Schwann cells, ×8000.

Light microscopy. Axonal swellings are found in the brain and the spinal cord. They range in size from 10 to 50 μm. Their number and distribution show regional differences. These swellings are abundant in the posterior horns of the spinal cord, in the nuclei of Goll's and Burdach's columns, and in the periaqueductal gray, substantia nigra, red nucleus, thalamus, hippocampus, and amygdala. They are ubiquitous in the cerebral cortex (Rozdilski *et al.*, 1971) and are found occasionally in the peripheral nerves. Their tinctorial properties resemble those seen in the infantile form (see p. 511).

Lewy bodies were found in the substantia nigra in juvenile cases and, rarely, in the cerebral cortex. The entire cerebellar cortex, particularly that of the vermis, is atrophic, with almost a total loss of Purkinje cells, rarefaction of the granular layer, and pronounced subcortical gliosis. A slight pallidonigral pigmentation was observed in a late infantile case (Rozdilsky *et al.*, 1971).

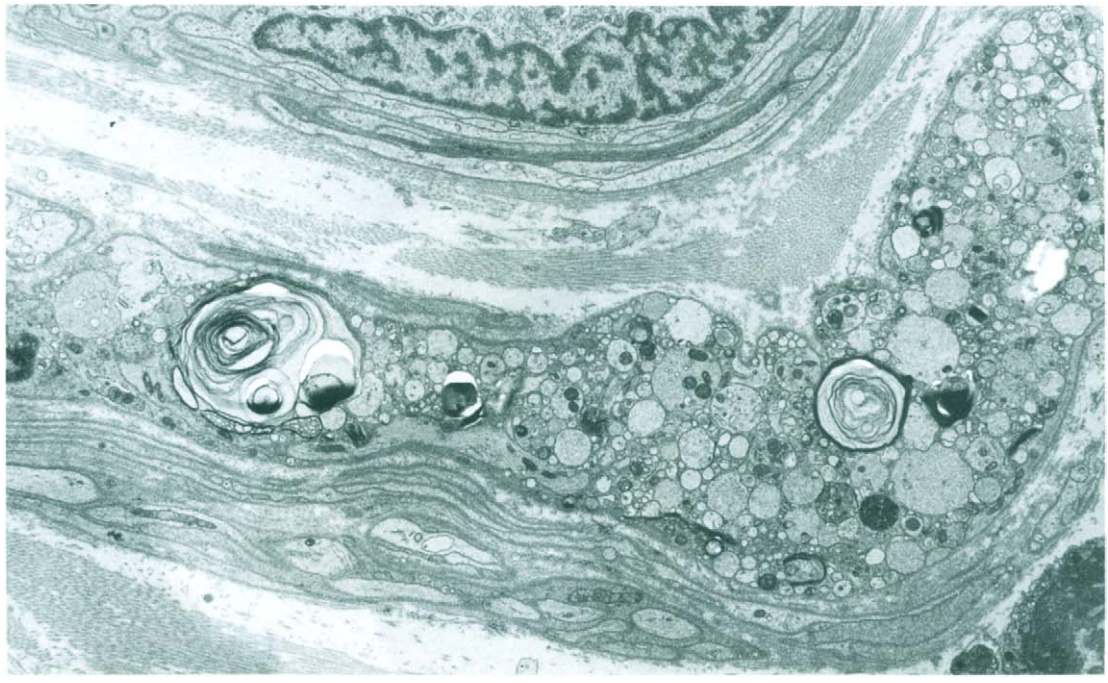


Fig. 234 Same case shown in Fig. 233. An accumulation of organelles and myelin figures in the cytoplasm of a Schwann cell, ×2600.

Electron microscopy. Axonal swellings were found in myelinated fibers and U-fibers, and occasionally in the presynaptic terminals. The pattern of axonal organelles is extraordinarily variegated, as it is in the infantile cases. One finds a tubulovesicular endoplasmic reticulum, often filling the entire spheroid, and convoluted tubular endoplasmic cisternae with weakly osmiophilic contents, forming loose irregular tangles. Also present are membrane-bound round bodies filled with floccular or granular osmiophilic material; dense bodies consisting of stacked or concentric lamellae, presumably in the lysosomes; and membrane-bound, very dense, irregularly shaped inclusions filled with granulovesicular material. Other structures include short, rod-shaped, or tubular organelles, forming circumscribed, but not membrane-bound, aggregates, and layered or circular double membranes surrounded by tubulovesicular material.

Intermediate Generalized Form of Neuroaxonal Dystrophy (Type II of Gilman and Barrett)

The first description of this condition was that of Rabinowicz and Wildi (1957) in two siblings. In this form of neuroaxonal dystrophy, generalized axonal swellings are associated with pigment deposition in the pallidum, resembling the situation in

Hallervorden–Spatz syndrome (see p. 543). Gaytan-Garcia *et al.* (1990) considered both syndromes to be variants of the same entity.

Clinical Picture The disease begins between the first and fourth years, usually with abnormalities of posture, hypotonia with possible spastic components, and seizures. The course of the disease is progressive, leading to dementia and blindness. The duration of the illness varies between 2 and 7 years. Most reported cases were in girls (Peiffer *et al.*, 1976).

Neuropathology *Gross appearances.* The main features are a pronounced cerebellar cortical atrophy and a reddish brown discoloration of the globus pallidus and the zona reticularis of the substantia nigra, and occasionally also the putamen. The pigmentation may not be appreciable to the naked eye in the brains of patients who died early in the course of the disease.

Light microscopy. Massive pigmentation is confirmed in the affected areas. Lipid deposition can be seen in the pallidum, and less so in the thalamus. Mulberry-like pigment granules in the pallidum stain deep violet–blue with the Klüver–Barrera method or dark brown to black with van Gieson's solution. They give a strongly positive iron reaction, which also gives rise to a diffuse blue coloration of the entire globus pallidus and the substantia nigra. The cells of the zona compacta appear chromatolytic and are devoid of melanin. Neuroaxonal swellings are present throughout the brain. In Ammon's horn they are localized in the marginal zone. They are particularly abundant in the globus pallidus and the substantia nigra, both in the zona compacta and in the zona reticularis. Sometimes they appear in greater number in the red nucleus than in the pallidum or the thalamus (Peiffer *et al.*, 1976). They give a strongly positive reaction of acid phosphatases and almost all oxidative enzymes.

Birefringent finely crystalline material appears under polarized light, independent of sudanophilic inclusions.

Spongy rarefaction of the cortex may be present in the molecular layer and sometimes also in the third layer. It may be accompanied by a proliferation of reactive astrocytes. Small globules scattered through the neuropil may be seen in Klüver–Barrera or van Gieson stains, about the size of an astrocytic nucleus. Bodian silver impregnations sometimes show small axonal swellings, equivalent to these globules. The intracortical astrocytes occasionally have nuclei resembling those of Alzheimer's type II glial cells. Larger spongy cavities are seen occasionally and may represent the residue of degeneration of axonal spheroids.

An almost complete loss of granule cells is seen in the cerebellum. The Purkinje cells are also considerably reduced in number. Scattered axonal spheroids are seen in the remnants of the granular layer and, less commonly, in the white matter of the folia. Dendritic swellings may be present in the molecular layer. A dense fibrillary gliosis occupies both the white matter of the folia and the central cerebellar white matter. A striking accumulation of axonal spheroids is often apparent in the pons and the medulla oblongata (Peiffer *et al.*, 1976). The spheroids are sometimes surrounded by loose microglial nodules and may undergo neuronophagia. The optic nerves and tracts may be distinctly atrophic.

Neuroaxonal swellings are abundant in the spinal cord, particularly in the posterior horns and Clarke's column, and less so in the anterior horns. Some neurons appear

swollen and chromatolytic, whereas others fade away or undergo neuronophagia. Axonal swellings and spheroids are also present in the nerve roots, cauda equina, and peripheral nerves.

Electron microscopy. Aside from the already described structures, the axoplasm contains closed or open membranous loops, isolated lamellae, and multitubular systems (Peiffer *et al.*, 1976).

Neuroaxonal Dystrophy in Adults (Neuroaxonal Leukodystrophy)

Minagawa *et al.* (1980) described a patient who, at the age of 30 years, developed personality changes, loss of memory, and disturbances of gait. Generalized seizures followed later. The patient died at the age of 33 years. An additional patient was a 60-year-old woman with a 4-year history of dementia, apraxia, dysarthria, weakness, and rigidity (Koo and Stern, 1990).

Macroscopically, the brain showed a slight dilatation of the lateral ventricles, thinning of the corpus callosum, and a slight brownish discoloration of the inner segment of the globus pallidus.

Light microscopy. Numerous neuroaxonal swellings and a prominent gliosis were seen in the cerebral and cerebellar white matter, with a minimal loss of myelin. The axonal spheroids were small and numerous in the subcortical white matter and larger but less abundant in the deep white matter. Spheroids, measuring 6–20 μm, were present in the gray matter of the cortex, subcortical nuclei, and cerebellum and, to a lesser extent, in white matter tracts. These structures were occasionally situated adjacent to cell bodies and were rarely located intracellularly. Spheroids were variably stained with eosin, PAS, and silver stains, but were consistently immunostained by antibodies directed to both phosphorylated and nonphosphorylated forms of neurofilaments. Ultrastructurally, spheroids contained accumulations of 10-nm-wide filamentous material, distinct from normal neurofilaments.

Pathogenesis The various forms assumed by the dystrophic axons have been ascribed to differences in their age. Some of the swellings in the cerebral cortex appear to be localized in axonal terminals that may be dystrophic (De Leon and Mitchell, 1985). The fact that the swellings do not expand the cortex, which commonly appears to be atrophic, indicates the loss of hitherto unidentified cortical elements. Spheroids are also present in the neuromuscular junctions (Miike *et al.*, 1986).

The striatopallidal involvement in the infantile and intermediate forms does not manifest itself clinically, as it is masked by pyramidal and spinocerebellar lesions. Numerous theories have been advanced to explain the formation of spheroids. The evolution of pyramidal symptoms and the corresponding morphological findings have led Martin *et al.* (1972) to postulate a dying-back process. Sugiyama *et al.* (1993) postulated a cytoskeletal abnormality of the neuronal cell bodies and axons involving deficient proteolysis and subsequent ubiquitination.

Seitelberger (1966) and Jellinger (1973) emphasized the separate identity of the infantile neuroaxonal dystrophy (INAD). In opposition to Cowen and Olmstead (1963) and other authors, they supported the fundamental relationship of infantile neuroaxonal dys-

trophy and Hallervorden–Spatz syndromes. Seitelberger explained the lack of pigment in INAD patients by the early onset of the disease at an age when the pallidum is still incapable of producing pigment. The appearance of lipid in the pallidum of patients with INAD would be the preliminary stage of pigment formation. This argument became unconvincing with the discovery of cases of Hallervorden–Spatz syndrome with abundant pigmentation with onset in early childhood (Radermecker and Martin, 1972).

Animal Modes Axonal spheroids in distal parts of the axons are found in Suffolk sheep that develop a progressive ataxia between the ages of $1\frac{1}{2}$ and 5 months (Cordy *et al.*, 1967). Fujisawa and Shiraki (1980) demonstrated secondary atrophy of some of the dystrophic synaptic terminals by quantitative studies in aging rats. Neuroaxonal dystrophy was also described in cats (Woodard *et al.*, 1974) and in dogs (Chrisman *et al.*, 1984).

Blakemore and Cavanagh (1969) found axonal swellings in various tracts and centers of rats denervated with bromophenylacetylurea. Neuroaxonal dystrophies induced by toxic substances or vitamin deficiencies have been reported repeatedly (Davis and Richardson, 1980). The autonomic nerves of rats with chronic experimentally induced diabetes also show lesions of neuroaxonal dystrophy (Schmidt and Plurad, 1986). A spontaneous animal model is represented by the *gracile axonal dystrophy* mutant mouse (Yamazaki *et al.*, 1988) with pathological changes confined to the CNS. Another inherited neuroaxonal dystrophy has been found in C6-deficient rabbits with changes in the CNS and the peripheral nervous system (Giannini *et al.*, 1992).

Alexander's Disease (Megalobarencephaly; Fibrinoid Leukodystrophy; Dysmyelinogenetic Leukodystrophy; Hyaline Panneuropathy)

This disease was first described by Alexander (1949) in a 15-month-old boy. Some later authors included the condition among the leukodystrophies, while others listed it among the phakomatoses. According to the patient's age at onset and the clinical symptomatology, one can distinguish three forms of the disease. Some authors, however, prefer to restrict the use of the term *Alexander's disease* to the infantile form (Soffer and Horoupian, 1979).

Infantile Form

Clinical Picture The principal feature includes enlargement of the infant's head and increased intracranial pressure (Garcia *et al.*, 1992) that cannot be ascribed to hydrocephalus, or at least not entirely. This has led to the term *megalobarencephaly.* These patients suffer from psychomotor retardation, seizures, and, in later stages, spastic paralyses. With rare exceptions (Klein and Anzil, 1994) only boys are affected. Neuroimaging evidence of leukoencephalopathy may provide an important indicator of the diagnosis (Arai *et al.*, 1992). The disease begins during the first or, rarely, the second year and leads to death within months or, unusually, a few years. A neonate with Alexander's disease

who died 1 week after birth was reported by Townsend *et al.* (1985). All reported cases have been sporadic. A dubious exception was reported by Wohlwill *et al.* (1959) in a family in which four siblings died of a similar illness, but in only one of them was a neuropathological examination performed.

Neuropathology *Gross appearances.* There is a striking increase in brain weight (1970 g in a 7-year-old child; Stevenson and Vogel, 1952). Most cases show a slight—or, rarely, a pronounced (Arend *et al.*, 1991)—dilatation of the lateral ventricles. Softening and cyst formation occur in about one half of the cases (Klein and Anzil, 1994).

Light microscopy. Abundant Rosenthal fibers are present under the pia (Fig. 235), under the ependyma, and around blood vessels. These wormlike expansions of astrocytic processes are brightly eosinophilic in H&E and are well seen in Holzer stains as well as in Klüver–Barrera stain or in Danielli's coupled tetrazolium reaction. They are PAS negative or weakly positive. The astrocytic processes are GFAP positive, but the granular deposits of the Rosenthal fibers are negative (Towfighi *et al.*, 1983), yet they may show some immunoreactivity with the immunogold staining technique (Johnson and Bettica, 1986). An excessive proliferation of abnormal astrocytes has been repeatedly observed in infants less than 1 year old (Borret and Becker, 1985). These astrocytes may contain brightly eosinophilic highly refractile granules in their cytoplasm. In some cases these

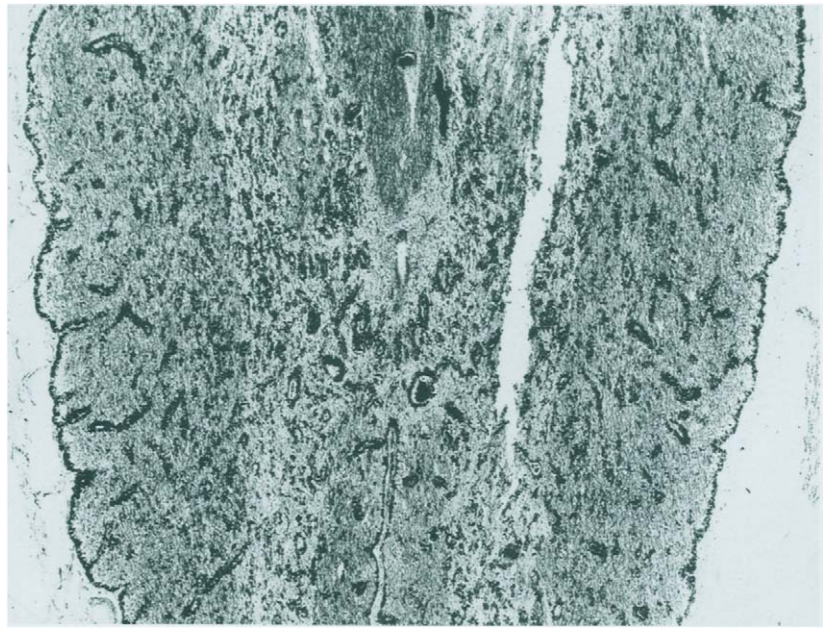


Fig. 235 Infantile form of Alexander's disease. A longitudinal section through the spinal cord, showing a massive perivascular and subpial aggregation of Rosenthal fibers. Myelin stain, ×20. (Reproduced from Vogel and Hallervorden, 1962.)

granular astrocytes may predominate in some parts of the CNS, while others contain typical Rosenthal fibers.

Late-myelinating areas, such as the centrum semiovale or the uncrossed pyramidal tracts, show hypomyelinization. Most authors have emphasized the absence of myelin breakdown. Putaminal and cerebellar cystic necroses have been reported (Arai *et al.*, 1992). Occasionally, segmental demyelination of a peripheral nerve can be demonstrated.

Juvenile Form

The first juvenile case of this disorder was reported by Stevenson (1957).

Clinical Picture The disease manifests itself around the age of 10 years or later. An early onset with difficulty in swallowing since the age of 2 years was reported by Goebel *et al.* (1981). The patients suffer from bulbar or pseudobulbar palsy as well as spastic paresis of the lower, and occasionally also the upper, limbs and ataxia (Russo *et al.*, 1976). Intellectual faculties remain normal, as a rule. The patients survive for periods ranging from 16 months to 12 years (Ando *et al.*, 1967).

Neuropathology *Gross appearances.* No changes are typically seen. In a case in which the lesions were localized in the brain stem and the upper spinal cord, the medulla was enlarged (Goebel *et al.*, 1981).

Light microscopy. The Rosenthal fibers are distributed diffusely, but are more abundant in the brain stem. Patchy demyelination, accompanied by astrocytic proliferation, is found in the brain stem and the spinal cord in most cases. Perivascular lymphoplasmacytic infiltration was found in the pons and the medulla oblongata in a few cases (Goebel *et al.*, 1981).

Adult Form

Seil *et al.* (1968) described the first patient with disease of adult onset. Russo *et al.* (1976) distinguished two subtypes, differing in their clinical course and neuropathological findings.

Clinical Picture The disease manifests itself in both groups between the third and fifth decades. The course of the disease runs between 9 and 17 years in the first group. Some patients present with a clinical picture resembling that of multiple sclerosis. The cases of Ogasawara (1965) and Rewcastle (1966) with earlier onset may be included in this group, because of their typical clinical course. In the course of the disease, ataxia, dysarthria, and spasticity increase (Parisi *et al.*, 1991). The second group is characterized by a fulminating course with symptoms appearing shortly before death (Walls *et al.*, 1984).

Neuropathology *Gross appearances.* Slight atrophy of the cerebral cortex and the spinal cord may be seen in cases with a protracted course (Seil *et al.*, 1968). A diffuse sclerosis of the white matter may be apparent in association with central or periventricu-

lar cysts in the white matter (Spalke, 1982). Foci of demyelination may be appreciated with the naked eye in the majority of the cases. In the group of fulminating cases, the brains are macroscopically unremarkable.

Light microscopy. Numerous well-circumscribed foci of demyelination are found in the centrum semiovale, basal ganglia, pons, medulla oblongata, and cerebellum in patients of the first group. In the patients reported on by Schlote (1984) and Parisi *et al.* (1991), Rosenthal fibers were distributed diffusely, with subpial aggregation (Fig. 236) in the cerebrum and the cerebellum. Microscopic malformations were present in the cerebral cortex, as well as a widespread proliferation of pilocytic astrocytes in the optic chiasm, in the walls of the lateral ventricles, and in the putamen, caudate nucleus, hypothalamus, pons, cerebellum, and medulla oblongata (Fig. 237). A pronounced lymphoplasmacytic infiltration may be present in these cases.

In the second group the systematized appearance of Rosenthal fibers was associated with myelinolytic syndromes such as central pontine myelinolysis, and occasionally with giant axonal dystrophy. The demyelination can also be diffuse and generalized (Walls *et al.*, 1984).

Electron microscopy. The appearances are similar in all forms of the disease. Deposits of a dense, osmiophilic, amorphous substance (Fig. 238), not membrane bound, are present between bundles of glial fibers in astrocytic processes (Schlote, 1966). Fragmentation of the glial filaments and hyperplasia of the mitochondria have also been observed

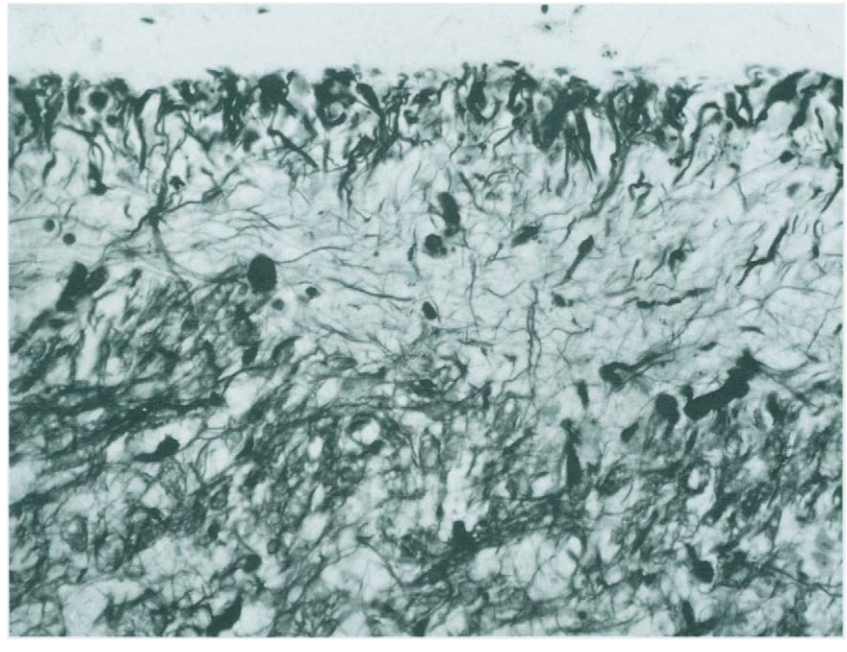


Fig. 236 Same case shown in Fig. 235. The subpial surface. Myelin stain, ×150.

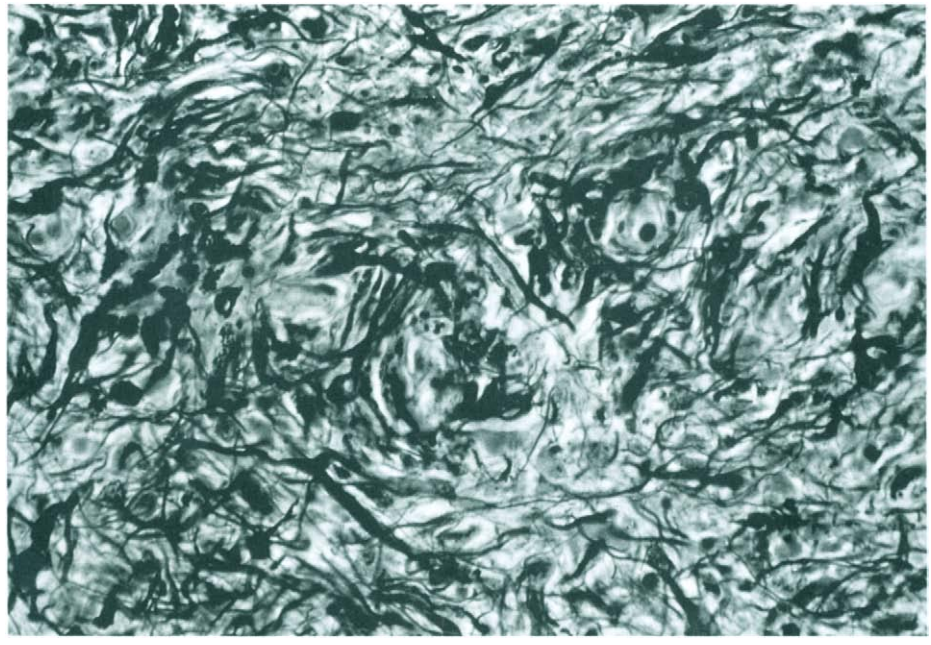


Fig. 237 Adult form of Alexander's disease. The medulla oblongata, showing a perivascular arrangement of Rosenthal fibers. Myelin stain, ×150. (Courtesy of W. Schlote, Frankfurt, Germany.)

(Escourolle *et al.*, 1979). In Bergmann's glia the granular deposits are found in the perikaryon, as they are in other astrocytes containing eosinophilic granules.

Pathogenesis Biochemical investigations of the cerebral cortex revealed a considerable increase in sialolactosylceramide (GM_3 ganglioside) (25 times the normal values) as well as GM_2 ganglioside (about five times normal). In the white matter the total ganglioside values were 3.4 times normal; of GM_2 in particular, the level was 6.2 times normal. However, no suggestion of storage was seen in the neuronal perikarya or the axons. The glial proliferation indicates a dysplastic process with secondary demyelination (Schlote, 1984). The possible role of diffuse astrocytomas or subependymal hamartomas was discussed by Pietrini *et al.* (1983). Dina *et al.* (1990) postulated a two-stage process in the formation of the fibers, starting with an excessive accumulation of glial filaments and followed by their gradual alteration.

Rosenthal fibers are most commonly seen in astrocytic tumors of the juvenile pilocytic type, but also occur in the neighborhood of nonglial tumors, such as craniopharyngiomas and hemangioblastomas (Russell and Rubinstein, 1989). They also occur in the walls of cerebellar and pineal cysts and in syringomyelia, particularly when associated with intramedullary spinal tumors, and also in and around plaques of multiple sclerosis (Ogasawara, 1965), and possibly in other conditions associated with longstanding gliosis. The deposits are proteinaceous in nature. On the basis of their experimental studies, Horou-

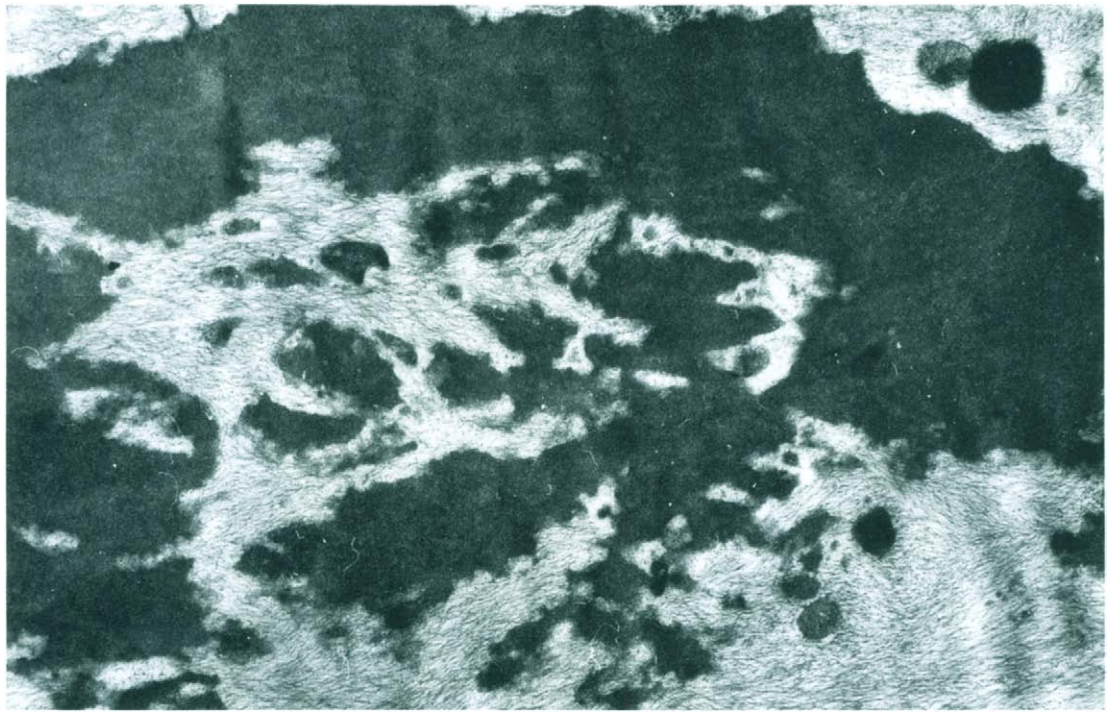


Fig. 238 Same case shown in Fig. 237. Electron microscopic appearance of a Rosenthal fiber, showing dense granular material surrounded by glial filaments, ×22,880.

pian *et al.* (1982) concluded that in focal lesions the protein is exogenous in origin and is derived from plasma proteins taken up by astrocytes, while in Alexander's disease they are probably endogenous and due to an error in the metabolism of astrocytic proteins.

One of the major constituents of the Rosenthal fibers are the crystallins (Iwaki *et al.*, 1989; Goldman and Corbin, 1991). Under normal circumstances the crystallins can form water-soluble aggregates, but in Alexander's disease their biophysical properties are altered to give insoluble aggregates composed of abnormally large ubiquitinated crystallin molecules. The gene for the crystallins has been located on chromosome 11, and a child with clinical features similar to those of Alexander's disease and a deletion in the corresponding part of chromosome 11 has been described (Gutmann, 1991).

Progressive Subcortical Gliosis

Neumann (1949) described a few cases with an insidiously progressive dementia clinically resembling AD or Pick's disease. Additional cases were mentioned in review articles (Neumann and Cohn, 1967), but it has not been possible to establish this condition as a definite nosological entity.

Clinical Picture The patient's age at the onset of the symptoms varied from 40 to 75 years. The duration of the illness was from 14 months to 7 years. Bergmann *et al.* (1990) described dysarthria and epilepsia partialis continua in the left half of the face and in the left arm. Most cases have been sporadic. Lanska *et al.* (1991) reported the neuropathological findings of six cases (four women and two men, ages 55–75) from two kindreds afflicted with a familial form of this disorder, segregated as an autosomal-dominant trait.

Gross appearances. Verity and Wechsler (1987) described marked frontoparietal–temporal atrophy with special involvement of the superior and middle temporal lobe gyri. Lateral ventricles were enlarged bilaterally and accompanied by marked atrophy of the caudate nucleus.

Light microscopy. The brains showed generalized atrophy, most pronounced in the frontotemporal lobes. The striking feature was pronounced subcortical gliosis, without severe involvement of the cortex. The deep cortical layers can be affected (Lanska *et al.*, 1991). Gliosis was also found in the basal ganglia, thalamus, brain stem, and anterior horns of the spinal cord. In one case reported by Verity and Wechsler (1987), putaminal gliosis was noted. Dissociation between the severity of the gliosis and an absence of changes in the neurons or the myelin sheaths is the main characteristic of the condition. In the familial cases the anterior claustrum and the pars compacta of the substantia nigra showed severe astrocytosis and neural degeneration.

Canavan's Disease (Infantile Spongy Dystrophy; Spongiform Leukodystrophy; Aspartoacylase Deficiency; *N*-Acetylaspartic Aciduria; van Bogaert–Bertrand Disease)

The first case of this disease was described by Canavan (1931), but it was not until 1949 that van Bogaert and Bertrand defined the condition as a nosological entity. Subsequently, congenital, infantile, juvenile, and adult forms have been described. Hagenfeldt *et al.* (1987) recognized the defective aspartoacylase activity, which was confirmed by Matalon *et al.* (1988). Combinations with other lesions may occur: with necrotizing encephalopathy and spinocerebellar degeneration (Appenzeller *et al.*, 1980) or with familial cerebral amyloidosis and spongiform encephalopathy (Adams *et al.*, 1982). Heterogeneity of the disease cannot be excluded, and cases reported in the earlier literature may be impossible to differentiate from CJD.

Clinical Picture The *congenital form* manifests itself with hypotonia immediately after birth. It can be associated with microcephaly (Vuia, 1976). The infants die during the first month. As spongiosis of the white matter can occur in other disorders of amino acid metabolism, such as maple syrup urine disease (see p. 160) or hyperglycinemia (see p. 185), these conditions must be excluded before a diagnosis of congenital spongy dystrophy can be made (Towfighi *et al.*, 1977).

The *early infantile form* manifests itself with hypotonia between the ages of 2 and 6 months. This is followed in later stages by rigidity or spasticity. Macrocephaly is a constant feature (Von Moers *et al.*, 1991). All patients exhibit severe psychomotor retarda-

tion. Generalized seizures, myoclonus, athetosis, vertical nystagmus, extensor spasms, and deafness may also be present. CT and MRI show a decreased density of the entire white matter (Buhrer *et al.*, 1993). Demonstration of *N*-acetylaspartic aciduria and a marked deficiency of aspartoacylase activity confirm the diagnosis (Bartalini *et al.*, 1992). Death usually occurs within 1–2 years, or occasionally later. A protracted clinical course with a survival beyond 6 years of age has been reported in some patients (Zelnik *et al.*, 1993). The disease frequently occurs in siblings and is inherited as an autosomal-recessive trait. It tends to affect children of Jewish descent, but not exclusively. A large cluster of cases has been reported from Saudi Arabia (Ozand *et al.*, 1990).

In the *late infantile* and *juvenile forms* the first symptoms appear after the age of 5 years, occasionally even in the second decade (Goodhue *et al.*, 1979). These consist of spasticity, cerebellar symptoms, and blindness. The course of the disease is protracted and may extend up to 15 years. Most cases are sporadic.

In the *adult form* symptoms may appear as late as the fifth decade and are sometimes mistaken for those of multiple sclerosis (Armbrustmacher *et al.*, 1981).

Pathology Gambetti *et al.* (1969) found severe degenerative changes in skeletal muscle. In addition, peculiar osmiophilic inclusions were present, in the form of round or oval, concentrically laminated, membranous bodies with a regular periodicity.

Neuropathology *Gross appearances.* Macrencephaly with a normal convolutional pattern is seen in the infantile form. Cerebral atrophy predominates in juvenile cases. The cerebellum is atrophic in all forms. A distinct lamination of the cortex becomes apparent on coronal sections. The white matter appears either porous and spongy or glassy and gelatinous and tends to sink below the cut surface. The U-fibers are preserved in most cases and tend to stand out prominently. The occipital lobe is most severely affected, as a rule; the temporal lobe, least so. The rarefaction of the tissue may also be apparent in the basal ganglia, the pons, and, rarely, the spinal cord.

Light microscopy. Extensive demyelination (Fig. 239) is accompanied by spongy rarefaction that ranges from a fine to a coarse status spongiosus (Fig. 240). A characteristic feature of Canavan's disease is the separation of the vacuoles by fine septa that take up myelin stains.

There is considerable variation in the localization of the lesions in individual families and also in sporadic cases. In most cases the spongy rarefaction and demyelination occupy the white matter of the cerebral hemispheres and the cerebellum. In some cases damage to the cortex is also present, particularly in the middle layers. In these cases the arcuate fibers are frequently involved. Other affected structures may include the pallidum, claustrum, thalamus, subthalamic nuclei, mamillary bodies, red nuclei, medial and lateral geniculate bodies, inferior colliculi, oculomotor nuclei, and parts of the substantia nigra. Cerebellar atrophy is frequently present in infantile cases, and constantly in the juvenile form. Lipid-laden macrophages are sparse in the affected areas.

Neuronal loss can be evident in all affected structures, and surviving neurons often appear shrunken. However, in several cases no signs of neuronal damage were observed (De Coo *et al.*, 1991). Axonal degeneration, sometimes in the form of swellings, may also be seen. Reactive astrocytes and Alzheimer's type II glial cells are common. Bizarre glial

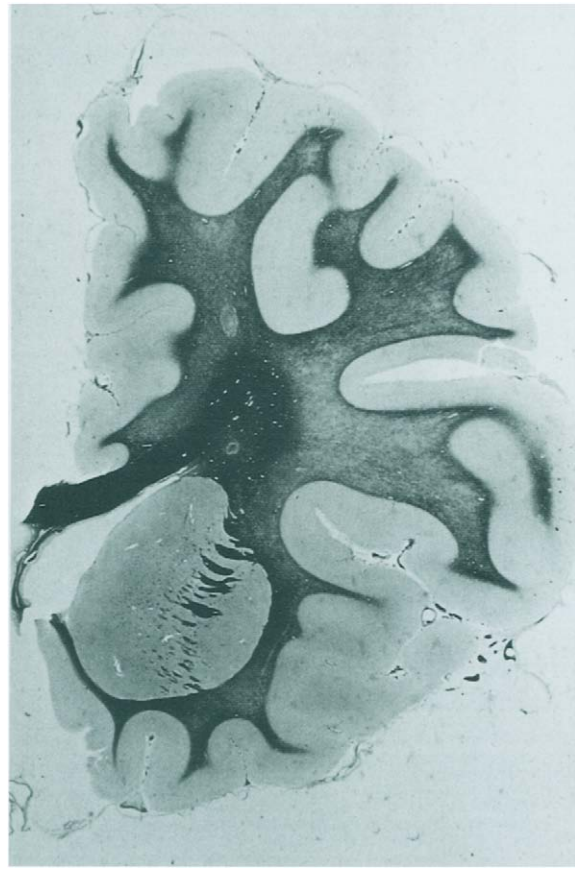


Fig. 239 Infantile spongy dystrophy. Conspicuous demyelination of the cerebral white matter. Heidenhain–Wölcke stain.

cells, resembling Alzheimer's type I astrocytes, are seen occasionally, particularly in the juvenile cases. Johnson (1970) observed a reduction in the number of ATPase-positive astrocytic processes.

Intracortical myelin sheaths may be rarefied in affected areas. A loss of retinal neurons and vacuolation of the optic nerve are constant features of the juvenile cases. Histiocytic infiltrates, an axonal neuropathy with swelling and fragmentation of the axons, and a loss of myelin sheaths have been observed in the peripheral nerves.

Perivascular calcifications may be present in the juvenile cases. Neuroaxonal dystrophy, occasionally reported in the juvenile form, has been ascribed to nutritional deficiency (Goodhue *et al.*, 1979).

Electron microscopy. Swelling of the dendrites, axons, and astrocytic processes has been observed, as well as splitting of the myelin sheaths along the interperiod line. The mitochondria of astrocytes are swollen, and often bizarre, with crystalline inclusions or a

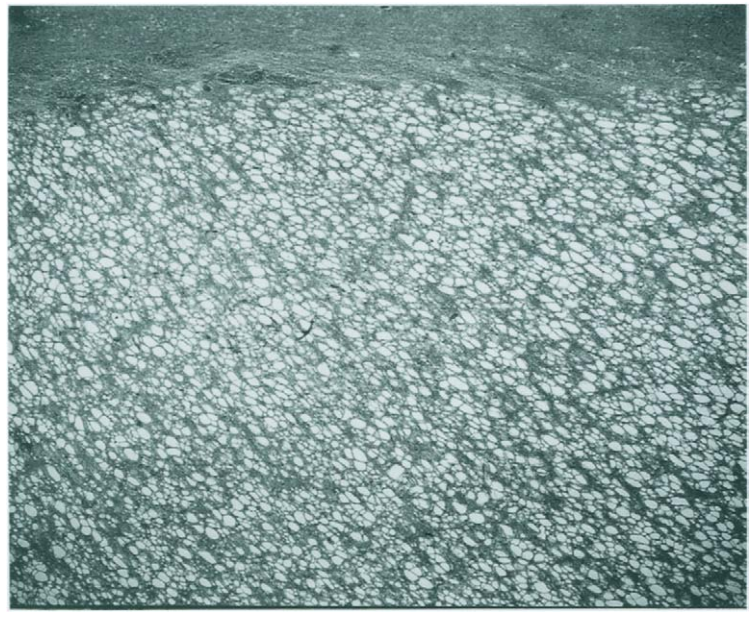


Fig. 240 Same case shown in Fig. 239. Status spongiosus of the white matter with coarse vacuolation. Hematoxylin–eosin stain, ×40.

granular matrix and triangular cristae at the margins (Boehme and Marks, 1981). Occasional lamellar inclusions in the neuronal cytoplasm have been seen in congenital cases (Vuia, 1976), but no mitochondrial abnormalities have been found in the astrocytes. The latter are also inconspicuous in infantile cases with death occurring early in the course of the disease (Adornato *et al.*, 1972).

Pathogenesis Due to the deficiency of the aspartoacylase, *N*-acetylaspartic acid concentrations elevated 80-fold in the urine and increased 20-fold in the plasma have been found in Canavan's disease compared with the control means (Jakobs *et al.*, 1991). Aspartoacylase is a myelin-associated enzyme (Johnson *et al.*, 1989) and *N*-acetylaspartic acid seems to be essential for CNS myelinization.

The splitting of the myelin sheaths in Canavan's disease leads to the formation of vacuoles at the sites of fusion (the interperiod lines) and produces the appearance of spongy degeneration with fine myelin threads, as seen on light microscopy. An A-to-C base change, at nucleotide 854, has been found in 85% of the Canavan alleles. This base change results in a missense *Glu2285Ala* mutation (Kaul *et al.*, 1993).

Animal Models A spontaneous spongy degeneration resembling the human spongy encephalopathy has been described in the Swiss–Webster mouse (Azzam *et al.*, 1984).

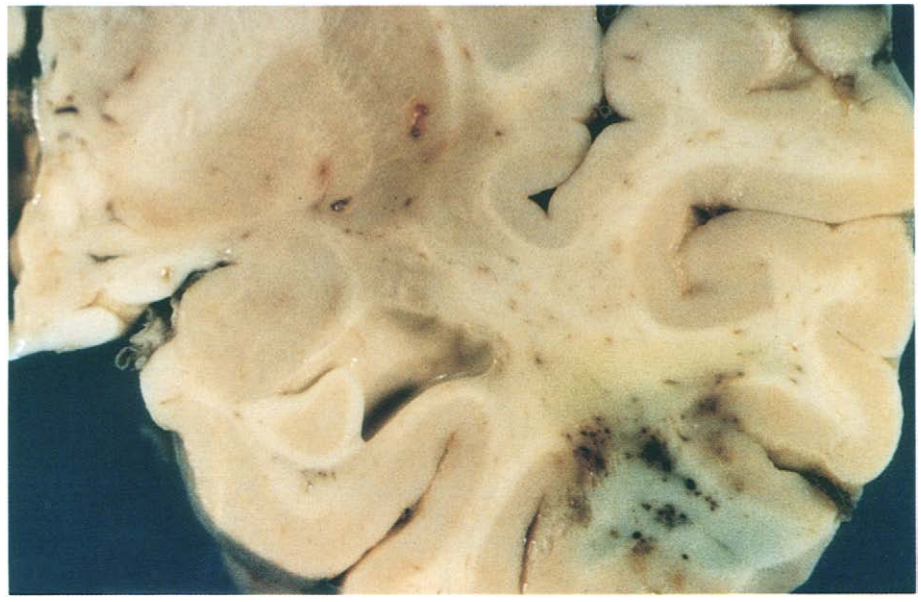


Fig. 195 A 66-year-old patient with myeloblastic leukemia. Hemorrhagic foci and areas of edema lightly stained by bilirubin. (Courtesy of E. Caputi, Buenos Aires, Argentina.)

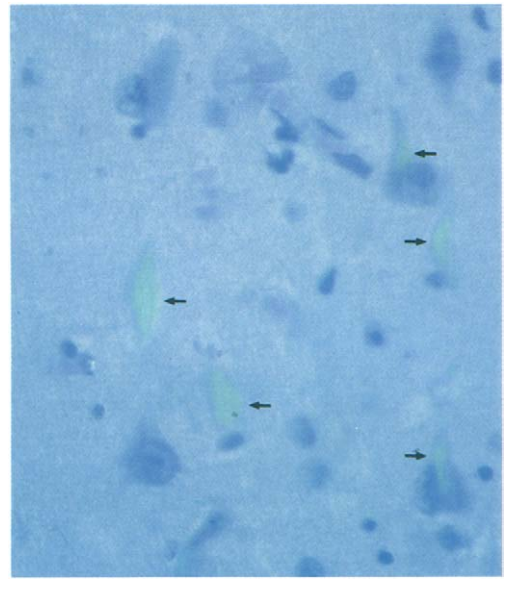


Fig. 200 Neurofibrillary tangles appear greenish under polarized light (arrows). Congo red stain, ×400.

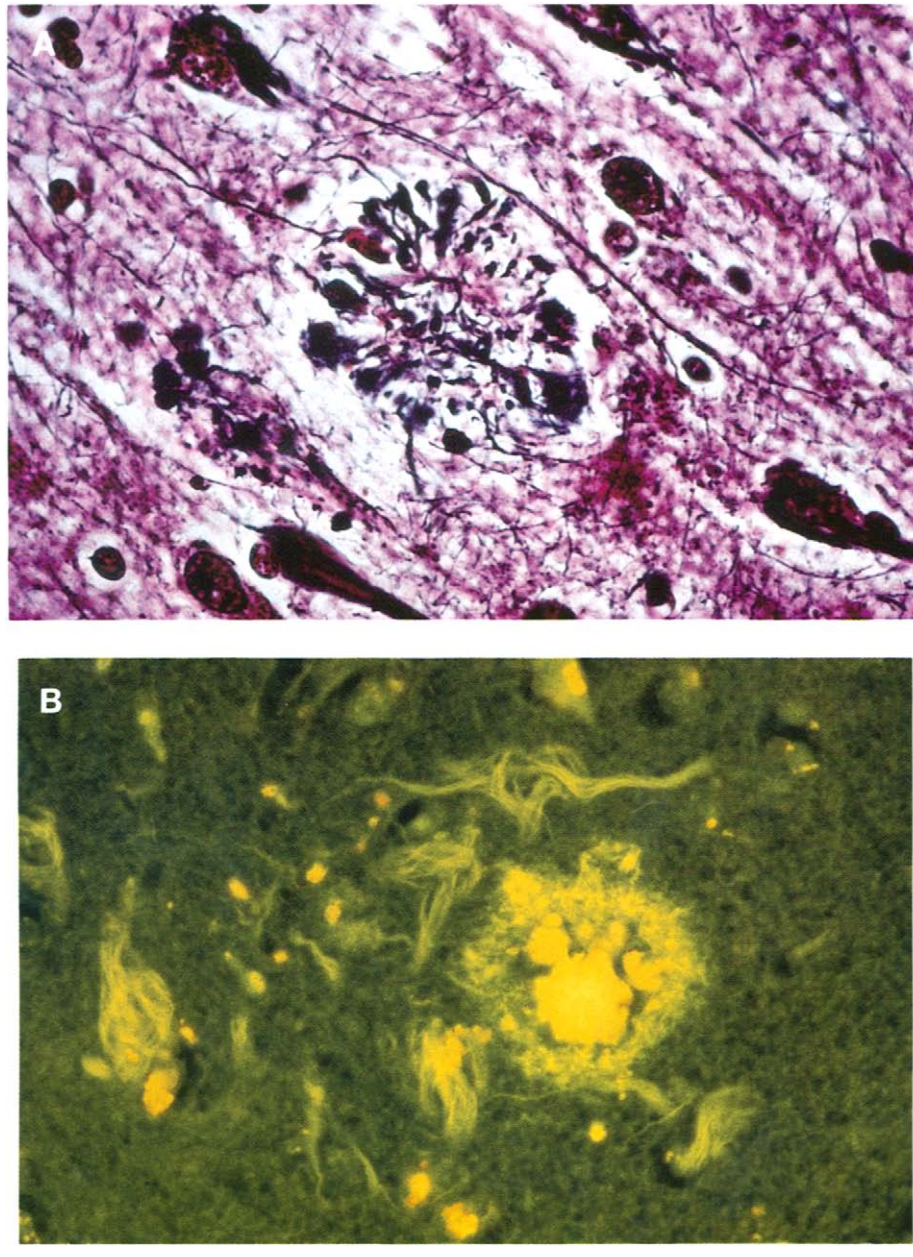


Fig. 204 Alzheimer's disease. (A) Silver proteinate (Bodian) stain of a senile plaque illustrating the numerous neurites contributing to its periphery. Several tangles are present at the edges of the picture. (B) A thioflavin-S preparation viewed with the ultraviolet (400 μ) light. The central feature is a plaque with a large core of amyloid surrounded by wisps of amyloid and neurites. Several neurofibrillary tangles are present surrounding the plaque. They are made up of delicate skeins of twisted fibers. See reverse for parts C and D.

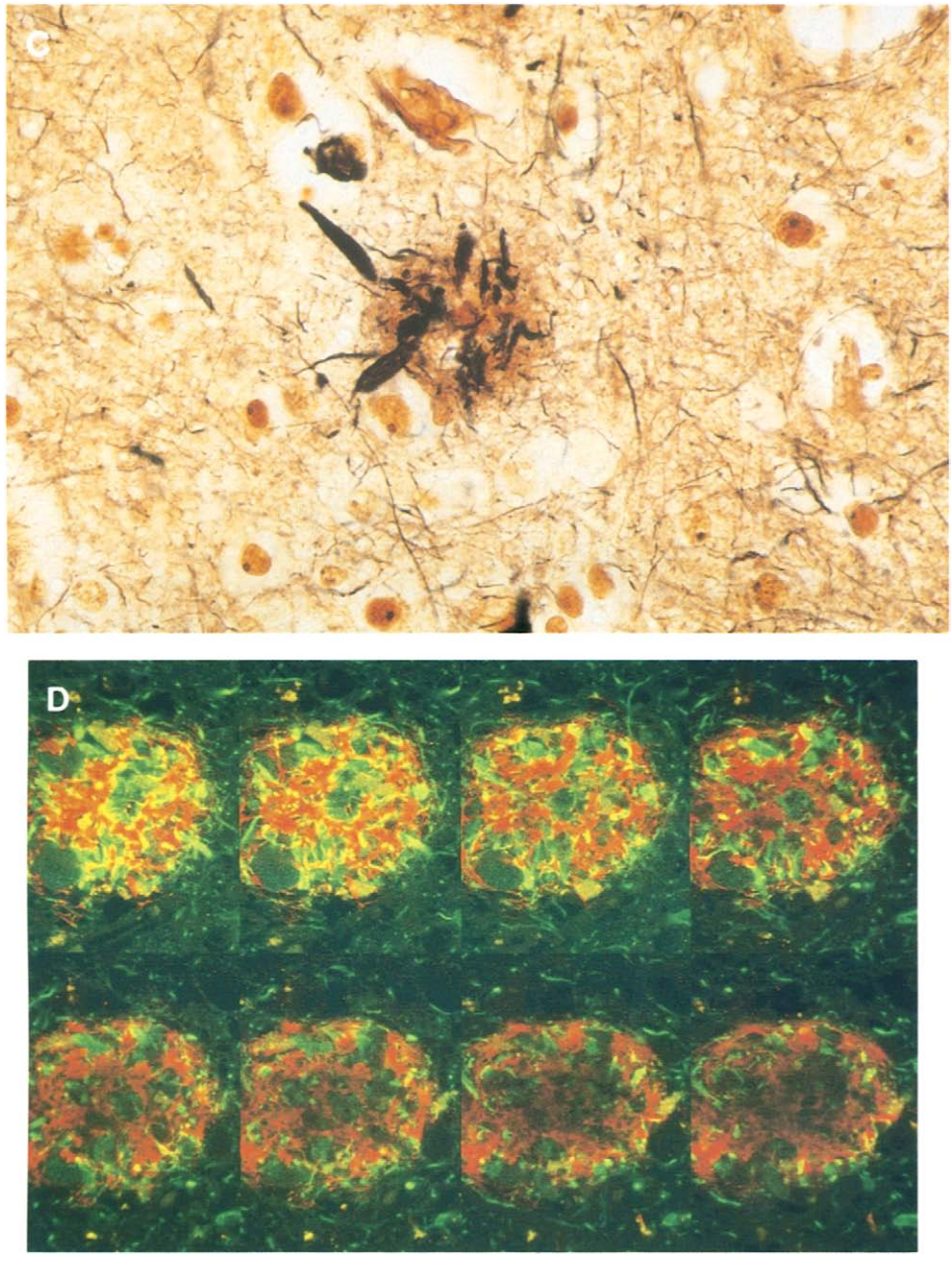


Fig. 204 *Continued.* (C) An anti-τ immunohistochemical preparation illustrating the abnormal neurites in several confluent plaques. (D) Step sections through the thickness of a plaque studied with the confocal microscope. Red indicates amyloid and green indicates τ. Yellow is the coincidence of amyloid and τ.

Degenerative Diseases of the Thalamus, Basal Ganglia, and Midbrain

Thalamic Degenerations

The majority of degenerative system diseases (Miyazu *et al.*, 1991) may include thalamic lesions. Primary thalamic degeneration is an exceedingly rare condition. Some cases have been classified as the thalamic form of CJD, in spite of the absence of spongiform changes and gliosis, but would be more correctly allocated to the thalamic degenerations. The nosological position of cases with thalamic degeneration without spongiosis, but with spongiform changes in the cerebral cortex (Mizusawa *et al.*, 1988), is more difficult to define. Kornfeld and Seerlinger (1994) differentiated the pure thalamic degeneration from the thalamic form of CJD by an absence of spongiform change. The well-characterized fatal familial insomnia with selective atrophy of the anteroventral and dorsomedial thalamic nuclei has been identified as a prion disease with a mutation in codon 178 of the *PrP* gene (Medori *et al.*, 1992a,b). The allocation of atypical cases reported prior to the discovery of the transmissibility of CJD is bound to be arbitrary.

Infantile Form

Aside from numerous children in whom neuronal loss in the thalamus with residual calcification (ferrugination) can be attributed to perinatal damage or prenatal factors (Parisi *et al.*, 1983), there are some cases in which no exogenous influences could be implicated. Abuelo *et al.* (1981) reported symmetrical thalamic degeneration in two siblings and suggested the possibility of a genetic etiology. In the secondary forms it appears that the thalamus is particularly vulnerable to exogenous influences in the late fetal period (Parisi *et al.*, 1983).

Adult Form

Clinical Picture With rare exceptions (Martin *et al.*, 1983) the disease affects middle-aged men. It manifests itself with a progressive dementia, of which the main symptoms are a gradual loss of memory, slowing of the mental processes, loss of initiative and spontaneity, and impairment of the ability to communicate. In a few cases choreoathetoid and myoclonic movements were observed, as well as disturbances of sleep and autonomic functions (Lugaresi *et al.*, 1986). Death occurs after some months or a few years, but cases with a protracted course of over 20 years have been described. Familial incidence has been repeatedly reported (Martin *et al.*, 1983; Little *et al.*, 1986).

Neuropathology *Gross appearances.* Thalamic atrophy can be appreciated only in cases with a protracted course.

Light microscopy. Under light microscopy the neuronal loss is bilateral and symmetrical, but varies in severity in different thalamic nuclei. The dorsomedial nucleus is most severely affected (except for the pars magnocellularis), followed by the lateralis posterior, the lateralis dorsalis, the reticularis, the pulvinar, and the ventral portion of the nucleus ventralis posteromedialis. The remaining cells are shrunken and hyperchromatic and may show GVD. The small neurons are generally unaffected (Martin *et al.*, 1983). The geniculate bodies and the centrum medianum are spared in most cases. Marked gliosis is present in all areas depleted of neurons.

The cerebral cortex shows no loss of neurons, or only a minimal one. A transneuronal loss may be present in chronic cases. Some reduction in the number of neurons has been observed in the dorsal part of the inferior olive (Goecke-Hoyer *et al.*, 1990). Other nuclei and tracts are only rarely and minimally involved.

Intracytoplasmic eosinophilic inclusions have been seen in thalamic nuclei in myotonic dystrophy. These are nonspecific, however, and are found in the thalami of healthy adults.

Choreas

Huntington's Chorea (Hereditary Chorea; St. Vitus' Dance; Chorea Major; Huntington's Disease)

This disease was described clinically by Huntington (1872). Its neuropathology was elucidated by Alzheimer (1911). It may coexist with other disorders (Cervós-Navarro, 1991a), such as syringomyelia, neurofibromatosis, muscular dystrophy, Pick's disease, amyotrophic lateral sclerosis (ALS), and spinal spastic paraplegia.

Clinical Picture The first symptoms appear most commonly between the ages of 25 and 45 years. They consist of lightning, arrhythmical, jerky, often repetitive, movements of the major muscle groups or individual muscles. Disturbances of speech and mental changes develop simultaneously and lead ultimately to dementia. On rare occasions the disease develops in advanced age, even as late as the eighth decade. Some members of families with Huntington's chorea develop dementia without chorea. In others the movements are athetoid rather than hyperkinetic–hypotonic. A reduction in glucose consumption may precede the cerebral atrophy, as demonstrated by CT scans. The positron

emission tomography (PET) showed both a severe reduction in uptake of the fluorodeoxyglucose bilaterally in the corpus striatum and a low uptake in the frontal lobes, as well as an asymmetry of the uptake at the thalamic level, with less uptake on the right than on the left (Sancesario *et al.*, 1992).

The average duration of the illness is 17 years, but it may range from 5 to 30 years. The inheritance is simple autosomal dominant and regional clustering of cases is frequently observed (e.g., Maracaibo, Venezuela).

A juvenile form with onset between the ages of 10 and 20 years occurs in 5–10% of the patients. In about 1% of the cases, the disease manifests itself in childhood. A rigid akinetic form (Westphal variant), occasionally associated with seizures, predominates in the juvenile and infantile cases (Campbell *et al.*, 1961). Dementia develops rapidly in the infantile form of the disease.

Neuropathology *Gross appearances.* The most striking feature is the atrophy of the caudate nucleus. The degree of atrophy varies considerably according to the stage of the disease. Vonsattel *et al.* (1985) classified the changes in the head of the caudate nucleus into five grades: 0, indistinguishable from that of normal controls; 1, normal profile, but microscopic abnormalities; 2, reduction in size, but ventricular surface still convex; 3, ventricular surface flat; and 4, ventricular surface concave. The anterior horns of the lateral ventricles are dilated and their lateral aspect is flattened due to the absent bulge of the head of the caudate (Fig. 241). This atrophy, however, is not pathognomonic, and confusion is possible with severe atrophies in Pick's disease, in the parkinsonism–dementia

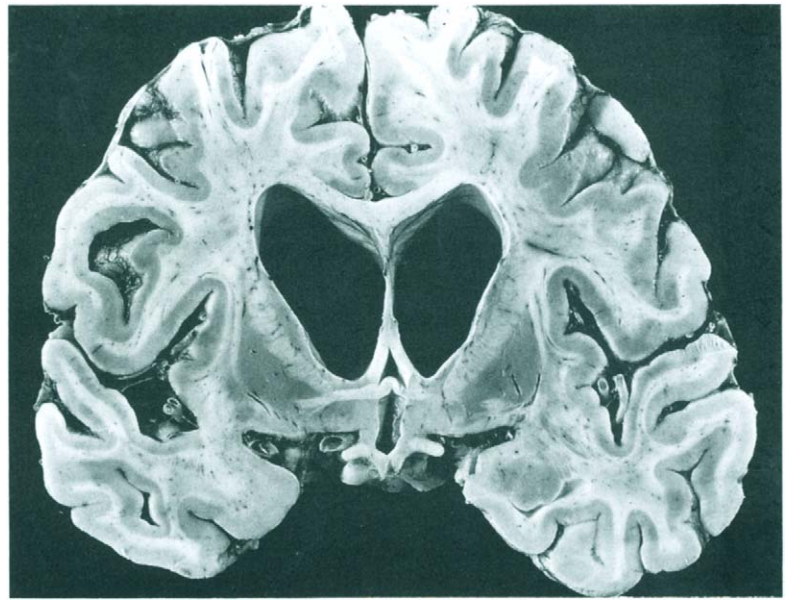


Fig. 241 Huntington's chorea. Generalized cerebral atrophy with prominent atrophy of the corpus striatum and dilatation of the ventricles.

syndrome, and in diffuse laminar atrophies. The diagnosis must therefore be confirmed microscopically. The atrophy also involves the putamen and the globus pallidus (Fig. 242A,B) and sometimes encroaches on the red nucleus and the substantia nigra. The corpus callosum is often thin. The striatal atrophy causes a spurious appearance of enlargement of the internal capsule and the anterior commissure. The cerebral cortex may also be

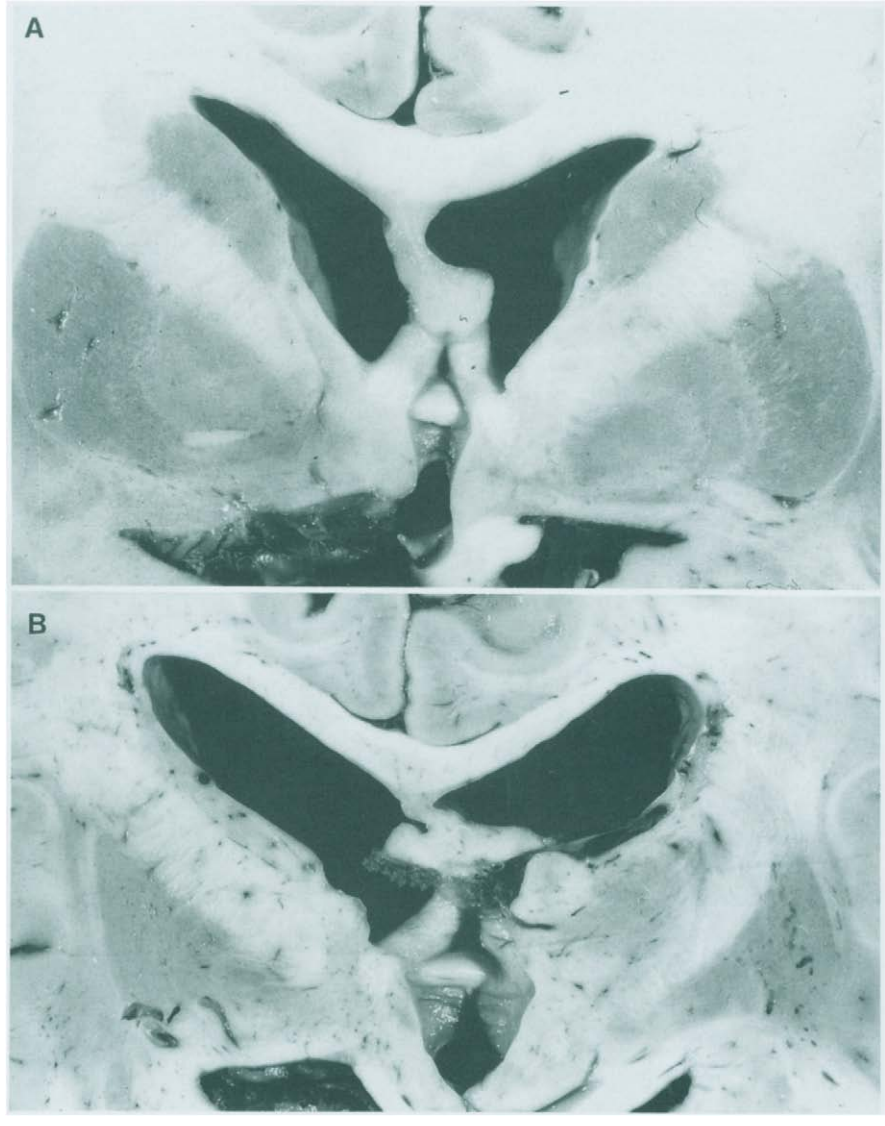


Fig. 242 (A) Normal basal ganglia and (B) those with Huntington's chorea.

atrophic, mainly in the frontal and temporal lobes or, rarely, in the entire hemisphere. Cortical atrophy is particularly severe in the infantile form (Fig. 243).

Light microscopy. A severe loss of the small striatal neurons is the main finding. The large neurons are generally better preserved (Oyanagi and Ikuta, 1987) and may therefore appear more numerous in the atrophic caudate nucleus. They may, however, be severely affected in the infantile form (Fig. 244A,B). The neuronal population of the striatum is not homogeneous, and various groups of neurons differ in their morphological appearances and their neurotransmitters (Ferrante *et al.*, 1987). On their appearances in Golgi impregnations, they can be divided into spiny and aspiny types. Various subsets contain some neurotransmitters, but not others. The spiny neurons are grouped in multiple well-circumscribed areas (the "patch compartment"), while the aspiny ones are distributed in between (the "matrix compartment"). Cases with relatively preserved neostriatal islets have been reported (Vonsattel *et al.*, 1992).

The aspiny ones contain NADPH dehydrogenase, somatostatin, neuropeptide Y, cholecystokinin, vasoactive intestinal peptide, and acetylcholine. The subset of aspiny neurons containing NADPH dehydrogenase, somatostatin, and neuropeptide Y is remarkably well preserved in Huntington's chorea. These are the neurons that receive cortical and nigral afferents. Chromogranin A- (Parker *et al.*, 1990) and parvalbumin- (Harrington and Kowall, 1991) immunoreactive neurons are also resistant. The spiny neurons contain GABA, encephalins, substance P, and dysmorphin and are severely depleted (Ferrante *et al.*, 1986). Using a marker for striatal medium-sized spiny neurons, Goto and Hirano (1990) found a significant loss of synaptophysin immunoreactivity in the striatum of pa-

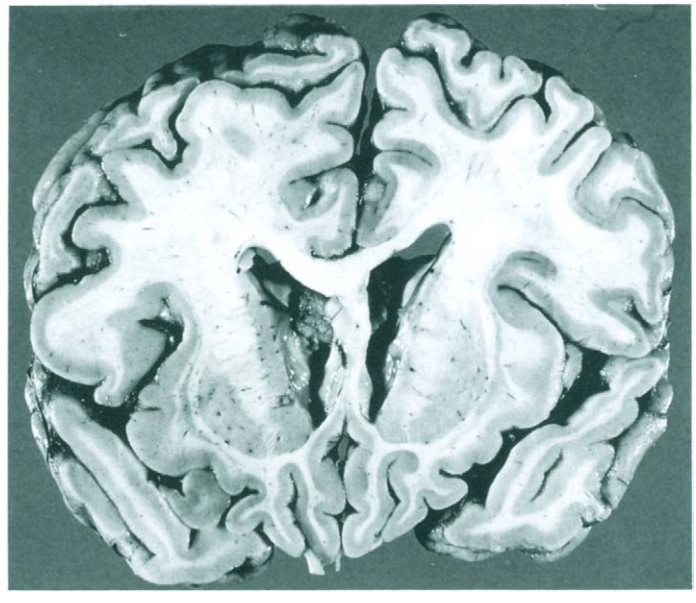


Fig. 243 Infantile form of Huntington's chorea. Striking atrophy of the cerebral cortex.

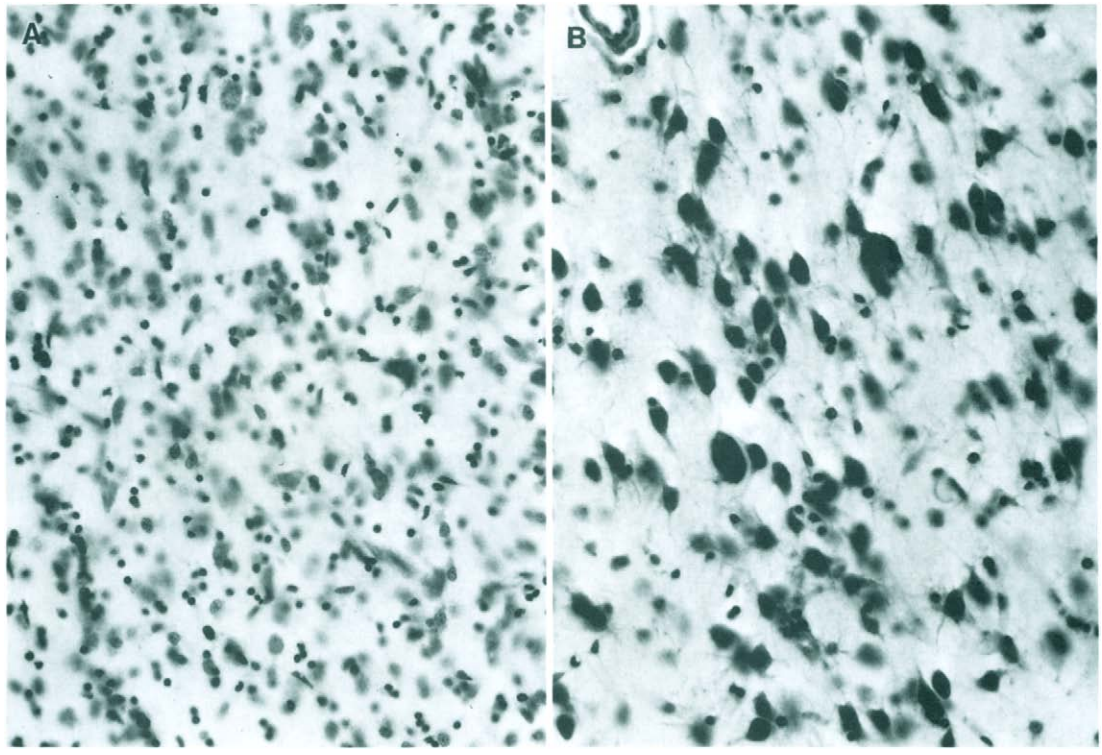


Fig. 244 (A) A loss of small neurons in the neostriatum in Huntington's chorea. (B) A normal control. Nissl stain, ×250.

tients with this disease as compared to that of controls and the residual staining displayed in an inhomogenous pattern, which strikingly resembled that of calcineurin (Goto *et al.*, 1989).

In the final stages of the disease, the atrophy may assume the appearance of a status spongiosus (Fig. 245A,B).

Campbell *et al.* (1961) found a predominance of putaminal lesions over those found in the caudate, while other authors emphasized a greater integrity of the large striatal neurons in the rigid form.

Morphometric studies revealed a neuronal loss in the pallidum in which parvalbumin-immunoreactive neurons are spared (Cudkowicz and Kowall, 1990) to be hardly less severe than in the striatum. The surviving neurons and glial cells contain abundant lipofuscin. Up to a 50% reduction in the number of small (internuncial) neurons has been found in the ventrolateral thalamus. A slight to moderate loss of neurons also occurs in the parvocellular part of the centrum medianum. These are inhibitory cells and their atrophy may be connected with the loss of GABAergic impulses from the atrophic striatum into the lateral hypothalamic nuclei. Striatal neurons projecting to the external segment of the

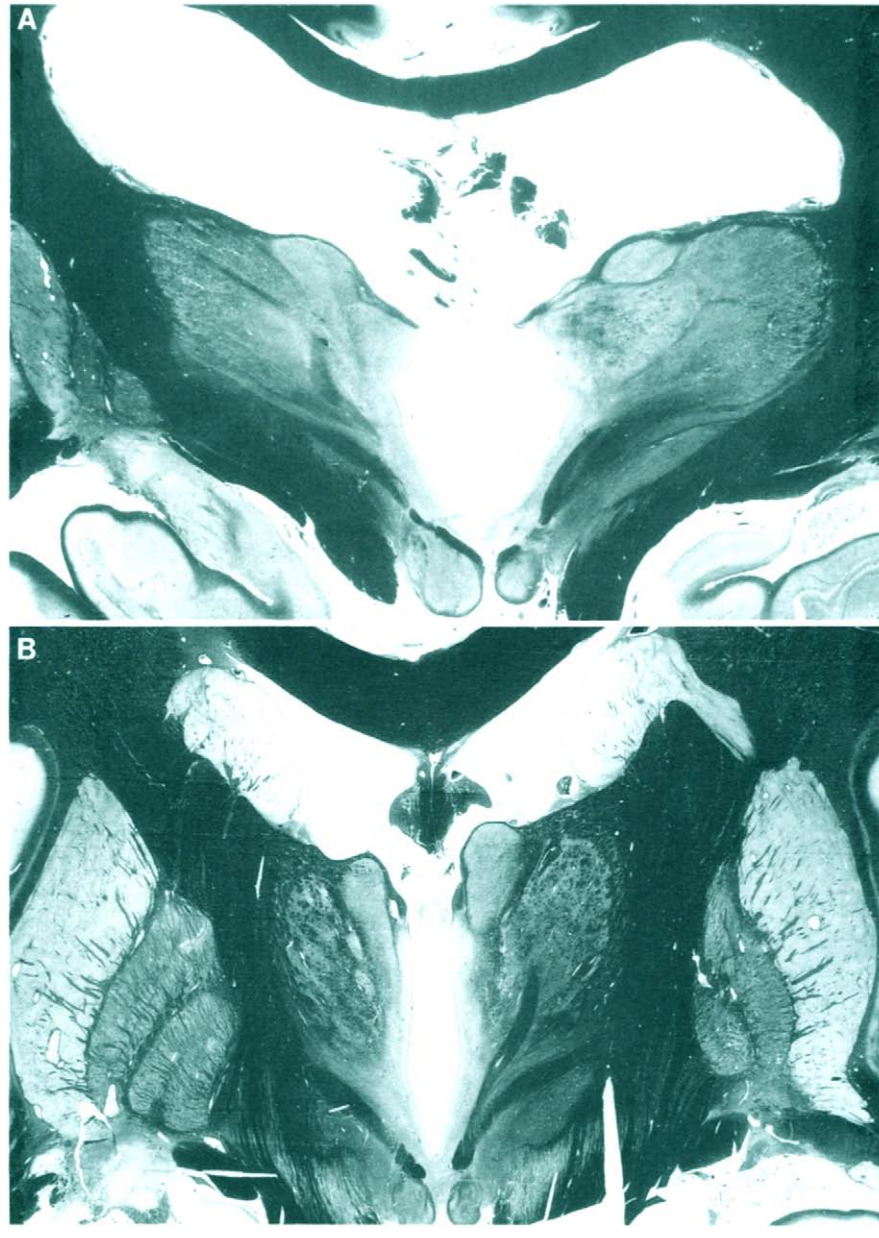


Fig. 245 Basal ganglia at the level of the mamillary bodies. (A) Huntington's chorea. (B) A normal control. Heidenhain–Wölcke stain.

globus pallidus or the substantia nigra show evident loss, whereas those projecting to the internal segment of the globus pallidus appear relatively spared at presymptomatic and early stages of symptomatic Huntington's chorea (Albin *et al.*, 1992). In the dorsal putamen the parvalbumin neurons are also degenerated (Ferrer *et al.*, 1994b).

A reduced amount of melanin and neuronal loss (Forno and Jose, 1973; Oyanagi *et al.*, 1989b; Myers *et al.*, 1991) in the substantia nigra has been observed in the rigid form of Huntington's chorea. Striatonigral projections containing substance P and methionine enkephalin immunoreactivity are reduced in the substantia nigra, while nigrostriatal projections were reported to be unaffected (Ferrante *et al.*, 1990). Zweig *et al.* (1992) found that lower locus coeruleus neuronal counts, reduced neuronal areas, and reduced locus coeruleus lengths were associated with features of advanced disease.

Some neuronal loss and mild gliosis may also be present in the cortex, particularly in layers III–V (Myers *et al.*, 1990; Heinsen *et al.*, 1992). A subtotal loss of Purkinje cells was found in the infantile and juvenile forms (Rodda, 1981). An accumulation of lipofuscin and scattered hemosiderin deposits are nonspecific associated features. Kremer *et al.* (1990) found up to a 90% neuronal loss in the hypothalamic lateral tuberal nucleus. The remaining neurons showed features of degeneration and there was astrocytosis. A loss of anterior horn cells was occasionally seen in the spinal cord (Forno and Jose, 1973).

Astrocytic proliferation and fibrillary gliosis are particularly prominent in the later stages of the disease. The density of reactive astrocytes is not proportional to the neuronal loss, although morphometric studies have revealed up to a 25% loss of glial cells (Bruyn *et al.*, 1979). Morphometric studies are difficult to interpret, however, as the reduction in the size of the perikaryon may alter the relationship between large and small cells. Furthermore, more than two types of neurons may be present in the neostriatum. Mandybur *et al.* (1991) observed different patterns of gliosis in the neocortex. An increased density of oligodendrocytes is observed in the head of the caudate nucleus for the lower grades (0, 1, and 2) (Myers *et al.*, 1991).

The neuropathological gradation correlates remarkably well with the clinical stage of the disease. It is of interest that the first clinical manifestations appear at grade 0, which suggests that functional disturbances may precede appreciable morphological changes (Vonsattel *et al.*, 1985).

The atrophy of the striatum leads to a crowding of the myelinated radial fibers, as seen in sections stained for myelin (Fig. 245). This appearance was described by Vogt and Vogt (1920) as "status fibrosus." The striae are thinner than normal, but retain their oligodendroglial population, thus conveying a spurious impression of oligodendrocytic hyperplasia. A loss of myelin may also occur in individual cases in cerebroolivary and olivocerebellar tracts, as well as in the anterior and lateral columns in the spinal cord (Forno and Jose, 1973).

Abnormalities revealed by Nihei and Kowall (1992) in neurofilament and neural cell adhesion molecule immunocytochemistry in the striatum suggest that neurofilament phosphorylation is altered and growth-related proteins are reexpressed. The total iron content has been found to be increased in the striatum (the caudate nucleus and the putamen). Copper levels are elevated in the putamen (Dexter *et al.*, 1992).

Electron microscopy. An increased amount of lipofuscin is found in neurons and astrocytes of the striatum and the cerebral cortex (Téllez-Nagel *et al.*, 1974). Structural abnormalities are present in the mitochondria, Golgi apparatus, and endoplasmic reticulum of nerve cells. Invaginations of the nuclear membrane with peripheral displacement of the nucleolus have been observed in surviving neurons, particularly in the nucleus accumbens (Bots and Bruyn, 1981). Forno and Norville (1979) found numerous unmyelinated axons containing synaptic vesicles but without synapse formation in areas of severe neuronal loss. The hyperplastic astrocytes contain abundant glial filaments. Averback (1981) found parasynaptic corpora amylacea in the striatum.

Pathogenesis The increased sensitivity of dopamine receptors in the striatum, the reduced concentration of dopamine and homovanillic acid in the caudate nucleus, the decrease in choline acetyltransferase, particularly in the caudate, and the reduction in the muscarinic cholinergic receptors in the striatum and the pallidum can be equally well interpreted as either causes or results of the disease (Bird and Spokes, 1982). The same applies to increased concentrations of the gonadotropin-releasing hormone in the hypothalamus and the reduced content of GABA and substance P in the basal ganglia. There are grounds for assuming a generalized cell membrane defect (Sanberg and Coyle, 1984). This could explain the dementia with a slight neuronal loss in the cerebral cortex. Several lines of evidence point to a decline in mitochondrial efficiency with age, and the mitochondrial inhibitor 3-nitropropionic acid administered intraperitoneally to rats older than 4 months causes a far greater striatal degeneration and mortality compared with those of younger animals (Bossi *et al.*, 1993). To account for the predominant appearance of symptoms in middle age, Finch (1979) proposed an interaction between the abnormal gene and normal aging phenomena. Cultivated lymphocytes from patients with Huntington's chorea revealed an abnormal sensitivity to ionizing, but not to ultraviolet, radiation (Moshell *et al.*, 1980).

Gusella *et al.* (1983) found an RFLP that allowed localization of the gene for Huntington's chorea on chromosome 4. More recently, the responsible gene (*IT 15*) has been accurately localized and sequenced (Huntington's Disease Collaborative Research Group, 1993). The gene is located on chromosome 4p16.3 and the abnormality consists of multiple repeats of the trinucleide CAG. This expands the gene and renders it unstable. The repeat length in Huntington's chorea varies from 38 to over 100, whereas in unaffected individuals this is between 9 and 34. No mosaicism or differences in the repeat lengths were observed in the DNA from different tissues. Therefore, the determination of the repeat number in the DNA of blood lymphocytes is probably representative of all tissues in a patient (Zuhlke *et al.*, 1993). The relative increased abundance of the larger transcript in the human brain may provide some insights into the mechanism by which a widely expressed gene may exert tissue-specific effects (Lin *et al.*, 1994).

Animal Models Animal experiments with kainic acid (Francis *et al.*, 1985), which produce a choreiform picture, led to an unsuccessful search for similar substances in the human form of the disease (Marsden, 1982). The role of chinolinic acid as a possible endogenous excitotoxic factor has remained unconfirmed.

The sequence of the murine Huntington's chorea gene has provided evidence for conservation and polymorphism in a triplet (CCG) repeat alternate splicing (Lin *et al.*, 1994).

Chorea–Acanthocytosis (Levine–Critchley Syndrome; Degeneration of the Basal Ganglia with Acanthocytosis; Amyotrophic Chorea)

Critchley *et al.* (1967) reported on a family with a variety of neurological symptoms and acanthocytosis. Another family was described in the same year by Estes *et al.* (1967).

Clinical Picture The disease manifests itself in adolescents or young adults with orofacial dyskinesia. In the further course of the disease, the dyskinesia becomes intensified and spreads, developing into generalized chorea. Occasionally, a loss of tendon jerks has been observed. Epileptic seizures may occur, occasionally as the first symptom. In advanced stages atrophy of the skeletal muscles may be present (Sato *et al.*, 1984; Yamada *et al.*, 1986). Dementia of variable severity may supervene. Many patients have affected relatives, but no consistent pattern of inheritance has been identified. Inheritance may be autosomal recessive (Hardie *et al.*, 1991; Malandrini *et al.*, 1993) or, in some families, autosomal dominant. Antibrain immunoreactivity is present in the plasma of the patients (Bosman *et al.*, 1994).

Hardie *et al.* (1991) identified seven nonfamilial cases of movement disorder with acanthocytosis in a period of 6 years.

Symptoms compatible with those of chorea–acanthocytosis, but without acanthocytes, have been described in many patients. Family studies indicate that abnormal erythrocyte band 3 structure and function and antibrain immunoreactivity may be phenotypes of two independent genetically determined factors that are part of the heterogenic defect of chorea–acanthocytosis (Bosman *et al.*, 1994).

Neuropathology *Gross appearances.* Usually, atrophy of the basal ganglia can be observed (Galatioto *et al.*, 1993; Malandrini *et al.*, 1993). Coronal slices showed moderate symmetrical dilatation of the ventricles, particularly affecting the frontal horns, and very marked atrophy of the caudate, putamen, and pallidum. These structures were symmetrically shrunken, were rather soft and spongy in consistency, and showed a brownish discoloration. A number of infarcts of varying age and size were observed, ranging from one affecting the left posterior frontal cortex and underlying white matter of several weeks' duration to a large left temporo-occipital infarct (Hardie *et al.*, 1991).

Light microscopy. Neuronal loss is severe in the caudate nucleus and less pronounced in the putamen, with variable preservation of the large neurons (Iwata *et al.*, 1984). Swelling of the neurons in the dentate nucleus and vacuolation of the cytoplasm in the neurons of cranial nerve nuclei have also been reported (Yamada *et al.*, 1986). Dense gliosis occupies the caudate and is patchy in the putamen (Yamada *et al.*, 1986). Slight gliosis is also present in the cerebral and the cerebellar white matter and in the centromedian nucleus of the thalamus.

In the peripheral nervous system a loss of large myelinated fibers, more accentuated distally, was seen in the peripheral nerves (Malandrini *et al.*, 1993). Other observations in the peripheral nerves include patchy demyelination and axonal degeneration (Sato *et al.*,

1984). Reductions of substance P in the striatum and of glutamic acid decarboxylase in the substantia nigra were found during biochemical studies (Sato *et al.*, 1984).

Familial Striatal Degeneration (Holotopistic Striatal Necrosis)

Roessmann and Schwartz (1973) described a familial striatal degeneration with onset in childhood and a progressive course. The symptoms include mental retardation, rigidity, dysarthria and dysphagia, athetoid movements, and seizures. Similar cases were reported by Erdohazi and Marshall (1979). The cases documented by Miyoshi *et al.* (1969) may be included in this group, although a vascular pathogenesis cannot be excluded. Dystonia, ataxia, and choroathetosis are common features in affected family members. The disease onset is associated with a preceding febrile episode in some, and is slowly progressive in others.

Neuropathology Neuropathology reveals a symmetrical striatal degeneration and diffuse atrophy of the cerebral cortex. A minor neuronal loss and reactive astrocytosis were evident in the globus pallidus in a case reported by Craver *et al.* (1994). The inheritance follows a pattern of probable autosomal dominance with incomplete penetrance and anticipation. The familial striatal degeneration with cerebello-extrapyramidal–myoclonic manifestations may, in our present state of knowledge, represent an atypical form of the Westphal variant of Huntington's chorea.

Infantile Bilateral Striatal Necrosis

It is debatable whether this condition, first described by Paterson and Carmichael (1924), is identical to the familial syndrome described above or instead constitutes a separate entity. Friede (1989) includes all familial cases with the sporadic ones as *infantile bilateral striatal necrosis*, but admits that the condition may not be a homogeneous entity. Major contributions include those of Röytta *et al.* (1981).

Clinical Picture Onset of the disease may be at birth, at an age of a few months, or at 1–3 years. It often occurs during the course of febrile infectious disease. Drowsiness or coma, abnormalities of muscle tone, and occasional convulsions are the principal features of the acute stage. The long-term survivors exhibit paralysis of the trunk and the extremities, muscle tone, and occasional involuntary movements. Cases with an early onset often die in the acute stage or within a few weeks or months.

Neuropathology *Gross appearances.* In the acute stage the putamen and the caudate nucleus are softened and yellowish; in later stages they are shrunken and sunken below the cut surface. The necrosis affects the entire striatum and is clearly demarcated from the surrounding structures, sparing the internal capsule.

Light microscopy. The necrosis affects the entire neuronal population without selectivity for the different cell types. Invasion by macrophages and formation of fat granule cells follow. Ultimately, the necrotic tissue is absorbed and replaced by a loose, spongy, glial scar. Patchy neuronal loss has been recorded in the pallidum, red nuclei, subthala-

mic nuclei, cerebral cortex, superior and inferior colliculi, and periaqueductal gray. Central pontine myelinolysis was reported in one case (Mathieson and Olszewski, 1960).

Other Choreiform Clinical Syndromes

Choreoathetoid movement disorders occur in a large number of neurological diseases. Aside from chorea and hemichorea of vascular origin, there are a number of syndromes in which choreiform hyperkineses constitute the principal abnormality.

Chorea Minor (Sydenham's Chorea)

This disease, affecting children up to the age of puberty, is not a system atrophy. The symptoms consist of choreiform hyperkinases ranging from barely abnormal wriggles to severe restlessness and grimacing. Behavioral disorders as well as obsessive–compulsive behaviors may be present (Lesch, 1991), but no dementia. The disease is self-limiting and lasts from some weeks to a few years, but usually a few months. Recurrences are not uncommon. A number of patients with Sydenham's chorea may be left with mild to moderate neurological and psychiatric sequelae (Bernsen and Renier, 1990).

Neuropathology Neuropathology reveals disseminated perivascular lymphocytic infiltrates and glial nodules, scattered in the gray matter without any specific localization. A definite arteritis is found occasionally, in addition to small embolic occlusions.

Pathogenesis Pathogenetically, this is a focal encephalitis in the context of poststreptococcal rheumatic fever. The prognosis is favorable, except for the associated cardiac complications in the form of valvular lesions.

Torsion Dystonia (Dystonia Musculorum Deformans)

The first clinical description of this condition goes back to Schwalbe (1908), who considered the syndrome a form of hysteria. Oppenheim (1911) appreciated the organic nature of the disease and coined the term *dystrophia musculorum deformans.* It is not a homogeneous entity and can be classified into two main groups: the symptomatic, associated with a variety of striatal lesions, and the idiopathic, in which no such lesions can be demonstrated. In the former group it can be a manifestation of Wilson's disease (see p. 407), Leigh disease (see p. 38), or infantile bilateral striatal necrosis (see p. 539), particularly the form with maternal (mitochondrial) inheritance genetically linked with Leber's optic atrophy (see p. 56). Lubang disease, an X-linked recessive dystonia–parkinsonian syndrome affecting Filipinos originating principally from Panay (Lee *et al.*, 1976), probably also belongs to this group. The idiopathic form affects predominantly Ashkenazi Jews, in whom the prevalence is five to 10 times greater than in the general population. An association of dyschromatosis symmetrica hereditaria with idiopathic torsion dystonia was reported (Patrizi *et al.*, 1994).

Clinical Picture The symptoms usually appear in childhood or at puberty. The first abnormal movements affect the neck muscles (Bressman *et al.*, 1994) and spread later to the trunk. The movements are variable and may resemble those of Huntington's chorea, on the one hand, or athetosis, on the other. After a few years, sometimes even after a few months, the abnormal movements render the patient incapacitated and unemployable. Spasmodic torticollis is the common initial symptom in adults and may progress to the full picture of torsion dystonia (Hitchcock, 1990). The frequent flexion postures of the wrist may lead to carpal tunnel syndrome caused by entrapment of the median nerve. In cases with striatal necrosis, bilateral putaminal lesions can be seen on CT and MRI (Burton *et al.*, 1984).

Dopa-responsive dystonia is a recently described variant of idiopathic torsion dystonia. It is distinguished from other forms by the frequent occurrence of parkinsonian, the diurnal fluctuation of symptoms, and its dramatic therapeutic response to L-dopa (Kwiatkowski *et al.*, 1991).

Neuropathology There is no consistent pattern of lesions. In the striatal group the most common lesion is a loss of large neurons, the small ones being relatively spared. In an extensive study of patients with the idiopathic variety, Zeman and Dyken (1967) failed to find any significant lesions. Such abnormalities as were present were trivial, inconsistent, and probably incidental. Minimal lesions have been observed in the internal nucleus of the globus pallidus and in the subthalamic nucleus. Gibb *et al.* (1992) described a mosaic pattern of striatal pathology in a male who developed severe generalized dystonia at the age of 10 years and died at the age of 18 years. The caudate and the putamen showed a network of cell loss and gliosis surrounding islands of preserved striatal tissue. The dorsal parts showed confluent gliosis, but the ventral parts were spared.

Similar neuropathological findings, with neuronal loss and a multifocal mosaic pattern of astrocytosis restricted to the caudate and the lateral putamen, were reported by Waters *et al.* (1993a,b).

In a case of dopa-responsive dystonia, Rajput *et al.* (1994) found normal numbers of hypopigmented neurons in the substantia nigra, normal tyrosine hydroxylase immunoreactivity, no inclusion bodies or gliosis, and little evidence of degenerative changes in the striatum (8% cell loss from the control level in the putamen and 18% in the caudate) with a similar, but not identical, subregional distribution as in Parkinson's disease.

Pathogenesis This disease appears to be a disturbance of feedback mechanisms controlling muscle tone. The abnormal postures and movements are the result of the simultaneous innervation of agonists and antagonists. Rajput *et al.* (1994) concluded that a disturbed dopamine synthetic capacity or a reduced arborization of striatal dopamine terminals may be the major disturbance in dopa-responsive dystonia.

The disorder may be inherited as an autosomal-dominant, autosomal-recessive, or X-linked recessive trait. Linkage analysis in one form of autosomal-dominant torsion dystonia permits the assignment of a "torsion dystonia locus" to the long arm of chromosome 9. Kwiatkowski *et al.* (1991) demonstrated that the gene causing dystonia in Ashkenazi Jews can be localized to the 11-cM interval between *AK1* and *D9S10*. It is noteworthy

that the gene for torsion dystonia has been localized to the same region, 9q34.3, as the *N*-methyl-D-aspartate receptor (Collins *et al.*, 1993). Assignment of the X-linked torsion dystonia locus to the proximal long arm of the X chromosome (Xq21) was demonstrated by Kupke *et al.* (1990).

Gilles de la Tourette's Syndrome

This disease, described in 1885 by Gilles de la Tourette, consists of a repetitive automatism of movements, usually beginning between the ages of 2 and 15 years, and an obsessive–compulsive disorder consisting mainly of echolalia and coprolalia. The obsessive–compulsive symptoms develop later and constitute a prominent feature of the disease. Occurrence of only chronic tics in the families with Gilles de la Tourette's syndrome has been observed (Pauls *et al.*, 1991). Isolated and minor structural alterations with mild ventricular dilatation, prominent sylvian fissures, and cysts were documented by CT or MRI (Robertson *et al.*, 1988). Polymicrogyria was found in 50% of the examined patients (Berthier *et al.*, 1991). The few neuropathological examinations yielded no significant results (Richardson, 1982).

Early psychogenic theories have been replaced by proposals invoking inherited abnormalities of synaptic neurotransmission. A disturbance in Purkinje cell metabolism has been postulated but never proved. Two systems have been pinpointed as possible sources of biochemical abnormalities: activity of central neurotransmitters (Kurlan, 1992) and purine metabolism (Singer and Walkup, 1991). A reduction or absence of dynorphin in the basal ganglia was demonstrated immunohistochemically in a severely affected patient (Haber *et al.*, 1986). In contrast, CSF dynorphin A concentrations are increased in most patients (Leckman *et al.*, 1988).

Meige's Syndrome (Breughel Syndrome; Spontaneous Orofacial Dyskinesia; Blepharospasm with Oromandibular Dystonia)

This syndrome, described by Meige (1910), consists of blepharospasm and irregular contractions of other facial muscles. Onset is usually in the fifth to seventh decades. Marsden (1976) called it "Breughel syndrome" after the Flemish painter who portrayed a woman suffering from this condition. Early reported cases were mainly sporadic, familial occurrence being more frequently recorded in the recent literature (Jankovic, 1985). In a young patient with blepharospasm, macular degeneration, and mental retardation, Kajiyama *et al.* (1985) found calcification of the basal ganglia.

An irregular mosaic pattern of neuronal loss with gliosis was found in the dorsal halves of the caudate and the putamen (Altrocchi and Forno, 1983). Kulisevski *et al.* (1988) also observed lesions in the substantia nigra, locus coeruleus, tegmentum of the midbrain, and dentate nucleus. The association of extrapyramidal symptoms with spinocerebellar pathological changes was reported in an autopsy case (Khara and Calabrese, 1991).

Pathogenesis Pathogenetically, functional disturbances in the striatum have been postulated in the form of a neurotransmitter imbalance with a dopamine predominance (Tolosa and Klawans, 1979; Weiner *et al.*, 1981).

Paramyoclonus Multiplex (Familial Essential Myoclonus)

This syndrome was described by Friedreich in 1881. It may be inherited in some families (De Jong, 1982) and is sometimes combined with essential tremor. Some cases of various choreiform syndromes have also been diagnosed as paramyoclonus multiplex.

Hallervorden–Spatz Disease (Neuroaxonal Dystrophy Type I of Gilman and Barrett; Localized Neuroaxonal Dystrophy; Progressive Pallidal Degeneration; Pigment–Spheroid Degeneration)

Hallervorden and Spatz described in 1922 a disease of the extrapyramidal system in which the brunt of the damage fell onto the globus pallidus and the substantia nigra. Wigboldus and Bruyn (1968) accepted only familial cases with late infantile or juvenile onset as genuine examples of Hallervorden–Spatz disease. Dooling *et al.* (1974) included infantile and adult cases and pointed out that many typical cases were apparently sporadic. Many authors consider Hallervorden–Spatz disease to be a subgroup of the neuroaxonal dystrophies because of the presence of prominent axonal swellings in the affected areas (Gaytan-Garcia *et al.*, 1990). We discuss our criteria of classification in the section on neuroaxonal dystrophies in the previous chapter (see p. 509).

Clinical Picture The infantile form of the disease manifests itself rarely immediately after birth, but usually during the first year. The onset of symptoms falls around the third year in the late infantile form (Ambrosetto *et al.*, 1992), between the ages of 7 and 12 years in the juvenile form, and after the age of 20 in the adult form, in which it may appear even in advanced age. The prominent features are rigidity, progressive spasticity, disorders of gait and speech, and insidious dementia. Occasional athetoid hyperkinesias have been observed (Higgins *et al.*, 1992b) in addition to ataxia, nystagmus, visual disturbances, and seizures. Dysphagia and foot deformities may also occur, as well as RP and acanthocytosis of the red blood cells (Higgins *et al.*, 1992b). Disturbances of psychomotor development, optic atrophy leading to blindness, loss of hearing, and progressive dementia mark the later stages of the disease. The adult form appears occasionally in the guise of familial parkinsonism. Környey (1974) observed an increased excretion of copper in the urine with normal blood levels. The duration of the illness ranges between 2 and 9 years in the infantile and late infantile forms and between 8 and 18 years in the juvenile form.

MRI pallidal abnormalities consist of decreased signal intensity on T_2-weighted images, compatible with iron deposits, and of a small area of hyperintensity in its internal segment ("eye of the tiger" sign) (Pedespan *et al.*, 1993). Comparison of MRI findings with the pathological studies demonstrates that the low signal intensity on T_2-weighted images at 1.5 T corresponds to iron deposits in a dense tissue, and that the high signal intensity of the eye of the tiger sign corresponds to an area of loose tissue with vacuolization (Savoiardo *et al.*, 1993).

Neuropathology *Gross appearances.* The striking feature is the grayish brown or reddish pigmentation of the globus pallidus and the zona reticularis of the substantia ni-

gra, both of which may appear abnormally voluminous. The brain may appear slightly or moderately atrophic, while the cerebellum is often atrophic in the infantile forms.

Light microscopy. A massive deposition of pigments is found in the pallidum and the red zone (zona reticularis) of the substantia nigra. The pigment usually gives a positive reaction for iron (Fig. 246) and may be green, bluish black, golden yellow, and brown (Fig. 247). The pigmentation is less pronounced in the infantile and late infantile forms than in the juvenile and adult ones. Spherical and mulberry-shaped calcium deposits, staining greenish to bluish black with thionin, also appear in the pallidum. In some late infantile and juvenile cases all of these changes are confined to the globus pallidus (Kessler *et al.*, 1984).

A considerable neuronal loss with astrocytic proliferation is evident in the pigmented areas. In preparations stained for myelin, a more or less severe loss of myelin sheaths is apparent in the affected structures ("status dysmyelinisatus" of Vogt and Vogt, 1920). Lewy bodies (Fig. 248) have been repeatedly observed in the substantia nigra (Antoine *et al.*, 1985).

An increased amount of sudanophilic lipid, particularly in the pallidum, is seen in infantile and late infantile cases. A spongy rarefaction, axonal spheroids, and loose glial nodules appear at the same site. A more limited scattering of lipid is seen in the thalamus. Lipid storage with ballooning of the cytoplasm was also observed in other parts of the brain (Környey, 1974).

Axonal swellings are the most prominent feature in the infantile and late infantile cases. Both in the pallidum and in the substantia nigra numerous spheroids exhibit the characteristics described in the generalized neuroaxonal dystrophies (see p. 510). Im-

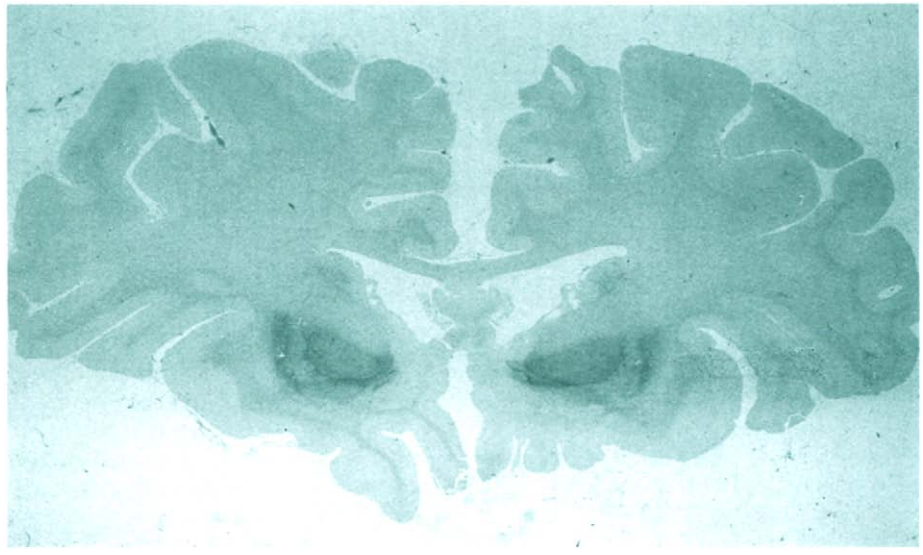


Fig. 246 Hallervorden–Spatz disease. A strongly positive iron reaction in the globus pallidus as well as in the putamen. Turnbull blue stain.

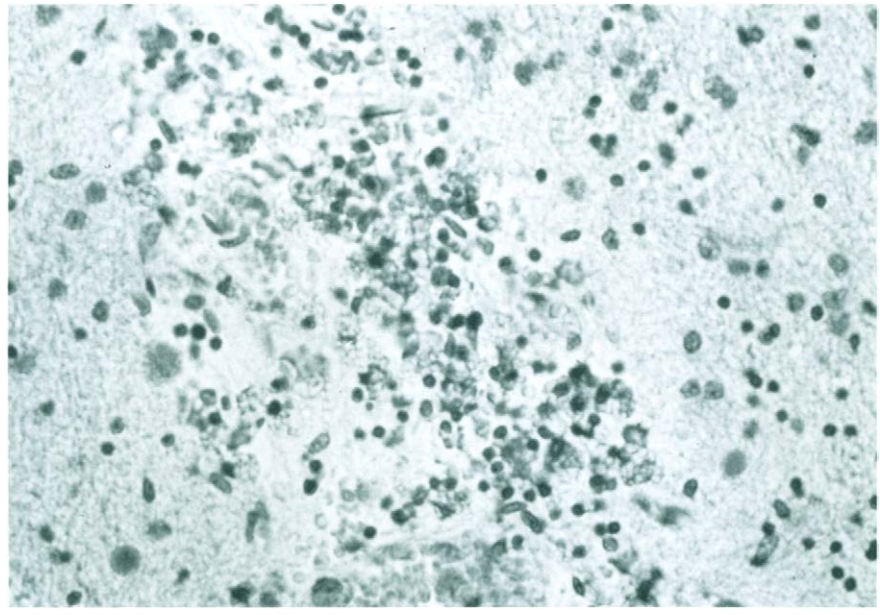


Fig. 247 Same case shown in Fig. 246. An accumulation of golden brown pigments. Hematoxylin–eosin stain, ×300.

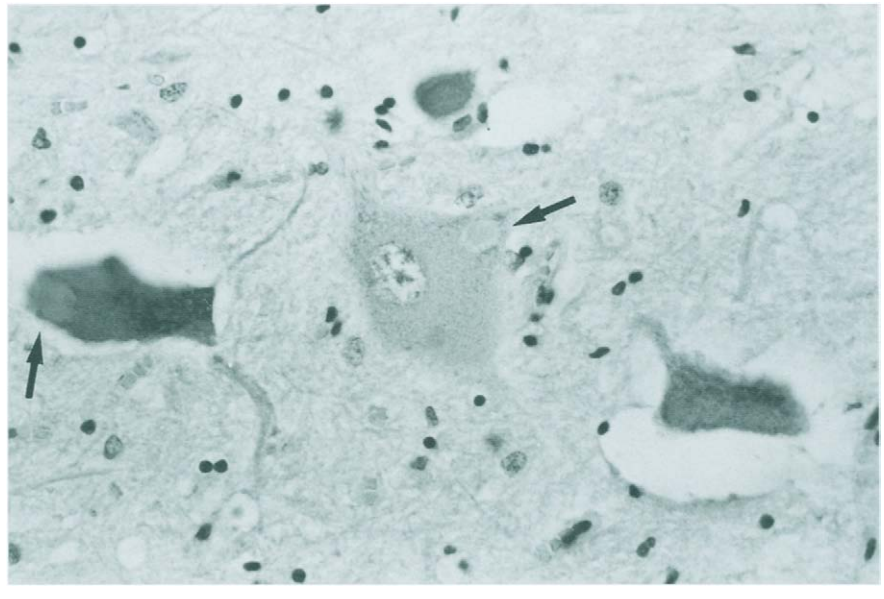


Fig. 248 Same case shown in Fig. 246. Lewy bodies (arrows) in the neurons of the substantia nigra, ×700.

munoreactivity of APP was observed in the spheroids and in the globus pallidus with Hallervorden–Spatz disease. The axonal swellings were not immunolabeled with β-protein. Isolated spheroids may also appear in other parts of the brain. In late infantile cases in particular, they are encountered in the cerebral cortex, thalamus, tegmental nuclei, and posterior horns of the spinal cord (Seitelberger *et al.*, 1963). Neuronal loss can occur in the retina (Inomata *et al.*, 1978), as well as pigment deposition in the outer layers. No lesions are found in the motor end plates. This absence has been considered an important criterion in the differentiation of Hallervorden–Spatz disease from infantile neuroaxonal dystrophy (INAD).

Biochemical examination of the pallidum revealed large quantities of iron, as well as increased amounts of copper, zinc, and calcium (Goldberg and Allen, 1979).

Electron microscopy. The pallidal and nigral pigments appear as irregular roundish structures of various intensity of electron density and a coarsely granular consistency. The ultrastructure of the neuroaxonal swellings resembles that seen in generalized neuroaxonal dystrophies, although there are some slight differences. Electron-dense inclusions were found in skin biopsies of clinically diagnosed patients (Stover *et al.*, 1981). Fingerprint bodies and multilamellar structures were seen in lymphocytes (Swaiman *et al.*, 1983).

Pathogenesis It is of interest that the pallidonigral pigmentation is accompanied by a tendency toward hyperpigmentation of the skin. This has led to hypotheses postulating disturbances in the neuromelanin or dopaminergic systems or the oxidative effect of the increased amount of iron. According to Kim *et al.* (1981), the pigments arise through peroxidation, while the spheroids are the result of an intraaxonal accumulation of lipopigments. Perry *et al.* (1984) assumed that a deficiency in cysteine dioxygenase led to a concentration of cysteine in the pallidum. The iron binding capacity of cysteine would lead to the formation of free radicals, which would damage the neuronal cell membranes. Hartmann *et al.* (1983) maintained that part of the pigments contained in spheroids consisted of neuromelanin originating from catecholaminergic neurons. Pettigrew *et al.* (1991) described a family with an X-linked form of mental retardation, early hypotonia with progression to spasticity and contractures, choreoathetosis, seizures, presence of a long narrow face with coarse features, cystic enlargement of the fourth ventricle with cerebellar hypoplasia, and iron accumulation in the basal ganglia with neuroaxonal dystrophy similar to Hallervorden–Spatz disease. Although the clinical findings among relatives were variable, the authors concluded that this is a distinct, previously unrecognized, X-linked mental retardation syndrome.

Parkinsonism

Parkinson (1817) described "shaking palsy," translated into Latin as *paralysis agitans* by Hall (1850). This term, and the eponym *Parkinson's disease*, have been widely used ever since. The term *parkinsonism* includes, apart from Parkinson's disease (PD) in the strict sense, similar clinical syndromes of various etiology. Parkinsonian features also occur in chronic manganese poisoning and occasionally in carbon monoxide poisoning. A similar syndrome may occur in drug abusers (see p. 555). Aside from PD in the strict

sense, postencephalitic parkinsonism, the parkinsonism–dementia complex of Guam, and striatonigral degeneration are considered in this chapter. "Parkinson plus," or parkinsonism associated with other neurological manifestations (Schnaberth, 1986), occurs in several multisystem atrophies.

Parkinson's Disease (Paralysis Agitans; Parkinsonism with Lewy Bodies; Hereditary Shaking Palsy; Idiopathic Parkinsonism)

PD may appear in combination with other neurological diseases, such as ALS or AD. The latter combination occurs six times more frequently than expected from coincidence in the appropriate age group (Boller *et al.*, 1980).

Many subgroups may be separated from the classical form: juvenile PD and PD with dementia as well as further variants have been described most frequently in familial cases.

Clinical Picture One percent of the people over 60 years of age and 2.6% of those over 85 suffer from PD. The average age at onset is 66 years. Those in their sixth and seventh decades are predominantly affected. Men represent 60% of the cases.

The clinical diagnosis of PD is highly inaccurate. Olivopontocerebellar atrophy (OPCA) and the different variants of PD are the major sources of diagnostic confusion. In 100 patients diagnosed prospectively by a group of consultant neurologists as having PD, the disease could be confirmed in only 76% as a final diagnosis. The retrospective application of recommended diagnostic criteria improved the diagnostic accuracy to 82% (Hughes *et al.*, 1992). The correct clinical diagnosis in most variants of PD was possible within 5 years of onset, but before this time many were misdiagnosed (Rajput *et al.*, 1991).

Resting tremor, akinesia, rigidity, and postural abnormalities constitute the principal symptoms. Pains in the limbs and changes of mood occur in the early stages. In advanced stages poverty of expressive and associated movements in characteristic, as well as propulsion and retropulsion and increased salivation. Disturbances of autonomic function are present in most untreated patients (Sandyk and Awerbuch, 1992). Of the associated conditions cerebrovascular insufficiency is common (Schnaberth, 1986). Cases with orthostatic hypotension are considered a subtype (Micieli *et al.*, 1987). The cerebral blood flow is regionally diminished.

The increased concentration of neutral and basic amino acids in the CSF has been ascribed to defective amino acid transport (Araki *et al.*, 1986); it is, however, nonspecific. The concentrations of tumor necrosis factor α in the brain and the CSF are significantly higher in parkinsonian patients than those in controls (Mogi *et al.*, 1994). CT scans may reveal cerebral atrophy, particularly in younger patients (Steiner *et al.*, 1985). CT measurements demonstrated that patients with bilateral symptoms of PD showed more severe cortical and subcortical atrophy than age-matched normal controls. The presence of unilateral symptoms of PD was significantly associated with contralateral brain atrophy only in patients with right hemi-PD (Starkstein and Leiguarda, 1993). Increased iron deposition in the substantia nigra of patients with PD is associated with decreased signal intensity of T_2-weighted MRI. However, the shortening of T_2 values in the substantia nigra did not correlate with disease duration or with clinical severity (Antonini *et al.*, 1993).

References to familial occurrence range in the literature from 4% to 41%. Both dominant and recessive inheritance have been assumed (Jankovic and Reches, 1986). Meanwhile, it has been amply documented that PD can occur on a genetic basis and the pedigrees described thus far have constantly shown an autosomal-dominant pattern of inheritance.

Pathology Auerbach's myenteric and Meissner's submucosal plexuses are constantly involved in PD; most frequently are Lewy bodies encountered in the Auerbach's plexus of the lower esophagus (Wakabayashi *et al.*, 1990) and in the lower sacral parasympathetic neurons (Oyanagi *et al.*, 1990). The peripheral parasympathetic ganglia are also involved (Takeda *et al.*, 1993). Other sites include the C cells of the thyroid, the adrenal medulla, and the nerves of the mesenteric and renal blood vessels (Barbeau, 1976). In a systematic survey of the CNS and the peripheral nervous system, Ohama and Ikuta (1976) found Lewy bodies in 27 different centers.

Electron transfer complexes I and IV of platelets are abnormal in PD but normal in Parkinson plus syndromes (Benecke *et al.*, 1993). However, the difference in platelet complex I activity is too small to be diagnostic of PD (Jenner *et al.*, 1993).

Neuropathology *Gross appearances.* Pallor of the substantia nigra and the locus coeruleus is apparent in most, but not all, cases (Fig. 249A,B). A total loss of pigment is rare.

Light microscopy. A neuronal loss of pigmented neurons is apparent in the pars compacta of the substantia nigra. The central parts of this nucleus are the most severely affected (Fig. 250A,B), while the medial parts are relatively spared. Remnants of pigment are taken up by perivascular macrophages (Fig. 251). Astrocytic and microglial prolifera-

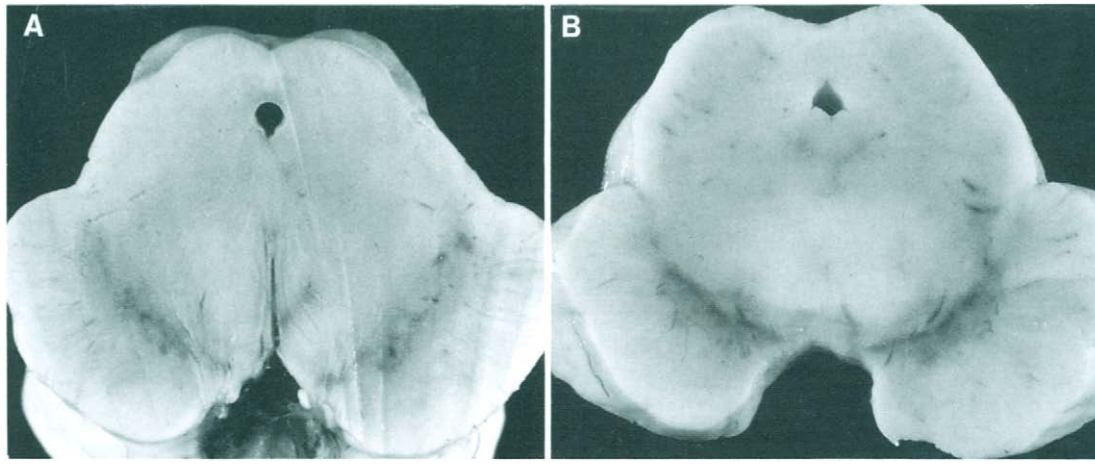


Fig. 249 A section through the midbrain at the substantia nigra. (A) Patchy depigmentation in Parkinson's disease. (B) A normal control.

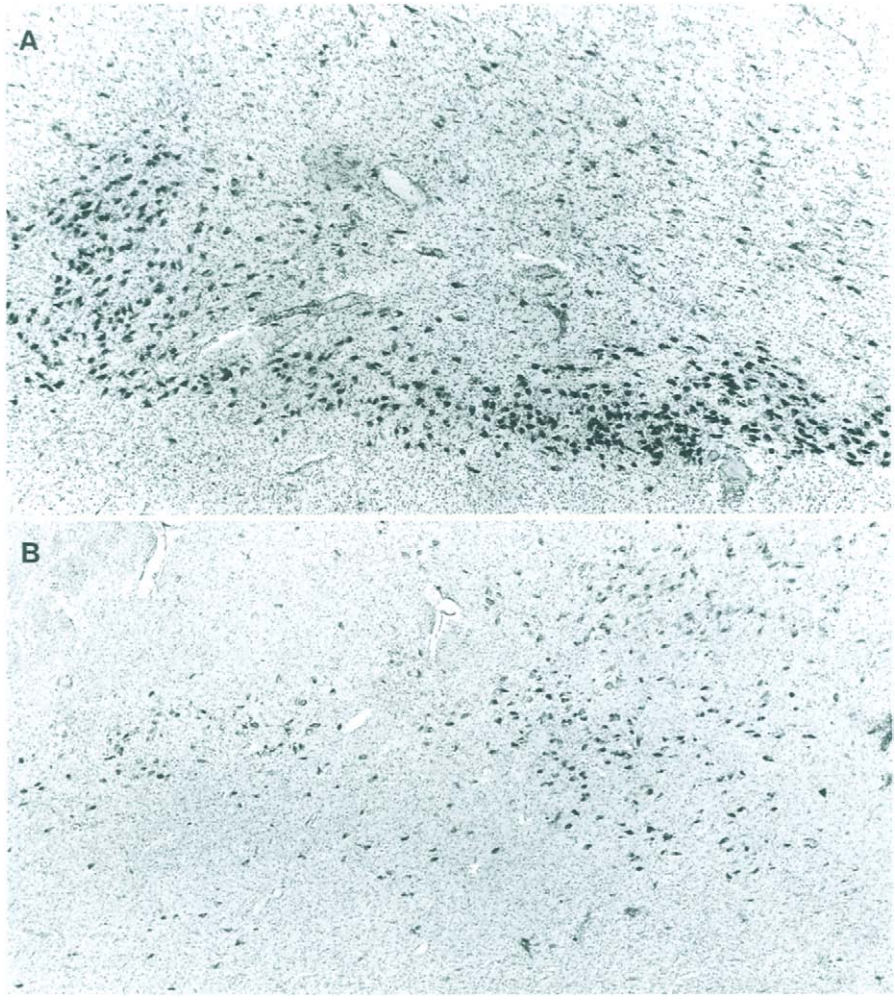


Fig. 250 The substantia nigra (A) of a normal control and (B) showing a severe loss of neurons in a patient with Parkinson's disease. Nissl stain, ×60.

tions occupy the areas of neuronal loss (Fig. 252A,B). A loss of pigmented neurons and fragments of extraneuronal pigment are also present in the locus coeruleus. The neuronal loss is less conspicuous in the dorsal nucleus of the vagus. The neurons of the striatum may be slightly affected; those of the pallidum, extremely rarely. A loss of cortical neurons, either diffuse or focal, has been frequently observed. An increase in the number of neurons with pigment dystrophy was found in the isocortex by Stockhausen and Braak (1984). A loss of neurons in the nucleus basalis of Meynert has been known for many years (Hassler, 1965). It may involve 70% of the neuronal population and may be more severe than that seen in AD (Nakano and Hirano, 1984; Gaspar and Gray, 1984). In many

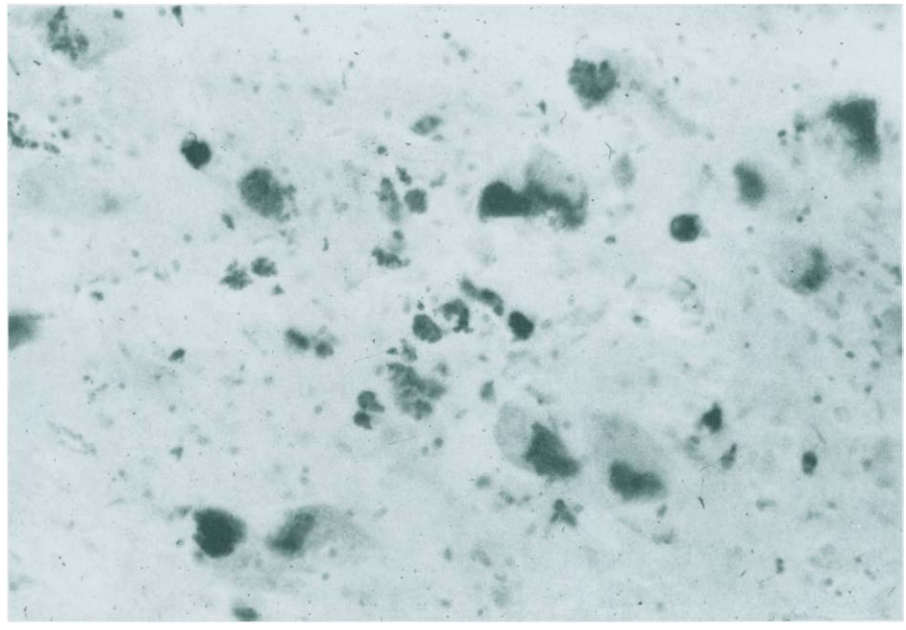


Fig. 251 Parkinson's disease. Residual pigment in phagocytic cells. Nissl stain, ×400.

cases this is associated with dementia (see p. 527). Degeneration affects the dopaminergic mesocortocolimbic system, as well as the serotoninergic raphe nuclei, pedunculopontine nucleus pars compacta, Edinger–Westphal nucleus, and many peptidergic brain stem nuclei. Cell losses in the subcortical projection nuclei range from 30% to 90% of the controls (Jellinger, 1991). Patients with marked akinesia and rigidity showed a higher neuronal loss of locus coeruleus, lateral substantia nigra, and medial substantia nigra and more severe gliosis, extreneuronal melanin deposits, and neuroaxonal dystrophy in the substantia nigra. More severe neuronal cell loss of the dorsal raphe nucleus was observed in PD patients with depression (Paulus and Jellinger, 1991). Substance P-containing neurons in the mesopontine tegmentum are severely affected in PD (Gai *et al.*, 1991). The Golgi-impregnated medium-sized locus coeruleus neurons are reduced in number and show a marked reduction in dendritic length, a severe loss of spines, dendritic varicosities, and swollen perikarya (Patt and Gerhard, 1993).

The neurons in the pars compacta of the substantia nigra, paranigral nucleus, parabrachial pigmental nucleus, tegmental pedunculopontine nucleus, supratrocheal nucleus, cuneiform nucleus, and lemniscus medialis were not stained by antiinsulin receptor antibodies (Moroo *et al.*, 1994). The oxytocin-immunoreactive cell number in the PVN of the PD patients was 22% lower than that of the control subjects (Purba *et al.*, 1994). A significant decrease in synaptophysin immunoreactivity was observed in all hippocampal strata, being more pronounced in the hippocampal subfield CA1 and the subiculum. Synaptophysin expression was also diminished in the molecular layer of the dentate gyrus (Ito *et al.*, 1990).

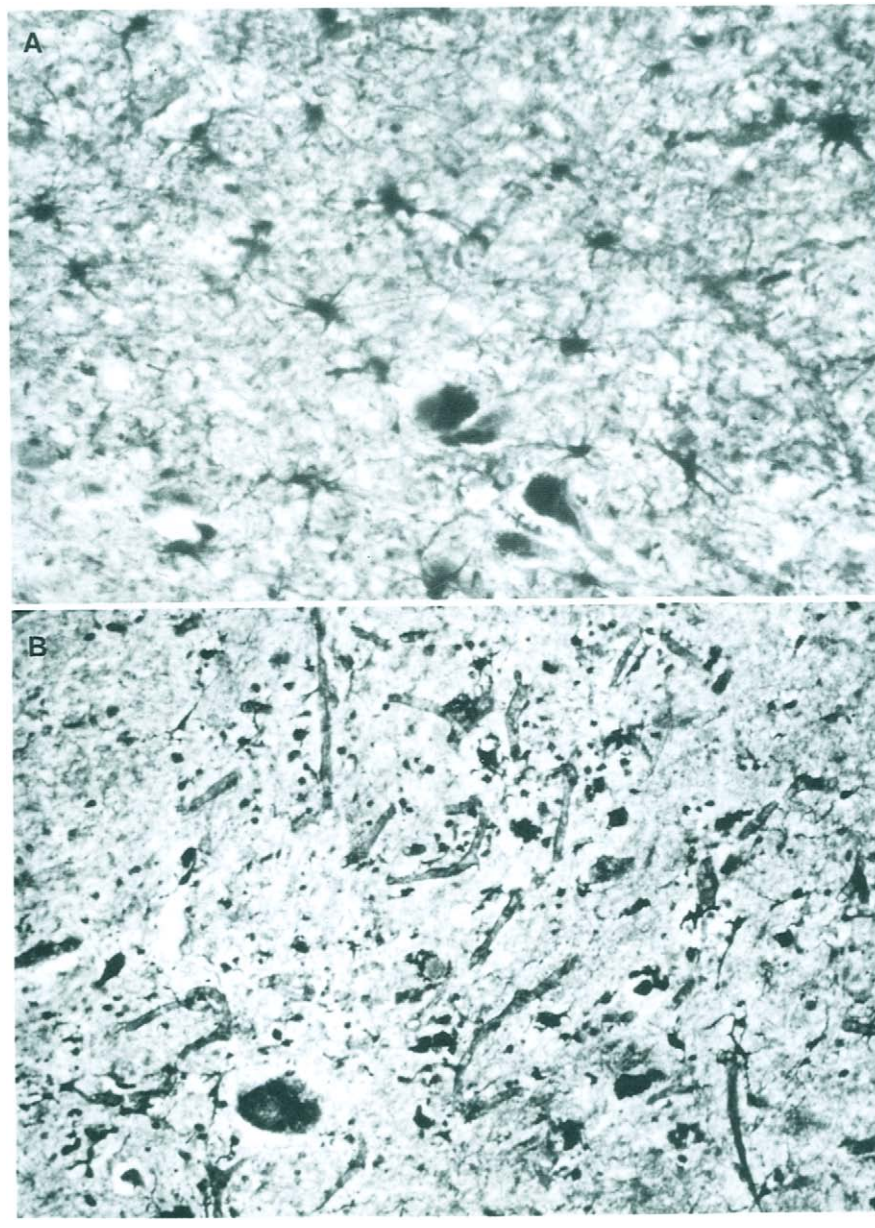


Fig. 252 Parkinson's disease. (A) An astrocytic proliferation in the substantia nigra. Cajal's gold sublimate, ×300. (B) A microglial proliferation in the substantia nigra. Rio Hortega's microglial impregnation, ×300.

Lewy Bodies In many affected melanin-containing cells one finds intracytoplasmic eosinophilic inclusions. These were first described by Lewy (1913). While some authors have claimed that they occur in 90% of the pigmented neurons, it is the general experience that they are far less numerous and require a thorough search of several high-power fields. They are spherical, homogeneous, argyrophilic bodies surrounded by a clear halo (Fig. 253A). They are frequently present in the locus coeruleus (Fig. 253B), where they may assume an elongated shape in the cell processes. By contrast with the swellings of neuroaxonal dystrophy, they are found predominantly in the dendrites.

Lewy bodies may also appear in isolated neurons of the cerebral cortex (Kosaka and Mehraein, 1979), in the basal ganglia and the midbrain outside the substantia nigra (Hunter, 1985), in the tegmentum, and in the hypothalamus, which is always involved in PD. Cases in which Lewy bodies appear in large numbers in the cerebral cortex and the basal ganglia have been classified separately as "diffuse Lewy body disease" (see p. 483). Cortical Lewy bodies are smaller, with comparatively loosely arranged fibrils and granular material, but no distinct core (Schmidt *et al.*, 1991). Predilection sites for cortical Lewy bodies include the cingulate gyrus, insular cortex, amygdala, and frontotemporal neocortex. It has been suggested that this distribution correlates with mesolimbic dopaminergic projections (De Keyser *et al.*, 1990).

Lewy bodies may be present in all hypothalamic nuclei, but are most common and numerous in the tuberomamillary, lateral, and posterior nuclei. However, the number of neurons in both nuclei in PD patients was similar to a group of nonneurological controls. This challenges the hypothesis that Lewy bodies are a sign of significant cell death (Kremer and Bots, 1993). They are rarely seen in the inferior olive. Lewy bodies are also present in the ganglia of the sympathetic chain in 70% of the cases (Forno and Norville, 1976). Lewy bodies are stained with antibodies to human complement proteins (Yamada *et al.*, 1992). Monoclonal antibodies against Lewy bodies were developed by Hirsch *et al.* (1985). They were found, however, to react with antigens in neurons of the normal substantia nigra. Immunohistochemically, the Lewy bodies bind antibodies against neurofilaments (Pollanen *et al.*, 1993), Alzheimer's NFTs, tubulin (Galloway *et al.*, 1988), and ubiquitin (Bancher *et al.*, 1989). These stain not only the appropriate cell components displaced by the Lewy bodies, but the proper substrate of the bodies (Pappolla, 1986). The entire extent of each neurofilament subunit is found in Lewy bodies but the neurofilament subunit may be altered during the processing of these filaments into Lewy bodies. These bodies may also appear in small numbers in other diseases. They are, nevertheless, highly specific for PD. They are frequently found as an incidental finding in autopsy material and are interpreted as an expression of a presymptomatic stage of PD (Forno, 1982; Gibb and Lees, 1988). They do not appear to be related to the lysosomal, acidophilic, intracytoplasmic granules, although they both appear in the same neuronal groups.

Another intracytoplasmic inclusion body observed in pigmented dopaminergic neurons of the brain stem in PD is the pale body, also known as a colloid or hyaline inclusion body. It is not clear whether the pale body represents a stage in the evolution of the Lewy body or whether these inclusions are unrelated and of little relevance to PD pale inclusions seen in progressive supranuclear palsy, Pick's disease, and corticobasal degenera-

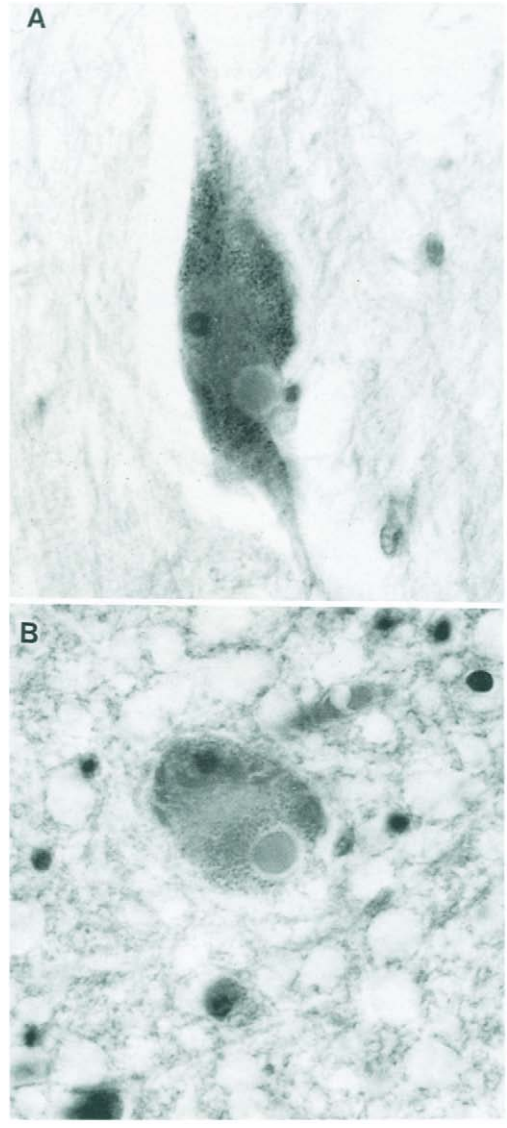


Fig. 253 Parkinson's disease. Lewy bodies in the nerve cells of (A) the substantia nigra and (B) the locus coeruleus. Nissl stain, ×800.

tion. There is a close relationship between pale bodies and typical Lewy bodies in the substantia nigra in clinical varieties of PD, and both inclusions share antigenic determinants (Dale *et al.*, 1992). Pale bodies and Lewy bodies reflect separate aspects of cellular pathology in PD, but their formation probably occurs in parallel.

Electron microscopy. Lewy bodies consist of intermediate filaments arranged radially in the periphery, while in the dense centers they present circular or elongated profiles. They thus show a typical sunflower appearance. The diameter of the filaments varies considerably (Forno, 1982). In the central parts their diameter measures between 7 and 9 nm, while in the periphery it ranges between 10 and 20 nm. Osmiophilic vesicles, 80–200 nm in diameter, are also present in the periphery of the Lewy bodies in early stages of the disease (Forno, 1982).

Electron microscopy showed that immunohistochemistry antibodies against synaptophysin and chromogranin immunolabeled the peripheral zones and occasionally the central cores of Lewy bodies of the classical, intraneuritic and cortical types. The ultrastructural labeling was found mainly in the vesicular structures, and also in the filamentous and granular structure of Lewy bodies (Nishimura *et al.*, 1994).

Pathogenesis The degeneration and destruction of the melanin-containing, tyrosine 3-monooxygenase-positive, dopaminergic neurons of the substantia nigra, the noradrenergic neurons of the locus coeruleus, and the serotoninergic neurons of the dorsal nucleus of the raphe account for most of the manifestations of PD. The reduction in D_1 dopamine receptors (Cash *et al.*, 1987) appears to be the result of degeneration of the pallidonigral neurons. The biochemical studies of Scatton *et al.* (1986) point to a degeneration of serotoninergic and noradrenergic neurons in the lumbar spinal cord. The large neurons of the zona compacta of the substantia nigra are dopaminergic and project onto the neostriatum (Leenders *et al.*, 1986). Their dropout leads to a preponderance of cholinergic impulses. This has led to attempts to correct the dopamine deficiency by administration of L-dopa, the natural precursor of dopamine, which, unlike dopamine, crosses the blood–brain barrier. Other therapeutically active measures are the administration of dopamine decarboxylase inhibitors, dopamine receptor stimulants, and anticholinergic drugs. The imbalance between cholinergic and dopaminergic neurons can also be influenced by stereotactic destruction of the ventrooral thalamus. Bilateral surgical intervention, however, carries a high complication rate.

Various hypotheses exist regarding the pathogenesis of idiopathic parkinsonism: these include genetic predilection aging, environmental factors, oxidative stress, excitotoxicity, autoimmunity, and trauma, suggesting that the pathogenesis of idiopathic parkinsonism is likely to be multifactorial.

The considerable variation in the involvement of neuronal systems other than the nigral system may explain some differences in the clinical manifestations of the disease. The predominant loss of ventrolateral nigrostriatal projections in PD, leading to a substantial loss of dopamine, especially in the putamen (Rinne, 1993), is thought to contribute to the motor symptoms of these patients. The hypothalamic involvement may be responsible for autonomic disturbances in PD, such as postural hypotension, impaired peripheral vasodilatation, deficient sudomotor functions, and abnormal central regulation of temperature, as well as for endocrine abnormalities, including deficiency of growth hormone-releasing factor and elevation of melanocyte-stimulating hormone.

The observation that cultured fibroblasts of patients with PD are abnormally radiosen-

sitive may point to a possible acquired defect in DNA repair mechanisms (Robbins *et al.*, 1985).

An increased iron content in the pallidum and the red zone of the substantia nigra was confirmed by several authors. While this is a common feature of several disorders of the motor system, in all others it is accompanied by a normal or raised level of ferritin, while this protein is reduced in PD, leading to an excess of free iron ions (Dexter *et al.*, 1992). In the zona compacta of the substantia nigra, an increase in total iron and of Fe^{3+}—but not Fe^{2+}—compared to that of control subjects has been reported using biochemical, histochemical, and physical methods (Jellinger and Kienzl, 1993). An increase in Fe^{3+} in neuromelanin, but not in neuronal cytoplasm, Lewy bodies and neuropil ferrous (Fe^{2+}), if present at all, represent less than 10% of the total iron (Galazka-Friedman *et al.*, 1993). The selective increases in Fe(III) and ferritin-positive microglia in the substantia nigra zona compacta of the PD brain is thought to be not the consequence of, but a contributory factor to, neuronal death (Ben-Shachar and Youdim, 1993), the definite causes of which remain to be elucidated (Sofic *et al.*, 1991; Jellinger *et al.*, 1993). The high concentrations of paramagnetic metal ions bound to neuromelanin are consistent with the hypotheses that metal ions promote oxidative reactions in pigmented neurons (Zecca and Swartz, 1993).

Recent research has shed additional light on a variety of metabolic disturbances in PD (Schapira, 1994). Uric acid and dopamine levels are significantly lower in the substantia nigra of PD patients, at 54% and 85%, respectively. In the caudate dopamine levels were significantly lower, while uric acid levels were not significantly reduced ($0.10 < p < 0.05$). The data support the hypothesis that uric acid is decreased in the nigrostriatal dopamine neurons in parkinsonian patients, which contributes to an environment susceptible to oxidative stress, particularly through dopamine oxidation reactions (Church and Ward, 1994). Other abnormalities include a reduction in the level of polyunsaturated fatty acids, a raised level of malondealdehyde, a high activity of superoxide dismutase, and an extremely low content of reduced glutathione.

A primary glutamatergic cell neocortical abnormality provides an attractive unifying explanation for the overlapping abnormalities found in idiopathic parkinsonism, AD, and ALS (Uitti and Calne, 1993). These findings suggest oxidative stress caused by free radicals (Olanow, 1992). The same parameters were investigated in material from presymptomatic parkinsonism (p. 561). Only reduced glutathione shows levels similar to those found in overt PD (Jenner *et al.*, 1992). The authors concluded that impairment of the glutathione pathway is the earliest metabolic disturbance. The decreases in glutathione transferase (Perry and Yong, 1986) and glutathione peroxidase, enzymes of the glutathione systems that mop up free radicals, were considered a possible pathogenetic factor. On the other hand, the increased number of glutathione peroxidase-positive cells that surround the dopaminergic neurons may contribute to the protection of neurons against pathological death (Damier *et al.*, 1993).

In addition, there is a considerable reduction in the activity of complex I of the mitochondrial respiratory cycle (NADH CoQ reductase). Since the discovery of inhibition of complex I of the mitochondrial respiratory chain in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism, several groups of investigators re-

ported mitochondrial respiratory dysfunctions not only in the brain, but also in the skeletal muscle and platelets in PD. The significance of this finding is unexplained (Schapira *et al.*, 1992).

There appears to be strong case for the operation of an oxidative stress on peculiarly vulnerable nigral cells that is not close to the normal aging process. Some loss of nigral cells occurs with advancing age: 21% per decade in the lateral ventral group, 54% in the medial ventral group, and 69% in the dorsal tier, which is the reverse of the findings in PD, in which maximal cell loss occurs in the lateral ventral group (91%), followed by the medial ventral group (71%) and the dorsal tier (56%) (Fearnley and Lees, 1991).

The first systematic genetic study of PD was carried out by Jones in 1949. His results indicated autosomal-dominant transmission with 60% penetrance. A growing accumulation of pedigrees of histologically confirmed Lewy body PD over the past several years has refocused attention on genetic factors (Duvoisin and Johnson, 1992). Several instances of familial parkinsonism have been recorded (Waters and Miller, 1994). These account for a proportion of the patients affected by the disease. A genetic background cannot be ruled out in a multifactorial pathogenetic mechanism. There is now considerable evidence to support a defect of the mitochondrial respiratory chain, and complex I in particular, in PD. The molecular basis of the deficiency and its relevance to the pathogenesis of PD remain unknown (Schapira, 1994).

The mtDNA "common deletion" in muscle was detected in specimens obtained from PD patients, but similar results were obtained in age-matched controls (DiDonato *et al.*, 1993). This suggests that the substantia nigra is exquisitely sensitive to age-dependent damage of the mitochondrial genome.

Animal Models A model for PD in sheep (Baskin *et al.*, 1994) as well as in baboons (Hantraye *et al.*, 1993) has been developed using unilateral intracarotid injection of low doses of MPTP via chronic continuous infusion.

Juvenile Parkinsonism (Juvenile Paralysis Agitans of Hunt; Progressive Pallidal Atrophy)

Willige (1911) was the first to mention a juvenile form of PD, in his review of cases of PD described up to then. Further publications followed. However, Hallervorden (1957) expressed doubts as to whether these were really cases of PD. Other cases appear less open to doubt, however (Odawara *et al.*, 1992). The juvenile form is particularly common in Japan, where it accounts for up to 10% of all cases of idiopathic PD (Yokochi *et al.*, 1984).

Clinical Picture According to Yokochi *et al.* (1984), all cases in which symptoms of PD appear before the age of 40 years belong to the juvenile group. Disturbances of gait have been observed as early as the first decade. The progression of symptoms is more insidious than in the classical form. Akinesia, rigidity, and dystonic posture, particularly of the feet, are the main manifestations of the disease in patients with onset in the first or second decade. Tremor is less pronounced than in classical cases,

mental changes are uncommon, and pyramidal signs may appear toward the end of the clinical course. Unusual symptoms may appear in some patients, such as pseudobulbar palsy, spastic paraplegia, head tremor, ophthalmoplegia, and peripheral neuropathy (Van Der Wiel and Staal, 1981). Some cases of juvenile parkinsonism with dementia have been reported (Inose *et al.*, 1988; Odawara *et al.*, 1992). These patients are viewed as having a pure form of diffuse Lewy body disease. In some patients the symptoms fluctuate during the course of the day (Yokochi *et al.*, 1984). The patients improve dramatically upon treatment with L-dopa, but may develop dyskinesias as a complication of this therapy. A familial clustering of cases was reported by Alonso *et al.* (1986).

Neuropathology *Gross appearances.* Only depigmentation of the substantia nigra is apparent.

Light microscopy. The changes are variable. Some patients show a severe loss of neurons in the substantia nigra, whereas others have only a lack of pigmentation with preservation of the perikarya of nigral neurons (Yokochi *et al.*, 1984). The locus coeruleus is involved, as a rule, but less so than the substantia nigra. Lewy bodies are generally sparse, and only occasionally abundant (Odawara *et al.*, 1992). A diffuse loss of neurons in the globus pallidus, putamen, and caudate nucleus was mentioned by many authors. In a case with first clinical manifestations at the age of 6 years, the lesion was localized to the substantia nigra. The number of neurons was abnormally low, the proportion of melanin-containing cells was reduced, and a large number of immature cells were present (Mizutani *et al.*, 1991). In a case reported by Dwork *et al.* (1993), inherited parkinsonism with symptoms starting at age 28, the investigators found a severe neuronal loss in the pars compacta and the pars reticulata of the substantia nigra with prominent gliosis, but neither Lewy bodies nor NFTs were present.

Pathogenesis In view of a normal homovanillic acid concentration in the CSF of a patient with juvenile parkinsonism, Naidu *et al.* (1978) postulated the existence of a subgroup of patients in whom the neostriatum was primarily affected. They included in this group patients with confirmed cell loss in the pallidum, putamen, and caudate with largely preserved nigral neurons.

Parkinson's Disease with Dementia

An absence of dementia and of oculogyric crises was formerly considered the principal criterion in distinguishing paralysis agitans from postencephalitic and arteriosclerotic parkinsonism. In examining a larger number of demented patients, in 18% of them Lewy bodies can be found in the pigmented neurons of the brain stem. Mental changes are present by careful examination in 72% of the patients with PD; 55% are demented. While some of these cases may represent a fortuitous association, the majority must be considered a variant of PD. The differences in the reported numbers of PD patients with dementia depend on the available clinical material and on observer bias. PD dementia is not homogenous on either clinical or pathological grounds (Ruberg and Agid, 1988). In view of the increasing number of observed demented patients, the question arises as to whether

this is due to a greater clinical awareness or whether some cases may be iatrogenic as a result of therapy.

It seems that some demented patients form an intermediate group between PD with dementia and generalized Lewy body disease (see p. 483). At the moment, however, it is impossible to draw a clear line between the two conditions.

Clinical Picture A mild or severe dementia may appear years or months before death (Sroka *et al.*, 1981). Otherwise, the symptomatology does not differ from that of classical PD. The course of the disease appears somewhat shorter in demented than in classical cases. Cerebral atrophy appears more in evidence on CT scans in demented than in nondemented patients (Schneider *et al.*, 1979).

Neuropathology The substantia nigra and the locus coeruleus are largely depigmented, as in other cases of PD. In both nuclei neuronal loss is conspicuous. The remaining neurons frequently contain Lewy bodies. Aside from cell loss, Alzheimer's NFTs, SPs, and granulovacuolar degeneration (GVD), indistinguishable from those of AD, are seen in the cerebral cortex. However, the density of neocortical Alzheimer-type changes is low in comparison with that of elderly AD patients (Duyckaerts *et al.*, 1993). In contrast with the parkinsonism–dementia complex of Guam and with progressive supranuclear palsy, no NFTs are found in the brain stem, but they are present in the nucleus basalis (Gaspar and Gray, 1984).

In a case of juvenile parkinsonism and dementia neuropathological examination revealed a widespread occurrence of Lewy bodies and spheroids in the CNS. Lewy bodies were found not only in the brain stem and the diencephalon, but also in the cerebral cortex. Massive numbers of small spheroids were observed in the globus pallidus, substantia nigra, mamillary bodies, and hippocampus. Electron microscopic examination showed that most spheroids were composed of degenerative organelles with only a few neurofilaments, and were different from those of Hallervorden–Spatz disease. There was also marked neuronal loss with gliosis in the CA3–CA4 sector of the hippocampus. Some NFTs occurred in the hippocampal, subcortical, and brain stem nuclei, but SPs were absent (Odawara *et al.*, 1992).

Pathogenesis The extent of the destruction of the substantia nigra does not correlate with the severity of the dementia. On the other hand, the neuronal loss in the locus coeruleus is more pronounced in demented patients. The loss of neurons in the nucleus basalis, which is twice as high in demented than in nondemented patients, plays an important role in the pathogenesis of dementia (Hassler, 1965; Whitehouse *et al.*, 1983). It has been suggested that the pathological process remained confined to the entorhinal–hippocampal complex in PD because it was somehow prevented from extending into the neocortex (Braak and Braak, 1990b). An alternative explanation is that the pathological threshold for the clinical expression of AD changes is reached much sooner in PD than in AD (Duyckaerts *et al.*, 1993). An earlier expression of dementia in PD would lead more rapidly to death. The dementia of PD, however, differs in quality from that of AD (Nakano and Hirano, 1984). The degeneration of the innominate–cortical pathway plays a decisive role here. Some patients with PD without plaques and tangles

may also be demented. The morphological substrate in these cases remains unexplained (Heilig *et al.*, 1985). Exogenous toxic factors were considered by Oyanagi *et al.* (1986). Coexistent vascular insufficiency may be responsible for the dementia in a proportion of these patients.

Parkinsonism–Dementia Complex of Guam

Hirano *et al.* (1961) described a high prevalence of parkinsonism in the Chamorro people of Guam. In most cases the disease was associated with a progressive dementia. Some cases are associated with the Guam type of amyotrophic lateral sclerosis (ALS). A similar condition was described in a Filipino immigrant (Chen *et al.*, 1982). A family with parkinsonism–ALS–dementia complex was reported from southwest Germany (Schmitt *et al.*, 1984). The incidence of new cases in Guam has regressed considerably.

Clinical Picture The disease affects men three times more frequently than women. It begins insidiously in middle age with akinesia and a festinating gait. Tremor and rigidity are aleatory. Dementia of variable severity is almost constant. The patients die 3–5 years after the onset of symptoms.

Neuropathology *Gross appearances.* Moderate to severe cerebral atrophy with frontotemporal accentuation is present in some cases, as well as in subcortical structures and in the brain stem (Hirano and Frias-Llena, 1986). The substantia nigra and the locus coeruleus are slightly to moderately depigmented.

Light microscopy. A diffuse neuronal loss with corresponding gliosis is found throughout the CNS. The loss is severe in the nucleus basalis (Nakano and Hirano, 1983) and in the large neurons of the nucleus raphae dorsalis (Yamamoto and Hirano, 1985). Alzheimer's NFTs and GVD are present in the hippocampus, cerebral cortex, thalamus, pallidum, and substantia nigra. Lewy bodies and SPs are absent. In the cases documented by Schmitt *et al.* (1984), no definite GVD could be demonstrated.

Electron microscopy. The structure of NFTs here does not differ from that of AD.

Pathogenesis Both a toxic etiology and an infection by unconventional viruses have been discussed (Chen, 1980). A secondary hyperparathyroidism as result of calcium and magnesium deficiencies has been considered. The cause of the disease remains unknown and, in view of the morphological differences, is probably different from that of PD. For a further discussion of pathogenetic mechanisms, see the discussion on the motor neuron disease of Guam (p. 647).

Familial Variants of Parkinsonism

Some familial syndromes have been identified among the various combinations of parkinsonism with other system degenerations.

Parkinsonism with Depression: Perry *et al.* (1975) described some families in which depression was the predominant feature and exceeded by far the general depressive

mood observed in patients with PD. They defined the syndrome as a separate nosological entity. Another family was described by Purdy *et al.* (1979). Golbe *et al.* (1990) reported two large kindreds in whom 41 members were affected. Although it was impossible to trace a common ancestor, it is likely that the two families were related, as they both came from the same village in Italy.

Clinical Picture The disease presents around the age of 50 years with depression that appears to be refractory both to drug treatment and electroconvulsive therapy. The patients suffer from weight loss, sleep disorders (Perry *et al.*, 1975), or hypoventilation (Purdy *et al.*, 1979). A more or less pronounced parkinsonism develops later. The patients die 2–6 years after the onset of symptoms, generally from respiratory failure due to muscular paralysis.

In the cases discussed by Golbe *et al.* (1990), the disease appeared in middle age, with a mean age of onset of 46.5 years and a mean age at death of 53.5. Tremor was unusual and occurred in only eight cases. Depression affected a minority of the cases and was never severe. Dementia was mild or late.

In a family with autosomal-dominant inheritance of an early-onset and rapidly progressive parkinsonian syndrome, three members had parkinsonism with depression, three had parkinsonism alone, and two suffered from depression alone (Bhatia *et al.*, 1993).

Neuropathology *Gross appearances.* Severe depigmentation of the substantia nigra is evident.

Light microscopy. A severe neuronal loss and dense fibrillary gliosis are seen in the substantia nigra. Lewy bodies are scanty, but large eosinophilic intranuclear inclusions may be present, adjacent to the nucleolus (Purdy *et al.*, 1979). The locus coeruleus was only slightly depigmented and contained no Lewy bodies. A spotty loss of neurons with a proliferation of reactive astrocytes was found in the caudate nucleus. Gliosis was also present in the dorsal nucleus of the vagus, the nucleus of the tractus solitarius, the optic tract, the reticular substance, and some vestibular nuclei.

Pathogenesis A deficiency of taurine, found by former authors in the plasma, CSF, and brain, could not be confirmed by Purdy *et al.* (1979). By contrast, an increased amount of taurine was found in the CSF of patients with PD (Araki *et al.*, 1986). The gliosis in the medulla oblongata described by Purdy *et al.* (1979) has been considered as a possible cause of respiratory disturbances.

Familial Parkinsonism–Dementia with Ophthalmoplegia: Mata *et al.* (1983) described a family in which three siblings developed parkinsonism and paralysis of the vertical gaze in the third decade. Pyramidal signs and progressive dementia developed later. Ambrosetto and Bacci (1984) interpreted the syndrome as a variant of supranuclear palsy.

Neuropathology *Gross appearances.* Pronounced cerebral atrophy was associated with depigmentation of the substantia nigra and the locus coeruleus.

Light microscopy. A severe neuronal loss with reactive gliosis was present in the sub-

stantia nigra and the locus coeruleus. No Lewy bodies were seen. Numerous NFTs were present in the substantia nigra, locus coeruleus, globus pallidus, periaqueductal gray, hippocampus, and dorsal nucleus of the vagus. No tangles were found in the cerebral cortex outside the hippocampus.

Yamamura *et al.* (1993) reported cases of early-onset parkinsonism with diurnal fluctuation of symptoms. The disease begins at the age of 20–30. The patients were bedridden with advanced parkinsonism a few years before death in the sixth decade. Pathological study revealed a marked cell loss in the substantia nigra zona compacta, especially in area A9, while the neuronal cell population of the ventral tegmental area (A10), locus coeruleus, superior raphe nucleus, and substantia innominata was relatively preserved. There are no Lewy bodies but argyrophilic, oligodendroglial, cytoplasmic inclusions composed of abnormal tubular structures have been demonstrated (Papp, 1992).

Asymptomatic Parkinson's Disease (Presymptomatic Parkinsonism)

In brain tissue from normal individuals with incidental Lewy bodies and cell loss in pigmented substantia nigra neurons compared with age-matched control subjects without nigral Lewy bodies, glutathione levels were reduced by 35% (Dexter *et al.*, 1994). In presymptomatic PD the cell loss is limited to the lateral ventral group (52%) (Fearnley and Lees, 1991). Postmortem studies of "incidental" Lewy body disease have shown that preclinical PD greatly exceeds clinically overt PD in prevalence (Gibb and Less, 1988). For every one necropsy case of PD, there are about 10 cases with nigral Lewy bodies, but insufficient neuronal loss to cause parkinsonism—a preclinical or incidental Lewy bodies disease (Jendroska *et al.*, 1994).

X-Linked Dystonia–Parkinsonism Syndrome (Lubang Disease)

Fahn and Moskowitz (1988) described a large Filipino (Lubang Islands) family with many males afflicted with dystonia and parkinsonism, suggestive of X-linked recessive inheritance.

Clinical Picture The ages of the patients ranged from 29 to 79 years. The mean age at onset of dystonia was 35 years, with a range of 12–48 years, and the mean duration of illness was 11.1 years. The first manifestations were noted in the lower extremities in 36%, the axial musculature in 29%, the upper extremities in 23%, and the head in 12% of the cases. The majority of the patients displayed gait abnormalities (90%), leg dystonia (79%), oromandibular dystonia (64%), neck dystonia (57%), blepharospasm (57%), and truncal dystonia (52%). Overall, the condition was severely disabling. Thirty-five percent of the cases displayed at least one of the parkinsonian symptoms: bradykinesia, tremor, rigidity, and loss of postural reflexes. Parkinsonism was diagnosed as definite in 14%, as probable in 2%, and as possible in 19% of the cases. Patients exhibiting parkinsonian symptoms had a significantly later mean age at onset (40.5 years) than those without parkinsonism (32.4 years), but no difference in the duration of illness was observed. Phenotypic expression of X-linked dystonia–parkinsonism in two women suggests that

lubang disease may be a codominant disorder and that it is possible for women to be affected (Waters *et al.*, 1993a,b).

Neuropathology Neuropathological data are as yet unavailable. With PET a selective reduction in normalized striatal glucose metabolism could be demonstrated (Eidelberg *et al.*, 1993). The locus is located in Xq12–q21.1, most likely between loci *PGK1* and *DXS72* (Kupke *et al.*, 1992).

An autosomal-dominant dystonia–parkinsonism syndrome with unusually rapid evolution has been separated from other forms of hereditary dystonia–parkinsonism (Dobyns *et al.*, 1993).

Postencephalitic Parkinsonism

In some parkinsonian patients the disease was the end result of the 1915–1920 epidemic of encephalitis lethargica. The disease should have disappeared by now, yet new cases are reported from time to time.

Aside from the delayed postencephalitic syndrome seen following encephalitis lethargica, parkinsonism is not uncommonly associated with encephalitis, either as a transient phenomenon in the course of an acute illness or as part of a chronic infection (Al-Mateen *et al.*, 1988; Geddes *et al.*, 1993).

Clinical Picture The symptoms appear earlier than in classical PD and are frequently asymmetrical. Oculogyric crisis are more prominent.

Neuropathology The depigmentation of the substantia nigra is more severe than in paralysis agitans (Fig. 254). The cell loss in the substantia nigra, locus coeruleus, and dorsal nucleus of the vagus show an atypical, indiscriminate, diffuse distribution (Bogerts *et al.*, 1983). The glial scars transgress the limits of the affected nuclei and extend into the periaqueductal gray, diencephalon, and tegmentum. In contrast with the case in PD, the nucleus basalis is generally spared. NFTs in postencephalitic parkinsonism are often seen in the various nuclei of the basal ganglia. They react with antibodies against neurofilaments (Gambetti *et al.*, 1983) and against tubulin (Yen *et al.*, 1983). Lewy bodies are rarely seen. Foamy spheroid bodies have been found in the substantia nigra pars reticulata in many degenerative conditions, especially in postencephalitic parkinsonism.

Pathogenesis The pathogenetic mechanism of the parkinsonian symptoms is similar to that of paralysis agitans. The presence of an influenza A antigen was demonstrated by fluorescence immunohistochemistry (Gamboa *et al.*, 1974). The fact that new cases appear from time to time leads one to suspect that other neurotropic viruses may also be responsible for nigral damage (Cervós-Navarro *et al.*, 1985).

Experimental Models of Parkinsonism Destruction of the ventromedial tegmentum of the midbrain produces a parkinsonian-type tremor in monkeys (Nakaoka, 1983). Following the observation by Davis *et al.* (1979) of severe neuronal loss in a patient exposed

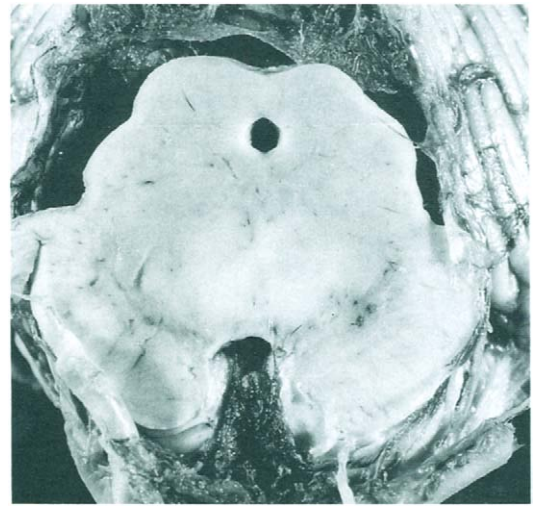


Fig. 254 Postencephalitic parkinsonism. Total depigmentation of the substantia nigra.

to MPTP, numerous experimental procedures produced a parkinsonian syndrome in primates treated with various pyridine derivatives (Kitt *et al.*, 1986). Unilateral infusion of MPTP through an internal carotid artery produced hemiparkinsonism (Bankiewicz *et al.*, 1986). Administration of MPTP results in extensive destruction of the substantia nigra (Gibb *et al.*, 1986) and probably also of dopaminergic neurons in the hypothalamus. Protracted administration of MPTP to rats leads to abnormalities of dopamine and serotonin metabolism in the caudate nucleus. The similarity of the chemical structure of MPTP to that of some herbicides opens the possibility of an environmental etiology of parkinsonism. Similar thoughts were expressed by Oyanagi *et al.* (1986).

Changes in the nigrostriatal pathways revealed by positron PET in MPTP abusers without clinical symptoms were interpreted as latent nigral damage, which may become overt with age-dependent neuronal loss (Calne *et al.*, 1985).

Striatonigral Degeneration (Striatopallidonigral Degeneration; Multisystem Atrophy of the Striatonigral Type; Parkinson Plus Syndrome)

Van Der Eecken *et al.* (1960) described a group of patients with parkinsonian symptomatology but with the morphological substrate of a striatonigral degeneration. Already in 1924 Fleischhacker had described an atypical form of paralysis agitans, which he defined as a "familial, chronic, progressive disease of middle age of pseudosclerosis type." The morphological findings were those of damage to the entire brain with a predilection for the striatum. This is only one of many cases of atypical parkinsonism reported in the ear-

lier literature under a variety of names and which appear to belong to the group of striatonigral degeneration. Striatonigral degeneration often appears in combination with OPCA and with autonomic dysfunction and has been included in the multisystem atrophies (Drayer *et al.*, 1986; Quinn, 1989).

Clinical Picture The disease affects middle-aged adults and occasionally juveniles, particularly in the familial form. Rare cases have been described in infants (Hedley-Whyte, 1992). The principal symptoms are slowness and paucity of movements, rigidity, slowing of speech and mastication, difficulty in swallowing, lack of facial expression, and small handwriting (Testa *et al.*, 1993). Orthostatic hypotension may be the first symptom. Pyramidal signs, with an extensor plantar reflex, sometimes unilateral, have been reported. Nystagmus may be present in some familial cases (Borit *et al.*, 1986). Slight ataxia and tremor appear occasionally. Mental changes can accompany the neurological symptoms. In cases associated with OPCA, cerebellar symptoms predominate in the early stages and parkinsonian features develop later. The duration of the illness is between 2 and 7 years in sporadic cases, or 15 years or more in familial ones. Fulminating cases with a course of a few months have also been described. The inheritance in familial cases is autosomal dominant (Rosenberg *et al.*, 1976).

Neuropathology *Gross appearances.* There is striking atrophy of the neostriatum (Fig. 255), often accompanied by pallidal atrophy and pallor of the substantia nigra. The shrunken putamen is reddish brown or greenish.

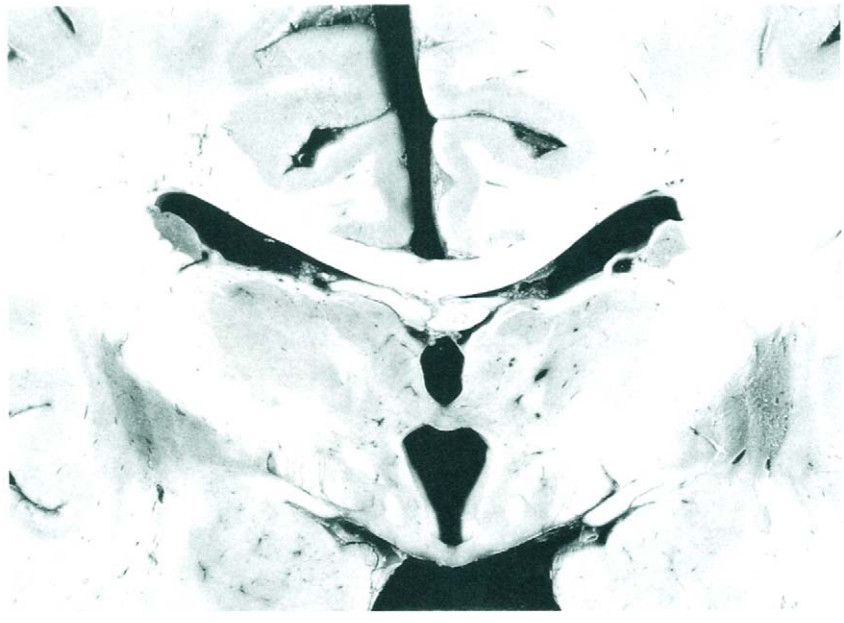


Fig. 255 Striatonigral degeneration. Atrophy of the neostriatum.

Light microscopy. The variability of the striatonigral degenerations is met in two forms: as a "pure" form and as a part of multisystem atrophies. In the restricted form there is a severe loss of neostriatal neurons, including the GABAergic cells and their fibers running toward the pars reticularis of the substantia nigra. The loss is more severe in the putamen, particularly in its caudolateral part, than in the caudate. The most severely involved part of the substantia nigra pars compacta is the ventrolateral zone, which projects to the dorsal putamen, the earliest site of striatal disease (Fearnley and Lees, 1990). In less restricted cases a moderate loss of neurons has been observed occasionally in the dentate and red nuclei. Neuronal loss is also found in the locus coeruleus.

Using an antibody to calcineurin, Goto and Hirano (1990) found a significant depletion of immunoreactivity in an inhomogeneous distribution pattern. The remaining immunoreactivity appeared as a characteristic patchwork of "islands" resembling the "striosomes" observed by the tyrosine hydroxylase or met-enkephalin immunostaining in the putamen from normal individuals. The striatopallidal fibers in the external nucleus of the globus pallidus are thin and pale in myelin stains. The internal nucleus is unaffected. There is a striking accumulation of pigments in the putaminal astrocytes (Fig. 256). These consist of lipofuscin, acid hematin, and neuromelanin (Fig. 257A–C) (Borit *et al.*, 1975). Astrocytic proliferation and fibrillary gliosis are prominent in areas of neuronal depletion (Fig. 258A,B). Fragments of extraneuronal melanin and finely

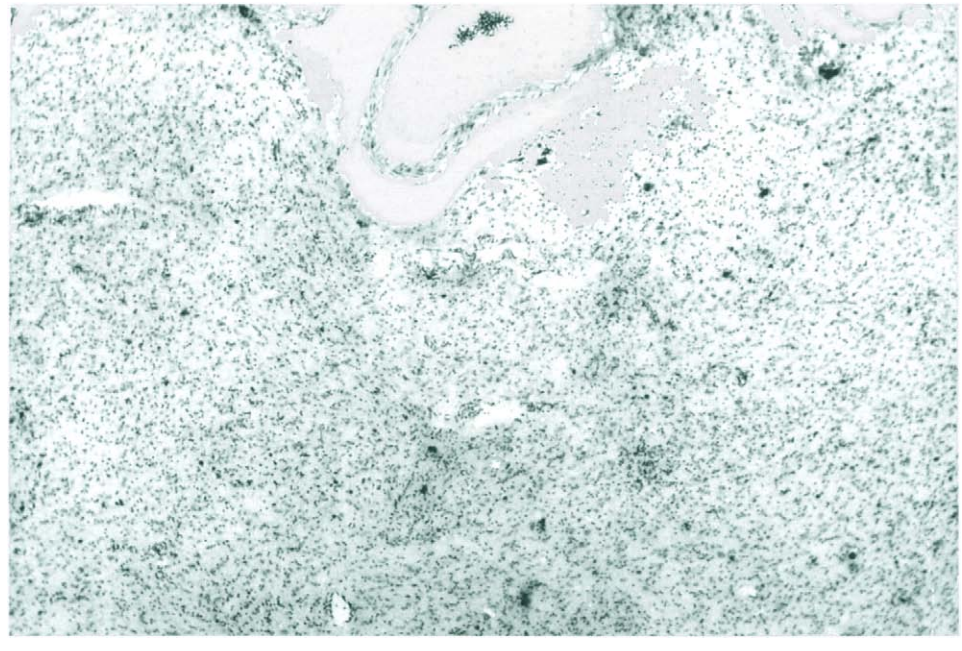


Fig. 256 Same case shown in Fig. 255. Deposition of pigment in the putamen. Turnbull blue stain, ×35.

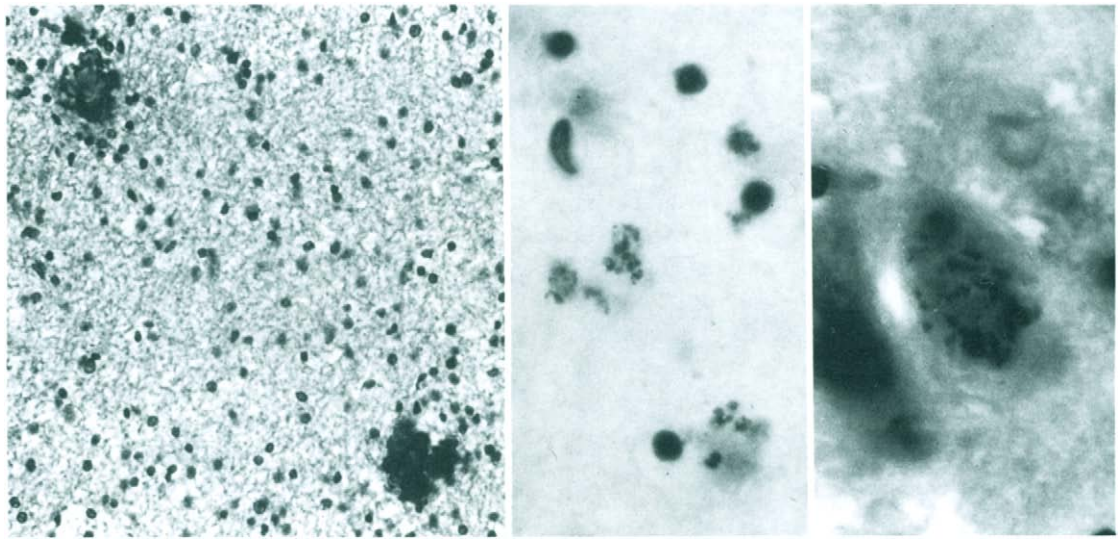


Fig. 257 Same case shown in Fig. 255. An accumulation of acid hematin in the putamen. Nissl stain, (A) ×130, (B) ×450, and (C) ×600.

granulated axonal swellings are seen in the substantia nigra. In contrast with the case in PD, no Lewy bodies are present (Gibb *et al.*, 1986). Bergmann *et al.* (1990) concluded, by a review of 69 literature cases, that striatonigral degeneration, Shy–Drager syndrome, and OPCA probably represent different varieties of the same degenerative process. Renkawek *et al.* (1993) found in a 48-year-old woman clinical features of striatonigral degeneration with NFTs characterizing progressive supranuclear palsy, suggesting a separate variant within multisystem atrophy syndromes.

Ultrastructurally, there is an excessive accumulation of lipofuscin (Fig. 259) consisting of tubular aggregates and an electron-dense lipid component. The axonal swellings contain abundant neurofilaments. The astrocytes contain telolysosomes filled with heavily electron-dense material (Fig. 260), in addition to pleomorphic conglomerates (Fig. 261). Oligodendroglial cells contain electron-dense inclusions, which, at a higher resolution, reveal fingerprint profiles (Fig. 262A,B). In cases forming part of the "multiple system atrophy" complex, oligodendrocytes contain microtubular inclusions identical to those described in sporadic OPCA (see p. 588). Electron-dense granules, 2–4 nm in diameter, may also be present. Usually, large residual bodies are also found in the perivascular spaces (Fig. 263).

Electron probe microanalysis revealed iron, phosphorus, and FeS in the pigments (Cervós-Navarro, 1991b), as well as traces of cobalt, magnesium, silica, sodium, strontium, titanium, and zirconium.

Pathogenesis The involvement of the putamen as the principal lesion explains the resistance to L-dopa treatment, as the defective conversion of L-dopa to dopamine in the

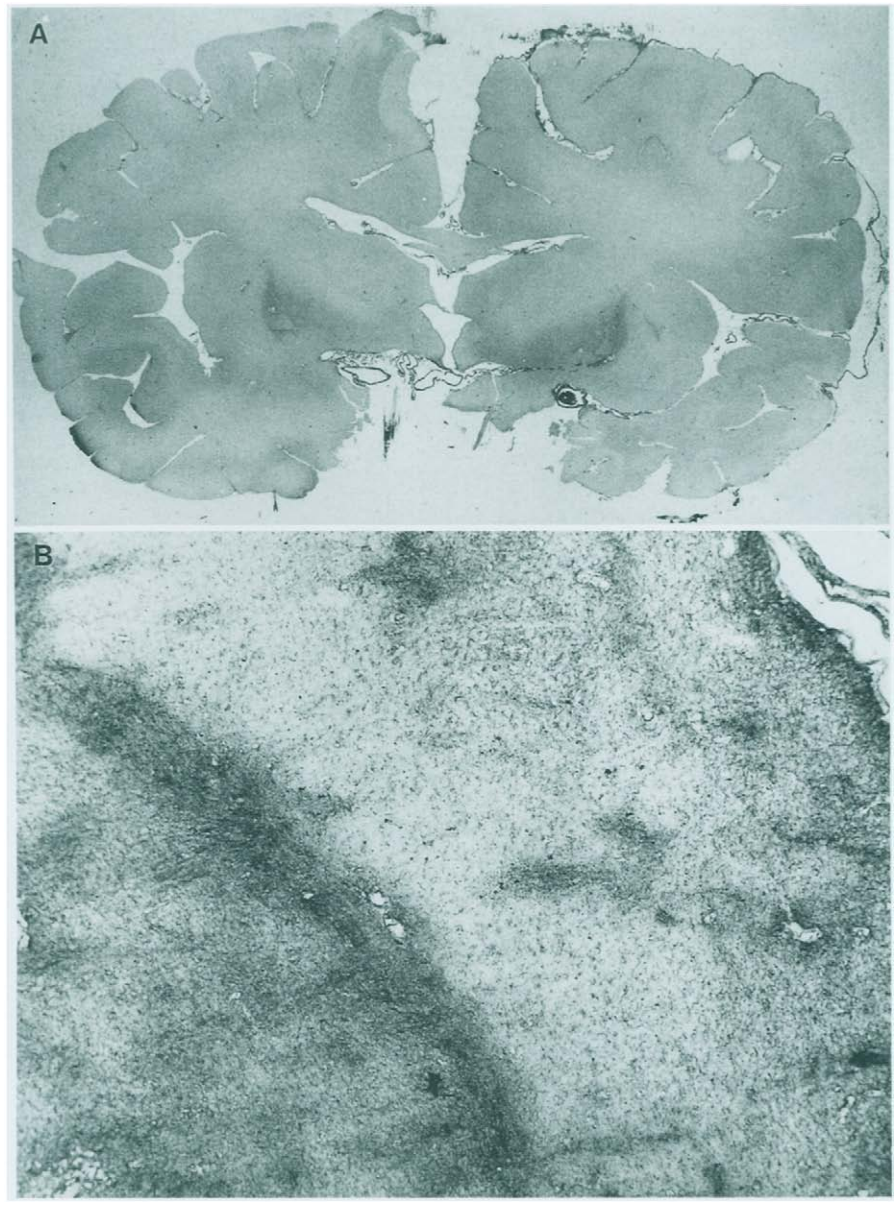


Fig. 258 Same case shown in Fig. 255. (A) Fibrillary gliosis in both putamina. (B) An accentuation in the lateral parts. Holzer stain, ×35.

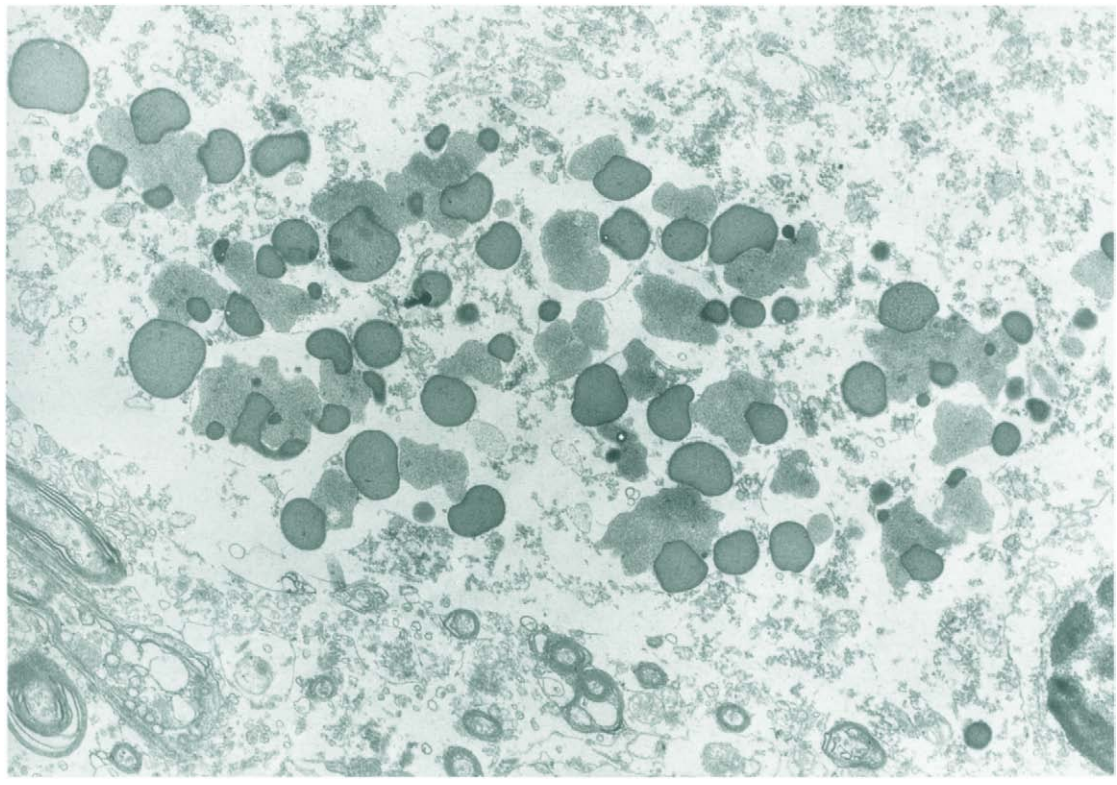


Fig. 259 Same case shown in Fig. 255. A putaminal neuron with accumulation of lipofuscin with a lipid component, ×4400.

substantia nigra cannot be compensated for by the striatum or, alternatively, to the loss of dopamine receptor cells in the striatum. An excitotoxic mechanism has been suggested as a possible pathogenetic factor (Montgomery and Storts, 1984).

Rett Syndrome

This clinical syndrome was described by Rett (1966). Neuropathological studies appeared subsequently (Rett, 1977; Jellinger and Seitelberger, 1986).

Clinical Picture The disease exclusively affects girls. It manifests itself during the first 2 years of age with autistic behavior, loss of purposeful hand movements, repetitive stereotyped movements, intermittent hyperventilation, ataxia, and dementia. The types of movement disorders seemed to be age related, with the hyperkinetic disorders occurring in the younger patients and the bradykinetic disorders occurring more frequently in older patients (Fitzgerald *et al.*, 1990). Dystonia and lactic acidosis may also be present. Clarke

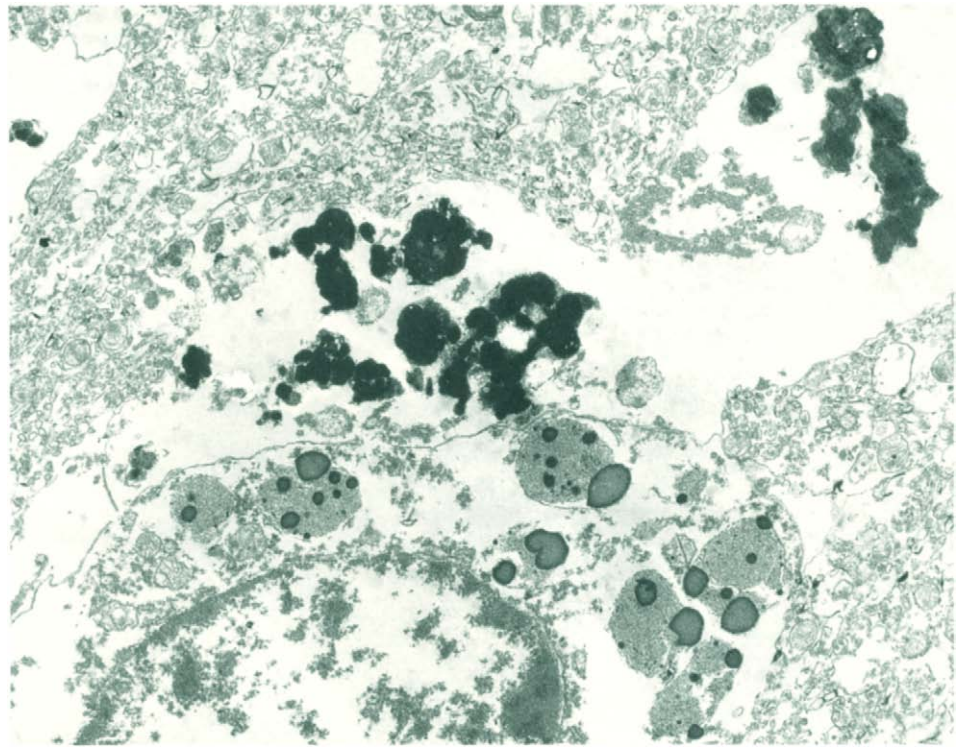


Fig. 260 Same case shown in Fig. 255. The putamen, showing a pleomorphic, largely electron-dense, residual body in an astrocyte, ×5000.

et al. (1990) presented a case with defects of the urea cycle and of carbohydrate metabolism. They concluded that Rett syndrome may be an etiologically homogenous condition, but that it includes a variable pattern of metabolic anomalies. The EEG shows paroxysmal activity during sleep, multifocal in younger and unifocal in older girls, and "pseudorhythmic flattening" (Espinar-Sierra *et al.*, 1990).

The disease is progressive, with a highly variable duration ranging from 2 years to two decades (Hanefeld *et al.*, 1986). Spastic pareses, vasomotor disturbances, and focal or generalized seizures may occur in cases with a protracted course. A familial incidence with X-linked dominance has been established (Hanefeld, 1986).

Pathology Vacuoles in endothelial and epithelial cells were found on skin and conjunctival biopsies, as well as lamellar bodies in various cell types. Electron-dense deposits attached to endothelial cell membranes were observed on conjunctival, muscle, and peripheral artery biopsies (Dieler *et al.*, 1990).

Neuropathology *Gross appearances.* Diffuse cerebral atrophy or microencephaly is apparent, with a reduction of the brain weight commensurate with the duration of the illness (Jellinger and Seitelberger, 1986).

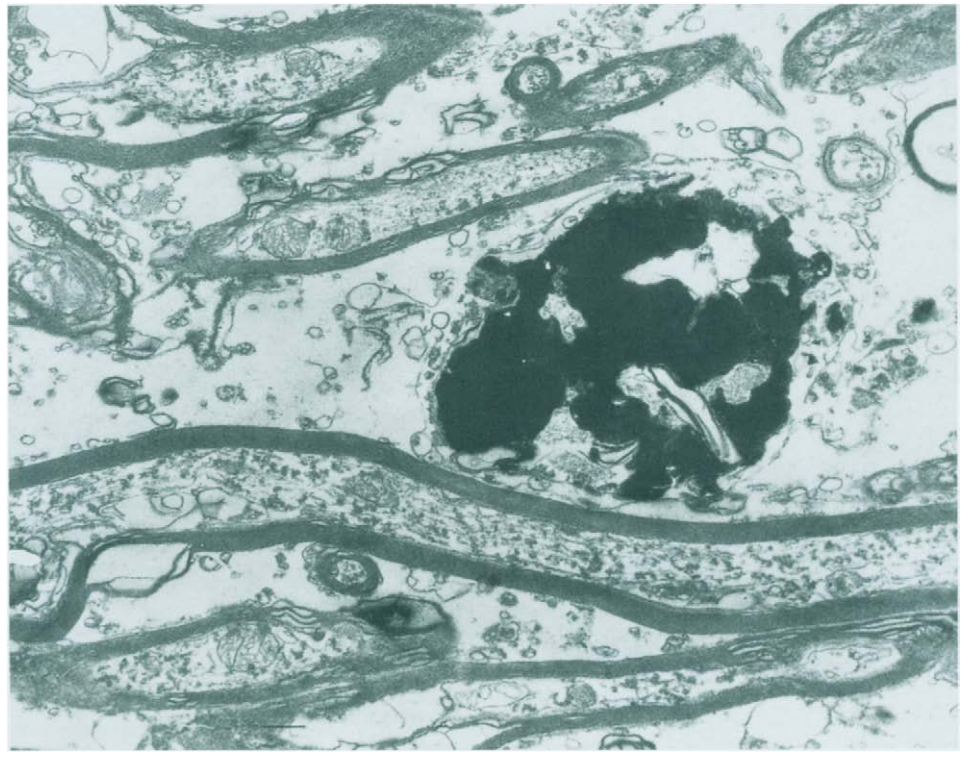


Fig. 261 Same case shown in Fig. 255. A large conglomerate of electron-dense material in the cytoplasm of an astrocyte, ×6300.

Light microscopy. Diffuse atrophy of the cerebral cortex is associated with slight astrocytosis. Inconstant spongy changes may be present in the cerebral and the cerebellar white matter without evidence of demyelination. There is an excessive accumulation of lipofuscin in neurons and astrocytes, but no suggestion of a storage disease. Microscopic foci of maldevelopment have been found in some cases (Jellinger and Seitelberger, 1986). Degenerative axonal swellings are present in the caudate nucleus and scattered through the cortex. A striking hypopigmentation of the zona compacta of the substantia nigra is evident in most cases, with a normal complement of neurons.

In the late, cachectic, stage of the disease, changes are seen in the peripheral nerves, consisting of poor myelinization of axons without evidence of myelin breakdown. Remyelinated axons are also present. The appearances suggest an axonopathy rather than hypomyelinization.

Electron microscopy. A moderate increase of lipofuscin is seen in the neurons and astrocytes of the cerebral cortex and the caudate nucleus (Jellinger and Seitelberger, 1986). Accumulations of vesicles are present in axodendritic synapses and preterminal neurites (Jellinger *et al.*, 1989).

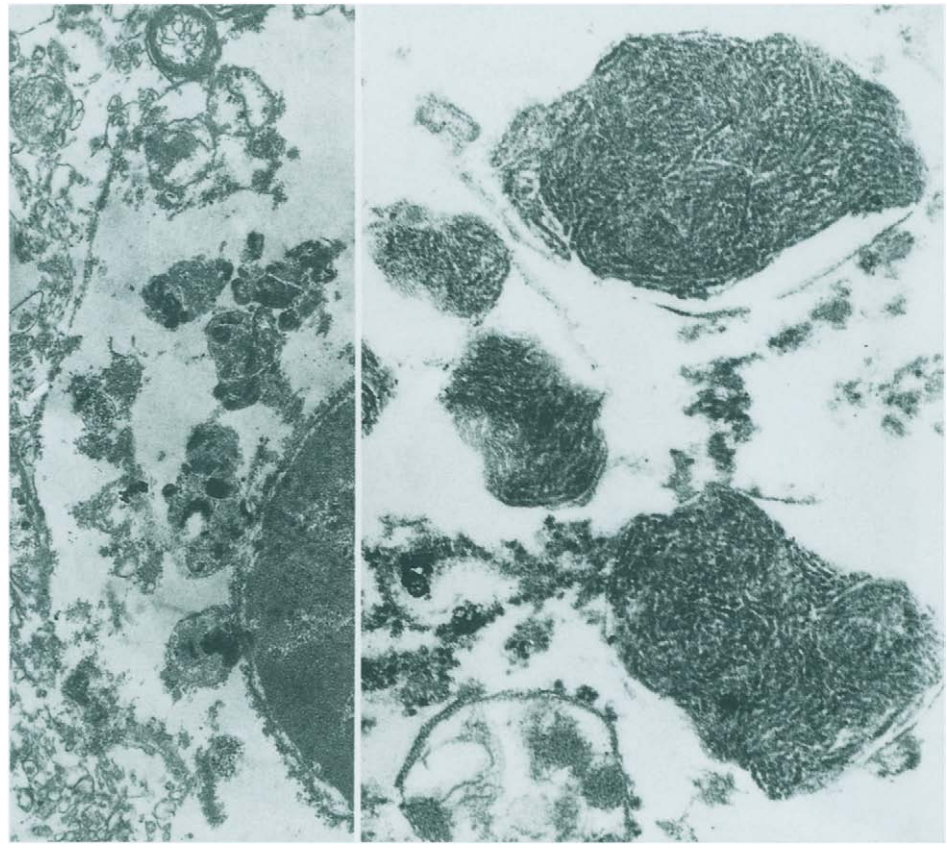


Fig. 262 Same case shown in Fig. 255. (A) An oligodendrocyte with a pleomorphic telolysosome, ×8000. (B) Fingerprint bodies can be seen at a higher magnification (×60,000).

Pathogenesis The clinical picture can be correlated with the findings in the substantia nigra, which suggest a disturbance of the dopaminergic striatonigral system, possibly also in the locus coeruleus and the nucleus raphae. Biochemical investigations revealed significant decreases in catecholamines and 5-hydroxyindoleacetic acid in various parts of the brain (Wenk *et al.*, 1991). These findings point to a severe defect in the synthesis of biogenic amines with an increase in their turnover. In the late stages of the disease, there appears a reduced activity of the D_2 dopamine receptor in the striatum.

Many clues to the possible pathogenesis of the disorder have been described, including chromosomal fragile sites at Xp22, abnormal metabolism of biotin and terahydrobiopterin, and disturbed X inactivation. Hyperammonemia has been described in some cases, and the link with the urea cycle enzymes is strengthened by recent reports of increased orotic acid excretion following intravenous alanine loading (Carpenter *et al.*,

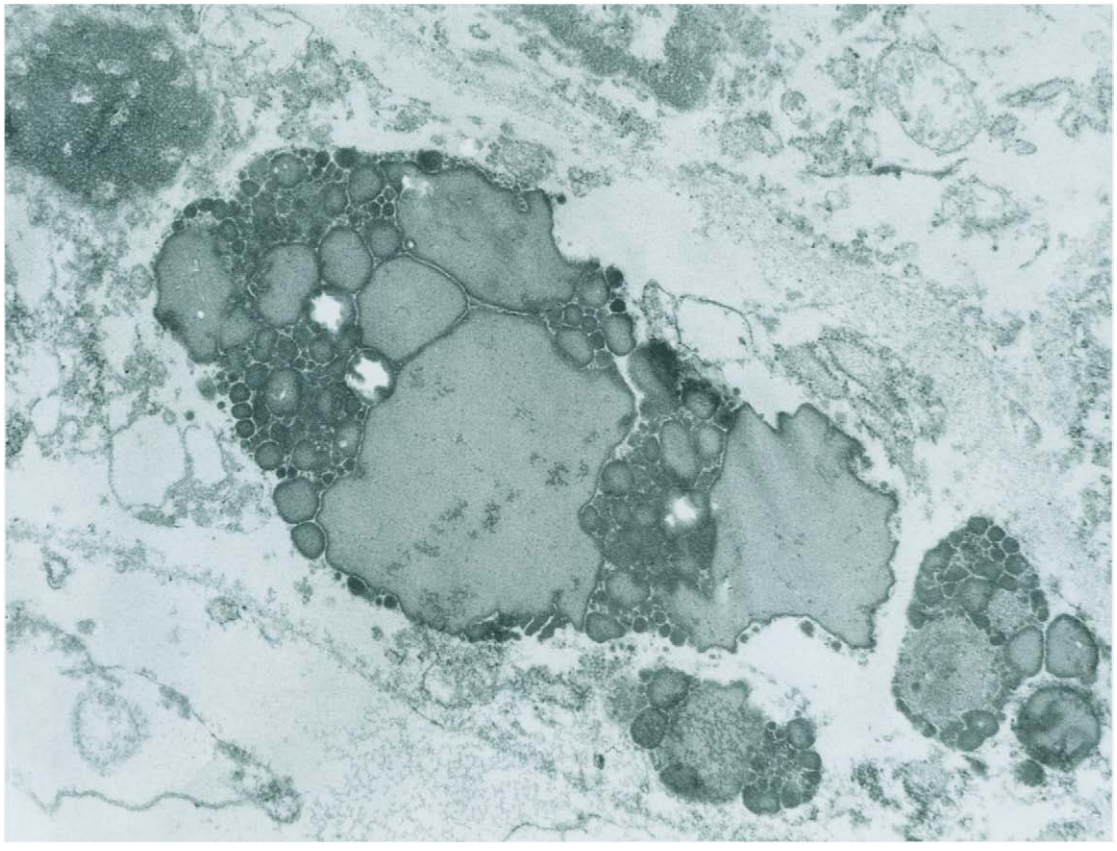


Fig. 263 Same case shown in Fig. 255. The putamen, showing a large conglomerate in the perivascular space of an arteriole.

1990). However, the gene defect is probably distinct from the ornithine carbamoyltransferase deficiency (Clarke *et al.*, 1990).

Elevated CSF β-endorphin immunoreactivity is consistent with the hypothesis that some symptoms of Rett syndrome may be associated with excessive endogenous opioid levels in the CNS (Myer *et al.*, 1992).

Degenerative Diseases of the Cerebellum, Brain Stem, and Spinal Cord (Spinocerebellar Degenerations)

The frequent combinations of lesions of the cerebellum, brain stem, and spinal cord within the framework of heredodegenerations justify the grouping of these conditions under the concept of *spinocerebellar degenerations* (Greenfield, 1954). About 60 clinical syndromes have been described in this group (Refsum and Skre, 1978), and their multiplicity defies an adequate classification until a better knowledge of their etiology is achieved. At present only a morphological classification can be proposed, based on the predominant localization of the lesions, into cerebellar cortical atrophies, multisystem atrophies, and spinal atrophies.

Cerebellar Cortical Atrophies

The cerebellar cortical atrophies can be subdivided according to the predominantly affected cell type into *granule cell atrophies* and *Purkinje cell atrophies*, with some overlap between the two groups. In the event of a loss of all neuronal elements of the cerebellar cortex, the term *total cerebellar cortical atrophy* is appropriate. Most atrophies are of the Purkinje cell type and further subdivisions are based on clinical criteria, such as the patient's age at onset and familial or sporadic occurrence.

Congenital Cerebellar Hypoplasia

This is a group of conditions that includes syndromes with different clinical presentation and morphological findings. They occupy a borderline between malformations and

degenerations. While some of them are pure malformations, occurring sporadically, others may show evidence of progressive degeneration or familial incidence suggestive of genetic defect, implying a degenerative or metabolic disorder operating in fetal life. Aside from localized agenesis of the vermis, hypoplasias of the cerebellar cortex of either the Purkinje or the granule cell type belong to this group.

Agenesis of the Vermis

Partial or complete agenesis of the vermis occurs in a variety of conditions in which it usually forms a cleft dividing the cerebellar hemispheres and communicating with the fourth ventricle. These conditions include Dandy–Walker syndrome, Joubert's syndrome (Joubert *et al.*, 1969), occipital encephalocele, and tectocerebellar dysraphia with occipital encephalocele (Friede and Boltshauser, 1978). In a rare variant no cleft is present, but the cerebellar hemispheres are fused in the midline (Michaud *et al.*, 1982). Most of these cases are sporadic and represent malformations presumably caused by exogenous factors. Only Joubert's syndrome is familial and is considered here.

Familial Aplasia of the Vermis (Joubert's Syndrome)

A familial aplasia of the vermis with ataxia and mental retardation was described by Joubert *et al.* (1969) in four siblings. So far more than 50 cases have been reported (Cantani *et al.*, 1990). A patient with the CHARGE association (coloboma of the eye, heart defect, atresia of the choana, retarded growth and development, genital hypoplasia, and ear anomalies or deafness) had intermittent hyperpnea and cerebellar hypoplasia characteristic of Joubert's syndrome (Menenzes and Coker, 1990).

Clinical Picture Abnormalities of respiration with episodic hyperpnea are noted soon after birth. Abnormal ocular movements, ataxia, and severe retardation appear later. Dysgenesis of the vermis and enlargement of the fourth ventricle can be observed on CT. In addition, MRI showed hypoplasia of the brain stem (Kendall *et al.*, 1990). Kubota *et al.* (1991) reported a case of cerebrooculohepatorenal syndrome (Arima's syndrome) in which the head CT scan showed agenesis of the cerebellar vermis and hypoplasia of the brain stem.

Neuropathology *Gross appearances.* The cerebellum is severely hypoplastic (Fig. 264) and the vermis is absent. The medial cleft between the hemispheres is covered with adherent leptomeninges (Fig. 265). The lateral foramina are atretic and the fourth ventricle is cystically dilated.

Light microscopy. Heterotopias consisting of neurons interspersed with sparse myelinated axons are found beside a normally structured cerebellar cortex. The decussation of the pyramids was almost totally absent in the case of Friede and Boltshauser (1978).

Pathogenesis Joubert's syndrome is an autosomal-recessive disorder (Cantani *et al.*, 1990). The origin of this syndrome is unknown, but a study of the peroxisomes is required since three cases of Joubert's syndrome with pipecolic acidemia have been re-

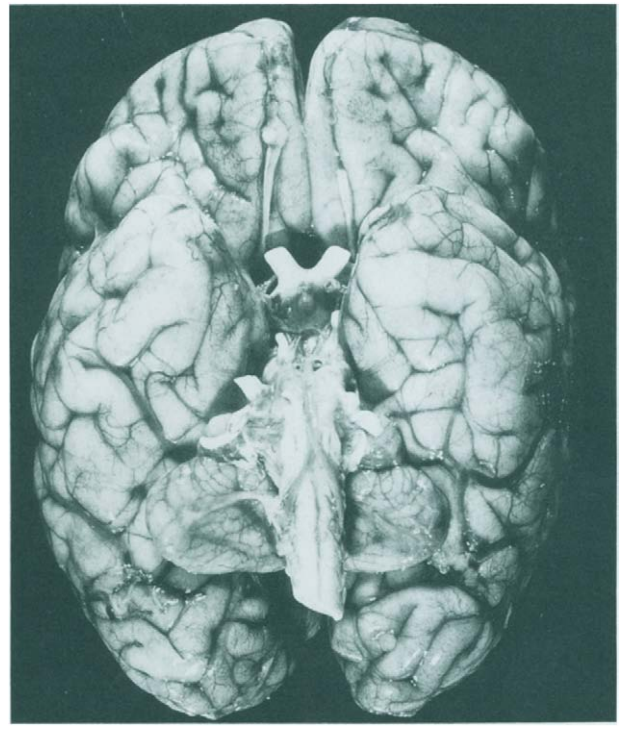


Fig. 264 Cerebellar hypoplasia. Severe atrophy of the basis pontis and the cerebellar hemispheres.

ported and resemblances exist between some recognized peroxisomal diseases and Joubert's syndrome.

Neocerebellar Aplasia and Hypoplasia

Barth (1993) classified all cases of neocerebellar hypoplasia into two groups. Type I is associated with a loss of anterior horn cells in the spinal cord and is considered later. Type II is characterized by microcephaly, hypotonia, seizures, and movement disorders and includes cases discussed in this section.

The first such case was described by Vogt and Astwazaturow (1912), and the disease entity was defined by Brun (1917, 1918), who subdivided it into *pontoneocerebellar aplasia* and *hypoplasia*. In the former the neocerebellar cortex is either absent or rudimentary; in the latter folia are present but are hypoplastic. Further examples of the former include the cases reported by Kawagoe and Jacob (1986) and Robain *et al.* (1987); those of the latter are from Norman and Urich (1958). Most cases appear to be sporadic, but familial incidence has been observed (Norman and Urich, 1958; Albrecht *et al.*, 1993).

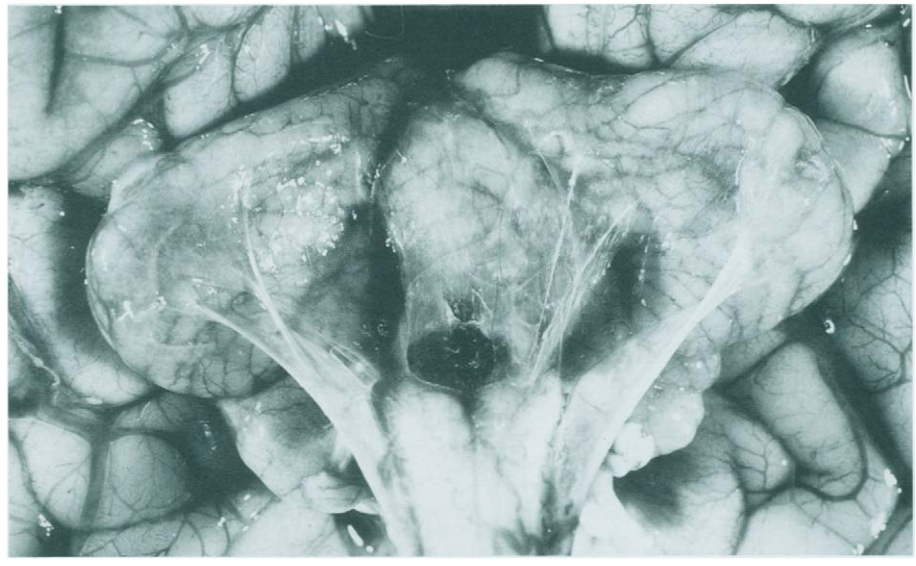


Fig. 265 Same case shown in Fig. 264. The cleft between the cerebellar hemispheres is bridged by adherent leptomeninges.

Clinical Picture The infants with pontoneocerebellar aplasia present immediately after birth with hypotonia, seizures, and respiratory difficulties. Most of these patients die within a few days, but some survive for a few weeks or months. Those with hypoplasia may survive longer and are mentally retarded. Incoordination and ataxia may range from mild to severe. Two siblings with developmental delay and a nonprogressive cerebellar ataxia had an autosomal-recessive neuronal migration defect that has not previously been reported. Cerebellar hypoplasia of congenital origin associated with hypogonadotropic hypogonadism has been reported by Abs *et al.* (1990). Hypoplasia also occurs in acrocallosal syndrome (Hendriks *et al.*, 1990). *In vivo* studies involving MRI have shown that autism is most consistently associated with developmental hypoplasia of the neocerebellum (Hsu *et al.*, 1991).

Neuropathology *Gross appearances.* The cerebellum is small and flattened, more strikingly so in cases of aplasia. On transverse section the cerebellum appears triangular. No recognizable folia are seen in aplasia, while defective folia are present in hypoplasia. The pons and the medulla are slender and flattened due to atrophy of the basis pontis and the inferior olives. In most cases the cerebral hemispheres are also hypoplastic and the total brain weight is reduced, in some cases considerably (Robain *et al.*, 1987).

Light microscopy. There is a striking contrast between the paleo- and neocerebellum (Fig. 266). In cases of aplasia, the cortex is largely absent in the neocerebellar parts or is represented by scattered rounded nodules with a thin layer of neurons on their surface,

containing sparse elements of the external and internal granular layers and a few Purkinje cells. The cortex in hypoplasia consists of short, stunted, poorly branched folia with a thin cortex consisting of sparse Purkinje and rarefied granule cells. The severity of the hypoplasia varies from case to case, ranging from severe depletion to almost normal appearances. The dentate nuclei are also hypoplastic and in most cases are fragmented into small islands (Fig. 267), consisting of sparse neurons, myelinated axons, and glial cells. The archi- and paleocerebellar elements are preserved, with the exception of the case of Albrecht *et al.* (1993) in which the superior vermis was severely atrophic and associated with a subcortical cyst. All nuclei with cerebellar connections are either hypoplastic or atrophic, and in particular the nuclei pontis are severely depleted. Prominent fibrillary gliosis may be present, suggestive of progressive atrophy as well as hypoplasia. The inferior olives and the perihypoglossal nuclei show similar changes that may be the result of retrograde transneuronal degeneration. Some gliosis may also be present in structures remote from the cerebellum, suggestive of a more widespread degenerative process (Albrecht *et al.*, 1993).

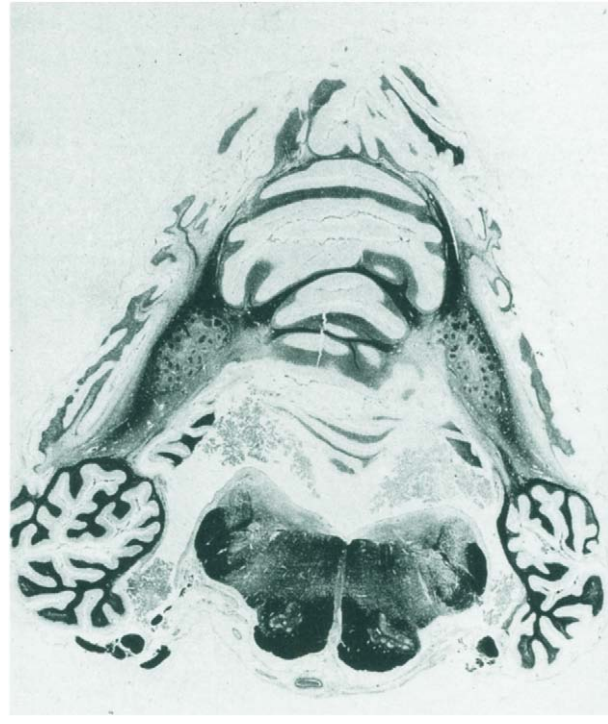


Fig. 266 Neocerebellar hypoplasia. Partial maldevelopment of the cortex of the cerebellar hemispheres with relatively normal development of the vermix and the flocculus. Segmentation of the dentate nucleus with pallor of myelin in the fleece and the hilum. Heidenhain–Wölcke stain.

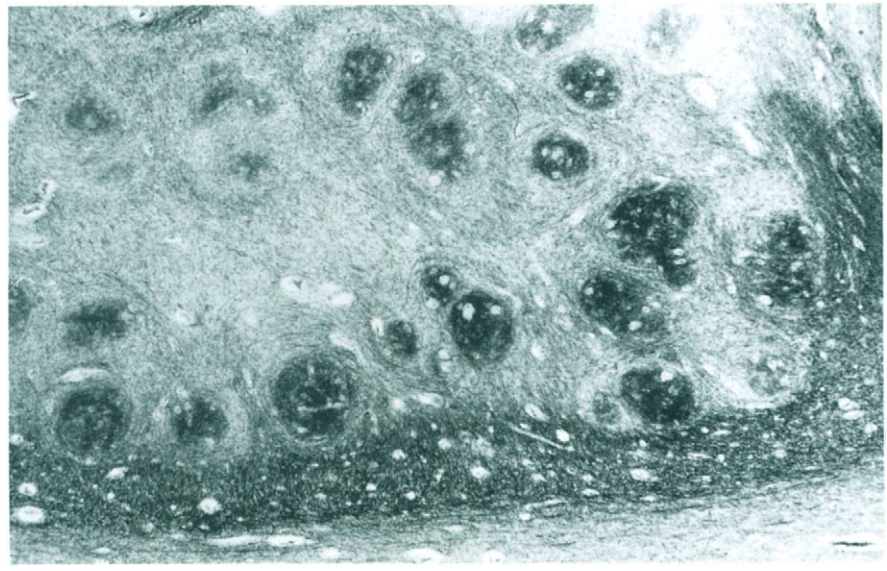


Fig. 267 Same case shown in Fig. 265. Segmentation of the cell band of the dentate nucleus into cell nests containing numerous myelinated axons. Heidenhain–Wölcke stain, ×30.

Cerebellar Hypoplasia with Spinal Muscular Atrophy (Norman's Disease; Amyotrophic Cerebellar Hypoplasia; Barth's Syndrome Type I)

The first case of this condition was reported by Norman (1961) as "cerebellar hypoplasia in Werdnig–Hoffmann's disease." Further contributions include those of Harding *et al.* (1988), Chou *et al.* (1990), and Pires *et al.* (1994). The term *amyotrophic cerebellar hypoplasia* has been suggested, while Chou *et al.* (1990) considered this an infantile form of OPCA with spinal muscular atrophy. With a few exceptions, most reported cases are familial.

Clinical Picture The infants with this disease are hypotonic and areflexic. Some are floppy since birth. They may show joint contractures and hip dislocations (Chou *et al.*, 1990). Their further development is marked by failure to thrive, respiratory difficulties, and psychomotor retardation. Nystagmoid eye movements, cortical blindness, and, rarely, tongue fasciculations have been observed in some cases (Kamoshita *et al.*, 1990). CT revealed an "empty" posterior fossa. Most infants die during the first year of life.

Pathology The skeletal muscles show neurogenic atrophy.

Neuropathology *Gross appearances.* The total brain weight may be within normal limits or may be reduced. The cerebral hemispheres appear normal, although in one reported case there was bilateral atrophy of the occipital lobes (Chou *et al.*, 1990). The cerebellum is disproportionately small and flattened, particularly in the neocerebellar

parts, where the folia are thin and widely separated, while the vermis and the flocculi are relatively better preserved. In one case with extreme cerebellar hypoplasia, a large retrocerebellar cyst was present (Chou *et al.*, 1990). The pons is flattened due to a considerably reduced basis pontis. The spinal cord shows atrophy of the anterior and normal posterior roots.

Light microscopy. The hypoplastic cerebellar folia show a considerable reduction in all neuronal elements, including the external and internal granular layers and the Purkinje cells, which can be completely absent (Kamoshita *et al.*, 1990). The cortex of the vermis and the flocculi is somewhat better preserved. The dentate nuclei show a variable degree of atrophy and the white matter is gliotic (Pires *et al.*, 1994). There is a severe loss of neurons and their transverse fibers in the basis pontis with well-preserved pyramidal tracts. The inferior olives are atrophic in most cases, although in one of the cases documented by Chou *et al.* (1990) bilateral pseudohypertrophy of the olives was observed, presumably secondary to the atrophy of the dentate nuclei. The spinal cord shows a loss of anterior horn cells, with degenerative changes, either chromatolysis or shrinkage, in the survivors. The swelling of neurons characteristic of Werdnig–Hoffmann disease is seldom present (Kamoshita *et al.*, 1990). The anterior roots are atrophic, in some cases strikingly so, but they do not show the extension of the glial segment as seen in Werdnig–Hoffmann disease.

Hereditary Cerebellar Cortical Atrophy (Holmes' Type of Spinocerebellar Degeneration; Late Parenchymatous Cerebellar Degeneration; Cerebelloolivary Atrophy of Critchley and Greenfield; Cerebellar Ataxia of Pierre-Marie)

Pierre-Marie (1893) presented a series of cases with dominantly inherited ataxia and preserved tendon reflexes as "hereditary cerebellar ataxia." Holmes (1907) described several members of a family with a similar clinical picture. While the patients of Pierre-Marie (1893) exhibited a variety of different morphological appearances, those of Holmes (1907) formed a well-defined pathological entity.

Critchley and Greenfield (1948) referred to this type of cerebellar degeneration as "cerebelloolivary atrophy." This term is open to misunderstanding, as it combines primary and secondary lesions and leads to confusion with olivocerebellar atrophies, in which the olivary degeneration is a primary lesion (see p. 588).

Clinical Picture Ataxia with intention tremor and choreiform restlessness begins after puberty, usually after the third decade, or occasionally as late as at the age of 60 years. The average age of onset is 40 years. An earlier onset may be precipitated by intercurrent diseases or malnutrition. Anticipation in successive generations has also been observed. Involvement of the cranial nerves, central impairment of hearing, and optic atrophy may occur, as well as dementia in the later stages. Atrophy, and occasionally pseudohypertrophy, of the skeletal muscles may be seen in some cases. Combinations with epilepsy, chronic progressive chorea, parkinsonian symptoms, or hemiballismus have been recorded. Several cases of an association between cerebellar ataxia and hypothyroidism have been reported (Bonuccelli *et al.*, 1991). However, no improvement in cerebellar

symptoms was observed after the regression of hypothyroidism. The inheritance is autosomal dominant.

Neuropathology *Gross appearances.* Mild cerebral atrophy may be present in older patients. The cerebellum is always severely atrophic, particularly the vermis and the dorsal aspects of the hemispheres (Fig. 268).

Light microscopy. Severe cerebellar cortical atrophy of the Purkinje cell type (Fig. 269) with orodorsal accentuation is combined with a secondary olivary atrophy. There is a widespread loss of Purkinje cells, and empty baskets may be demonstrated by silver impregnations (Fig. 270). In the more severely atrophic part of the cerebellum, the molecular and granular layers may also be involved and distinctly attenuated. The climbing fibers generally undergo transneuronal degeneration, but were reported by some authors to be intact. The loss of Purkinje cells stimulates a reactive proliferation of Bergmann's cells with fibrillary gliosis (Cervós-Navarro, 1991). Neuronal loss in the inferior olives is

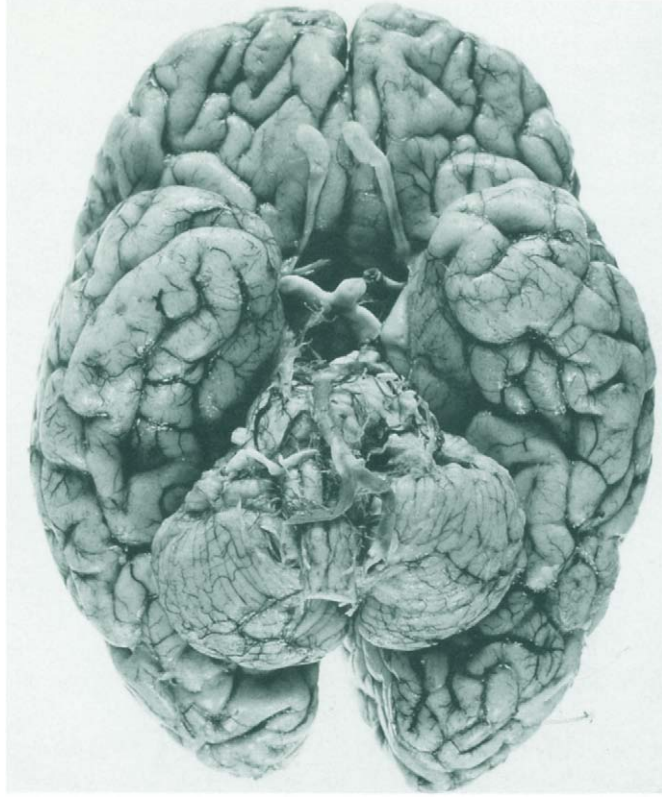


Fig. 268 Cerebellar cortical atrophy of the Holmes type. The occipital poles extend beyond the posterior margin of the cerebellum.

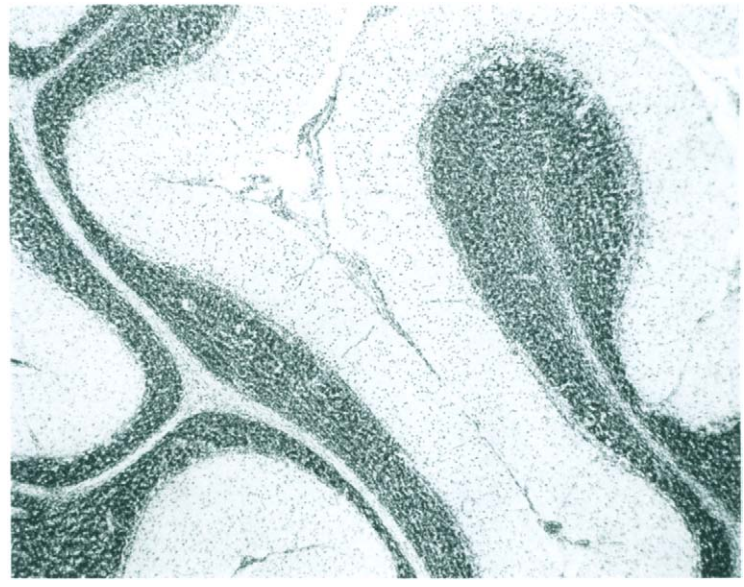


Fig. 269 Same case shown in Fig. 268. Marked rarefaction of the Purkinje cell layer. Nissl stain, ×40.

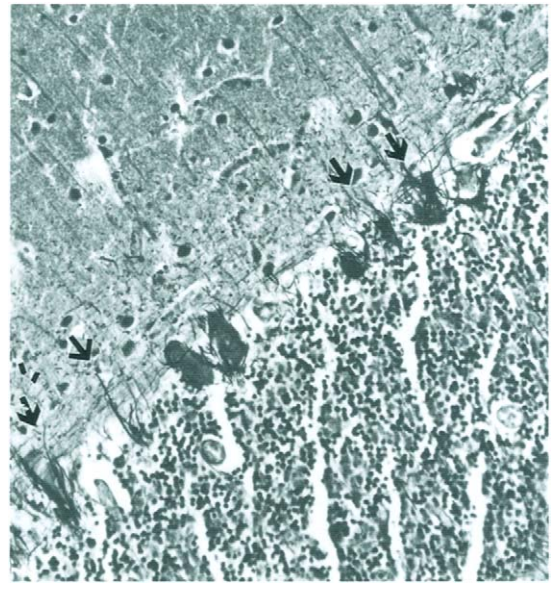


Fig. 270 Same case shown in Fig. 268. Empty baskets (arrows) replace the missing Purkinje cells. Bielschowsky stain, ×180.

pronounced in the dorsal and medial aspects (Koeppen *et al.*, 1979). Even in the absence of obvious myelin loss, there is diffuse gliosis throughout the cerebellum and in the inferior olives, where it exceeds the normal adult gliosis. A mild rarefaction of the crossed pyramidal tracts may be present in the spinal cord.

Cerebellar Ataxia and Hypogonadism (Boucher–Neuhäuser Syndrome)

In four siblings reported on by Holmes (1907), ataxia was associated with hypogonadism. The association of spinocerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy was recognized as an autonomous single-gene disorder by Limber *et al.* (1989), on the basis of three documented family cases, and was called Boucher–Neuhäuser syndrome, using the names of the first authors of the two early reports. Reports of different families in which members have spinocerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy support that this triad of manifestations represents a specific single-gene disorder (Baroncini *et al.*, 1991). DeMichele *et al.* (1993) reported sporadic cases of cerebellar ataxia associated with hypogonadism. Endocrine evaluation showed heterogeneity of the hypogonadism, which was hypogonadotropic in one patient and hypergonadotropic in the others. The syndrome appears to be a heterogeneous multisystem disorder, and in some cases a mitochondrial metabolism deficiency could be suspected.

Holmes (1907) mentioned genital hypoplasia in four siblings with cerebellar ataxia, but the first family fully investigated endocrinologically was that reported by Boitelle *et al.* (1956) under the name *spinocerebellar degeneration with hypogonadotropic infantilism.* Additional cases have been described within a few families.

Clinical Picture The principal symptoms are absence or defective development of sexual characteristics and cerebellar ataxia with dysarthria. The hypogonadism precedes the neurological manifestations. Mental retardation or dementia is present in most cases. Spinal symptoms are inconspicuous, but are present in all cases. Occasionally, other symptoms may be present, such as dysphagia, nystagmus, deafness, dyskinesia, anosmia, or strabismus. Lowenthal *et al.* (1979) found an abnormal distribution of amino acids in the serum, urine, and CSF in two siblings. CT of the head revealed atrophy of the cerebellum and the brain stem, suggestive of OPCA (Berciano *et al.*, 1982). However, MRI in one case showed only atrophy of the cerebellum with a normal brain stem (Ricart *et al.*, 1994). The inheritance was thought to be X-linked recessive, but an autosomal-recessive mode appears to be more likely (Neuhäuser and Opitz, 1975; Berciano *et al.*, 1982).

Neuropathology The inferior olives showed a severe loss of nerve cells in all cases examined, while degeneration of the Purkinje cells was prominent in only a few cases (Howell and Matthews, 1978). The vestibular and cochlear nuclei may also be affected. A slight loss of myelin with gliosis has been seen in the cerebral and the cerebellar white matter, as well as in the corticospinal and dorsal spinocerebellar tracts.

Pathogenesis The expression of two different, but closely linked, mutated genes has been postulated (Rushton and Genel, 1981).

Autosomal-recessive inheritance of this syndrome is borne out by the observations that

all of the cases so far ascertained from different families have been siblings in a single generation with unaffected parents, and that consanguinity was present in one case. Finally, males and females are equally affected.

Congenital Cerebellar Cortical Atrophy of the Granule Cell Type (Congenital Nonprogressive Cerebellar Ataxia)

In this and the following conditions an absence or loss of granule cells forms one of the principal features.

The clinical picture was first described by Batten (1905). Neuropathological confirmation of congenital atrophy of the granular layer was presented by Norman (1940).

Clinical Picture Ataxia and mental retardation are already apparent during the first year of life and remain nonprogressive. In the absence of fatal intercurrent diseases, the patients may reach adulthood. Familial incidence has been recorded in a few cases.

Neuropathology *Gross appearances.* The cerebellum is atrophic, with thin folia and gaping sulci.

Light microscopy. The granule cells are almost totally absent, with relative preservation of the Purkinje cells. In some cases (Sarnat and Alcala, 1980) the Golgi, basket, and stellate cells may also be absent. In other cases the Golgi cells are preserved, but may be shrunken and hyperchromatic.

Axonal swellings and dendritic abnormalities in the form of staghorn deformities and asteroid bodies have been repeatedly observed in Purkinje cells. Rarely, disorganization of the laminar structure may be seen, suggestive of migration disorders.

Tangential fibers are absent in the superficial layers of the attenuated molecular layer, but are well preserved in the deeper parts, where they may be slightly thickened. The organization of their terminal fibers into baskets is often absent, and they may form an irregular curtain in the Purkinje cell layer.

Pathogenesis Primary atrophy of the granular layer has never been established as a heredodegenerative disease. For a long time it was considered pathognomonic of the late infantile amaurotic idiocy. Other causes include toxic factors. The condition must be distinguished from a common postmortem artifact: the conglutination of granule cells ("sugar icing artifact"). Experimentally, a loss of granule cells can be produced by cytotoxic substances, irradiation, and viral infections. Sarnat and Alcala (1980) suggested that the absence of granule cells, as well as basket, Golgi, and stellate cells, may be due to noxious agents or metabolic disorders operating early in fetal life and preventing the formation of the external granular layer.

Congenital Granuloprival Hypoplasia of the Cerebellar and Hippocampal Cortices

This variant, in which a congenital absence of granule cells was combined with an absence of the fascia dentata in the hippocampus, was described by Chou *et al.* (1987) in two siblings.

Clinical Picture Both of these infants were wobbly and hypotonic. At the age of a few months, psychomotor retardation became apparent. Focal seizures, sometimes right sided, sometimes left sided, developed later and became more severe over the years. Athetoid movements appeared in the later stages. Repeated biochemical investigations yielded negative results. The siblings died at 3 years, 7 months, and 5 years, 10 months, respectively.

Neuropathology *Gross appearances.* Both children were microcephalic, their total brain weights being just over one half of normal values. Both the cerebral hemispheres and the cerebellum were small. Cut surfaces showed an apparently normal cerebral cortex and a considerably reduced white matter. The cerebellum was well proportioned, but showed thin folia and widened sulci.

Light microscopy. The striking feature in the cerebral hemispheres was the total absence of the small neurons of the dentate fascia in the hippocampus. The cerebellar cortex was devoid of granule cells, with preservation of the Purkinje cells, which showed minimal abnormalities compared with those observed in other cases of deficiency of granule cells.

Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy

Infantile cerebellar atrophy in progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy is a clinically defined entity with infantile spasms, early arrest in psychomotor development, severe hypotonia, transient or persistent subcutaneous edema, and blindness (Salonen *et al.*, 1991). The onset of symptoms is from 2 weeks to 4 months; pregnancy and delivery are normal, and most patients are considered healthy during the first weeks of life. About 20 sporadic cases and six families with more than one affected child have been found in Finland. The patients may live in a vegetative state up to an age of 15 years.

Neuropathology The patients show severe cerebral and extreme cerebellar atrophy, which was most pronounced in the vermis. The molecular layer of the cerebellar cortex is abnormally thin, and the Purkinje cells are reduced in number and size, deformed, and disoriented. The inner granular layer either is totally absent or shows a sparse population of scattered neurons (Haltia and Somer, 1993).

Marinesco–Sjögren's Syndrome (Oligophrenia; Cataract and Cerebellar Atrophy; Hereditary Oligophrenic Cerebellolentiform Degeneration; Marinesco–Garland Syndrome)

The first family with this condition was reported on by Marinesco *et al.* (1931). In the same year Sjögren observed his first patients, but did not publish his observations on 14 cases until 1950. Some authors include the syndrome among the spinocerebellar degenerations.

Clinical Picture All of these patients share the features of cataracts, cerebellar ataxia,

and mental retardation. The cataracts are bilateral and generally considered to be congenital, although they are usually discovered months or even years after birth. The form of the cataract varies in different patients and is nonspecific (Dotti *et al.*, 1993). The cerebellar symptoms are present from the beginning of the illness and include dysarthria, nystagmus, and ataxia of the trunk and the limbs. The mental retardation appears to be developmental and remains stationary. Other associated symptoms include skeletal anomalies and muscular weakness (Superneau *et al.*, 1987). Hypogonadotropic hypogonadism was observed by Skre and Berg (1977). CT and MRI showed diffuse brain atrophy of a mild to moderate degree, involving primarily the white matter of the cerebrum, cerebellum, brain stem, and cervical spinal cord (Bromberg *et al.*, 1990). The course of the disease is protracted and many patients die after the age of 40, or even 60, years. The mode of inheritance is autosomal recessive.

Pathology Muscle fiber necrosis, followed by regeneration and focal myofibrillar degeneration, is predominant in young patients. Myofibrillar degeneration with autophagic phenomena is more prominent in adult patients (Goto *et al.*, 1990).

Occasionally, RRFs were found and electron microscopy showed a subsarcolemmal accumulation of abnormal mitochondria (Torbergsen *et al.*, 1991). Conjunctival biopsies revealed a marked increase in the number of lysosomes in fibroblasts (Zimmer *et al.*, 1992).

Neuropathology *Gross appearances.* Atrophy of the cerebellum (Fig. 271) is particularly prominent in the vermis. An almost total loss of Purkinje and granule cells is accompanied by gliosis. The remaining Purkinje cells show vacuolation of the cytoplasm and are occasionally multinucleated. In the case recorded by Vosskämpfer and Schachenmayr

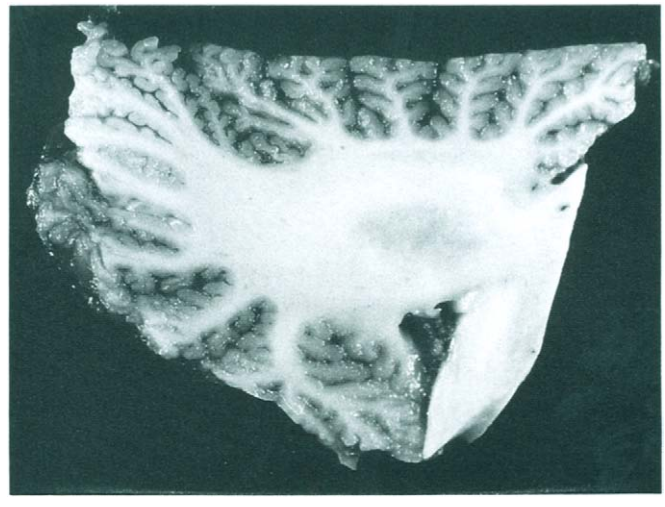


Fig. 271 Marinesco–Sjögren syndrome. Atrophy of the cerebellar cortex. (Courtesy of W. Schachenmayr, Giessen, Germany.)

(1988), the Purkinje cells were preserved, with a severe loss of granule cells (Fig. 272). Neuronal loss and gliosis have been seen in the nuclei pontis and the inferior olives. Segmental demyelination of the peripheral nerves was diagnosed by Hakadama *et al.* (1981).

Sporadic, Noncongenital, Cerebellar Cortical Atrophies

Localized Cerebellar Cortical Atrophy (Atrophie Tardive *of Marie–Foix–Alajouanine)*

The classical description of this condition is that of Pierre-Marie *et al.* (1922) under the title *atrophie cérébelleuse tardive à prédominance corticale.* It is a heterogeneous group of disorders, in which some cases occur within the context of central neurofibromatosis and cerebral calcification. CT has revealed progressive asymptomatic atrophy of the vermis in patients of advanced age (Koller *et al.*, 1981).

Clinical Picture The symptoms appear usually after the age of 55 years, with insidious and slowly progressive unsteadiness of gait and posture. Men and women are equally affected. Occasional early or "apoplectiform" onset has been recorded. The upper limbs are generally unaffected by the ataxia and no major intellectual decline is apparent. Speech disturbances occur only in late stages of the disease. The duration of the disease is 10–20 years or more.

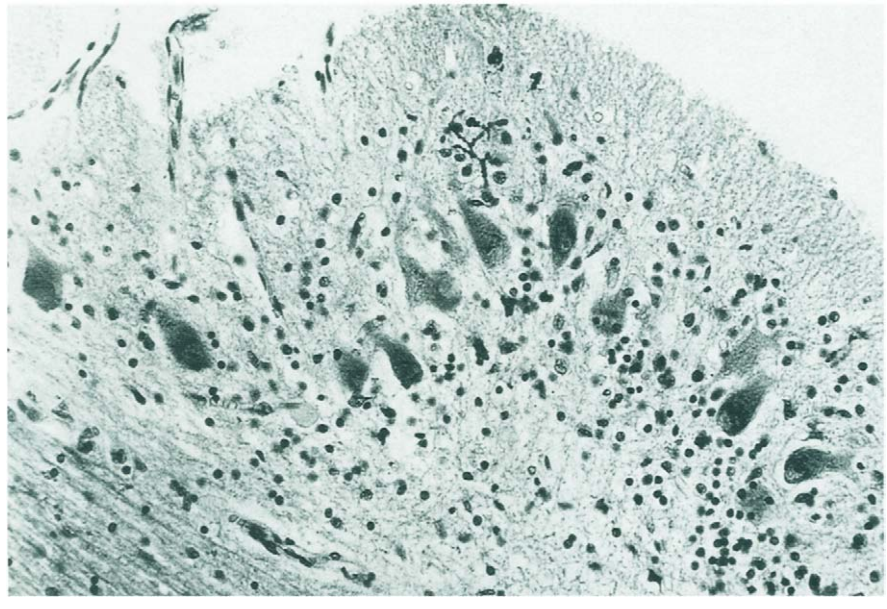


Fig. 272 Same case shown in Fig. 271. An extensive loss of granule cells in the cerebellar cortex. Nissl stain, ×350.

Neuropathology *Gross appearances.* Symmetrical atrophy is confined to the orodorsal part of the cerebellum, particularly the superior vermis and the adjacent anterior lobe (paleocerebellum), while the inferior aspects remain unaffected (Fig. 273). Gaping sulci are conspicuous in the superior vermis, between the lingula, lobulus centralis, culmen, and anterior aspect of the declive. The affected folia are firm and atrophic. This widening of the sulci tends to be more prominent than in the diffuse cerebellar atrophies, even those associated with a total loss of neuronal elements.

Light microscopy. The affected areas show a loss of Purkinje cells with empty baskets. Other parts of the cortex are not completely unaffected. The atrophy is more marked peripherally than in the deeper parts of the folia. The fleece of the dentate nucleus is rarefied, particularly in its orodorsal parts. Some cell loss is also present in the dorsomedial parts of the inferior olive and in the dorsal accessory olive, with a corresponding loss of olivocerebellar fibers and attenuation of the restiform bodies. Of the deep nuclei, only the roof nuclei show minor changes. Aside from rarefaction of the myelin in the atrophic folia, myelinization remains normal.

Pathogenesis The lesions bear a striking resemblance to those observed in the cerebellar atrophy of alcoholics. It would be of interest to have more information on the alcohol consumption of the patients of Marie *et al.* (1922).

Diffuse Cerebellar Cortical Atrophy

The occurrence of spontaneous subacute cerebellar atrophies within the context of system degenerations is debatable. Many cases are associated with neoplasms (Henson and Urich, 1982), while others may be due to toxic or nutritional factors (Solheid *et al.*, 1986).

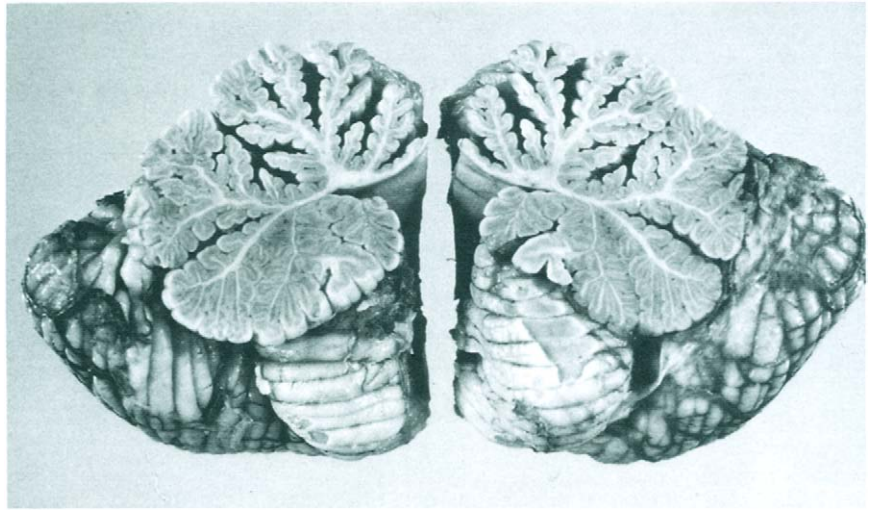


Fig. 273 *Atrophié tardif* of the cerebellum. Localized cortical atrophy of the orodorsal parts.

Clinical Picture A severe cerebellar syndrome develops rapidly with severe ataxia, affecting the upper and lower limbs, mostly in the fourth or fifth decade. Both sexes are equally affected. Disturbances of speech and nystagmus are common. Organic dementia develops almost invariably. The patients are often cachectic and die within a few months or years.

Neuropathology The cerebellar atrophy is inconspicuous and uncharacteristic. Sometimes there is a slight widening of the sulci and an overall reduction in the size of the cerebellum. Severe atrophy is uncommon.

The atrophy is almost invariably of the Purkinje cell type. The few remaining Purkinje cells show acute degenerative changes. Sudanophilic lipid is frequently present in the cortex.

Animal and Experimental Models In the mouse mutant *pcd* (Purkinje cell degeneration) all Purkinje cells degenerate 3–4 weeks after birth; other systems are involved later (O'Gorman, 1985). Other cerebellar mutants include *weaver*, *staggerer*, *tottering*, and *leaner*, as well as their double mutants. All of these show different types of cerebellar cortical atrophy. An atrophy of the Purkinje cell type has been described in horses (Palmer *et al.*, 1974). A hereditary cerebelloolivary degeneration of the Purkinje cell type associated with striatonigral degeneration occurs in dogs (Montgomery and Storts, 1984). In the hereditary Sawin–Anders ataxia of rabbits, the central cerebellar nuclei are affected as well as the vestibular and cochlear nuclei (O'Leary *et al.*, 1974). Cerebellar hypoplasia caused by fetal viral infections has been repeatedly observed in cats. Parvoviruses cause predominantly a granule cell atrophy, while other viral infections affect both granule and Purkinje cells (Krücke *et al.*, 1975). Meyer and Foley (1953) produced a Purkinje cell degeneration by intracerebellar injection of eosinophils or eosinophil extracts. In this context Hill and Sherman (1968) pointed out the familial occurrence of cerebellar ataxia associated with ascaris infestation.

Olivopontocerebellar Atrophy

The first accurate anatomopathological description of this disease is that by Menzel (1891) under the term *hereditary ataxia and cerebellar atrophy*. Déjerine and Thomas (1900) described the first sporadic cases and introduced the term *olivopontocerebellar atrophy*.

The fact that in most cases other centers and systems are involved, particularly the basal ganglia, substantia nigra, and thalamus and occasionally the cerebral cortex, led to the conclusion that "pure" cases of OPCA did not exist (Jellinger and Tarnowska-Dzidusko, 1971) and that the disease should be included among the multisystem atrophies. It is preferable, however, to differentiate the individual syndromes to obtain insight into their pathogenesis, rather than to subsume all cases under the overall concept of *multisystem atrophies*.

Classification In his classical monograph Greenfield (1954) divided the cases of OPCA into a mixed, generally hereditary, spinocerebellar type, corresponding to the family described by Menzel, and a pure, generally sporadic, type, as described by Déjerine and Thomas. In view of the fluid transitions and overlaps in the neuropathological find-

ings in different cases, some authors preferred a simple classification into hereditary and sporadic types without regard for the distribution of the lesions. Both groups are numerically about equal. In recent years, however, more genetic than sporadic cases have been published. Possibly, some apparently sporadic cases may, in fact, be due to autosomal-recessive inheritance.

Taking into account clinical, neuropathological, and genetic features, Königsmark and Weiner (1970) divided OPCA into a sporadic type and five different hereditary types. The following are the five genetic types:

I. (Menzel) dominant OPCA with variable degeneration of the spinocerebellar tracts and the posterior columns

II. (Fickler–Winkler) recessive pure OPCA

III. Dominant OPCA with RP

IV. (Schut–Haymaker) dominant OPCA with a variable phenotype, some loss of anterior horn cells, degeneration of the spinocerebellar tracts and the posterior columns, and involvement of cranial nerves IX, XI, and XII

V. Dominant OPCA with extrapyramidal signs, ophthalmoplegia, and dementia

Biochemical (Perry, 1984) and enzymatic investigations led to further subdivisions. Huang and Plaitakis (1984), in their study of 25 patients, identified a sporadic form with orthostatic hypotension, a recessive type with a deficiency of glutamate dehydrogenase, and three dominant forms. Their classification was based partly on biochemical, partly on clinical, criteria, and two groups were defined solely by their genealogies. However genetically correct, this last principle does not take into account the phenotypic variation within a single family.

Hereditary Olivopontocerebellar Atrophy (Familial Pontoolivary Atrophy; Pontocerebellar Atrophy; Spinopontocerebellar Heredodegeneration of the Menzel Type; Hereditary Ataxia of Marie–Nonne)

While Menzel (1891) described the neuropathological features of this condition in adults, Blauner (1914) was the first to report on a family in which the disease appeared in childhood.

Clinical Picture The first symptoms may appear in early childhood, in adult life, or even in old age. The average age at onset is 36 years. In families with several involved generations, anticipation has been observed in subsequent generations.

The predominant symptom is disturbance of gait, which, over the course of years, may lead to total abasia. The upper limbs may be affected in the later stages both by ataxia and by extrapyramidal symptoms. Dysarthria is almost constant.

Blindness was present in several families. A loss of abdominal reflexes, pyramidal signs, and cranial nerve symptoms have been reported. Amyotrophy occurs in about 25% of the cases in later stages of the disease. The average duration of the disease is 15 years from the onset of symptoms. Patients with early onset may survive for several decades. Neuroimaging may be helpful in forming the clinical diagnosis. Both CT (Wittkämper *et al.*, 1993) and MRI (Wüllner *et al.*, 1993; Ormerod *et al.*, 1994) demonstrate atrophy

of the brain stem and the cerebellum. The appearances, however, are not entirely specific and may be negative or equivocal in early cases. PET shows reduced cerebral blood flow in the affected areas (Sun *et al.*, 1994).

Inheritance may be recessive (Huang and Plaitakis, 1984) or dominant (Menzel 1891; Schut and Haymaker, 1951; Perry, 1984).

Neuropathology The great variation in neuropathological findings cannot be correlated with definite clinical patterns. Heterogeneity of lesions may be found in various members of the same affected family (Schut and Haymaker, 1951).

Gross appearances. The cerebellum is atrophic (Fig. 274) and the basis pontis and the medulla oblongata are flattened (Fig. 275). The cerebellar atrophy affects predominantly the neocerebellar parts, but in some cases the paleocerebellum is preferentially involved.

Light microscopy. Neuronal loss is prominent in various parts of the nuclei pontis. Surviving nerve cells show degenerative changes. The inferior olives are reduced in size and show a severe loss of neurons (Fig. 276A and B). The surviving cells are shrunken. The glia shows increased cellularity and a dense network of fibrils both in the basis pontis and in the inferior olives. The dendrites of the surviving cells may show a proliferation of neurofibrils and their axons may exhibit focal swellings. The arcuate nuclei, as a rule, are involved in the process.

The number of Purkinje cells may be considerably reduced, and the granular layer may be rarefied. The surviving Purkinje cells show a loss of dendrites and abnormal dendritic spines in Golgi impregnations (Ferrer *et al.*, 1994c). The fleece of the dentate nucleus shows rarefaction corresponding to the loss of Purkinje cells. Transneuronal degeneration may lead to a loss of neurons in the dentate nucleus.

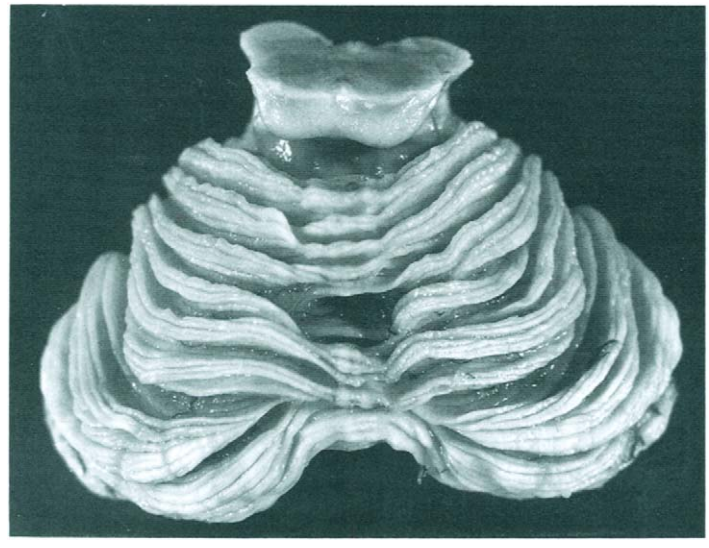


Fig. 274 Olivopontocerebellar atrophy. Severe atrophy of the cerebellum.

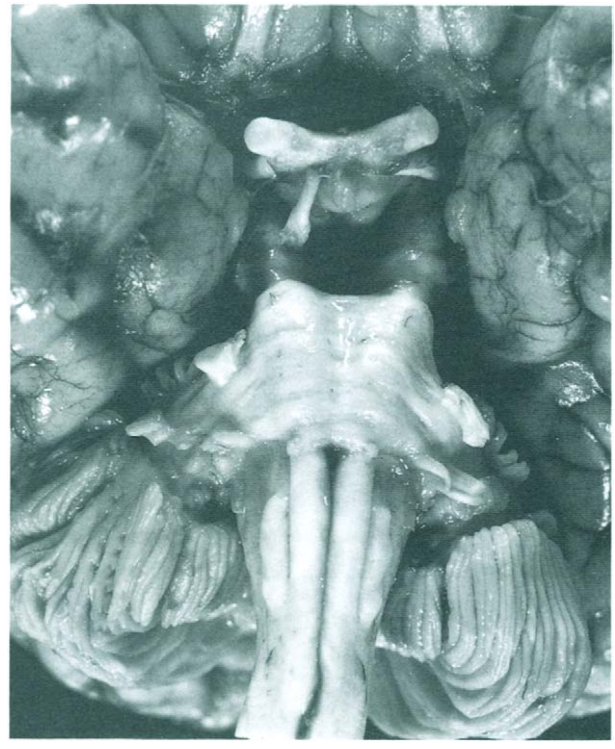


Fig. 275 Olivopontocerebellar atrophy. Severe atrophy of the basis pontis and the medulla oblongata.

The afferent pathway of the nuclei pontis and the inferior olives may also undergo atrophy. The central tegmental tract (Fig. 277) and the corticopontine tracts show a loss of myelin and the cerebral peduncles may be reduced in size (Critchley and Greenfield, 1948). The loss of myelin is also prominent in the cerebellar white matter (Fig. 278).

Changes in the lateral geniculate bodies have been seen particularly in cases with early onset. Degeneration of the striatonigral system has been repeatedly observed. An association with Shy–Drager syndrome (see p. 668) has been reported (Sung *et al.*, 1979). Lewy bodies are rare. In one case of OPCA with a glutamate dehydrogenase deficiency, Chokroverty *et al.* (1984) found generalized neuronal storage of lipofuscin.

In a similar case Chokroverty *et al.* (1990) found a loss of anterior horn cells. Examination of the retina in blind patients revealed a loss of ganglion cells as well as of rods and cones. Axonal swellings in the peripheral nerves and calcifications in the autonomic nervous system were found in one family with five affected members (Staal *et al.*, 1981).

Electron microscopy. Degenerative changes have been found in the dendrites, axons, and perikarya in the Purkinje cells with an accumulation of mitochondria. The normal cerebellar glomeruli were largely absent. The structures interpreted as Lafora's bodies were probably polyglucosan bodies, which are a normal aging phenomenon (Gertz *et al.*, 1985). Curvilinear bodies and crystalline inclusions were seen in the perikarya of Purkinje cells.

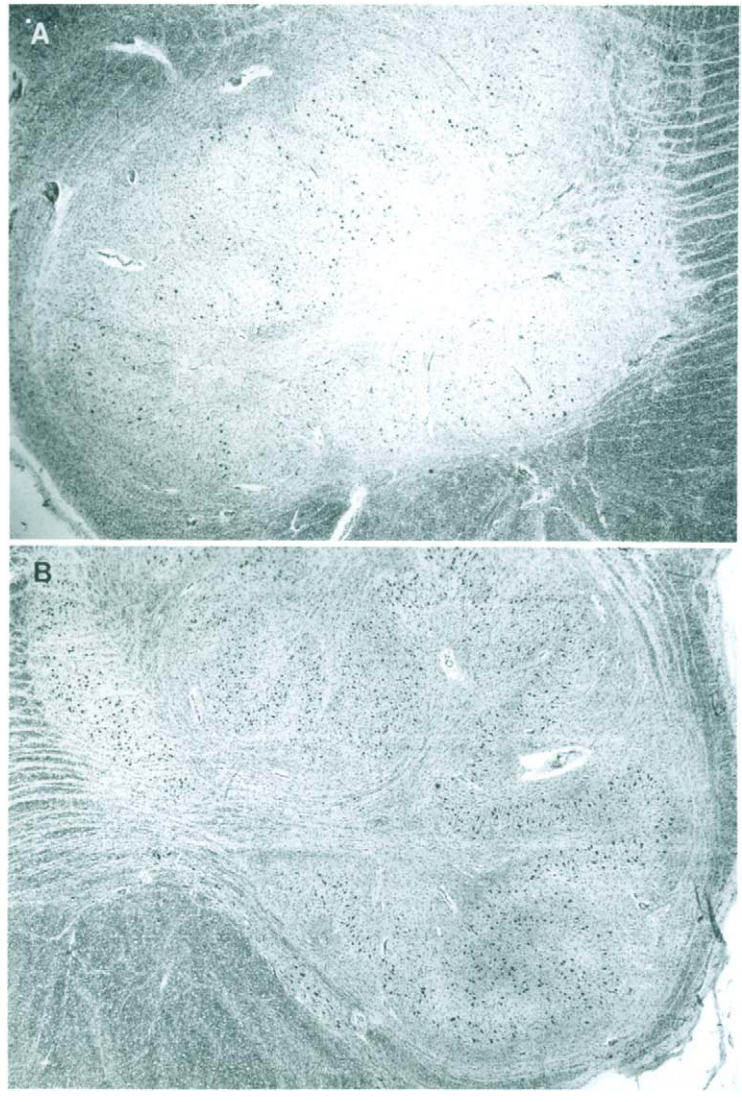


Fig. 276 Same case shown in Fig. 275. (A) An extensive loss of nerve cells in the inferior olive. (B) A normal control. Nissl stain, ×40.

Sporadic Olivopontocerebellar Atrophy (Déjerine–Thomas Type of Olivopontocerebellar Atrophy; Cerebellar Ataxia; Sclerosis of the Cerebellar White Matter)

Clinical Picture With rare exceptions, this disease manifests itself after the age of 50 years. Cerebellar ataxia is the principal symptom. Disturbances of bladder and rectal

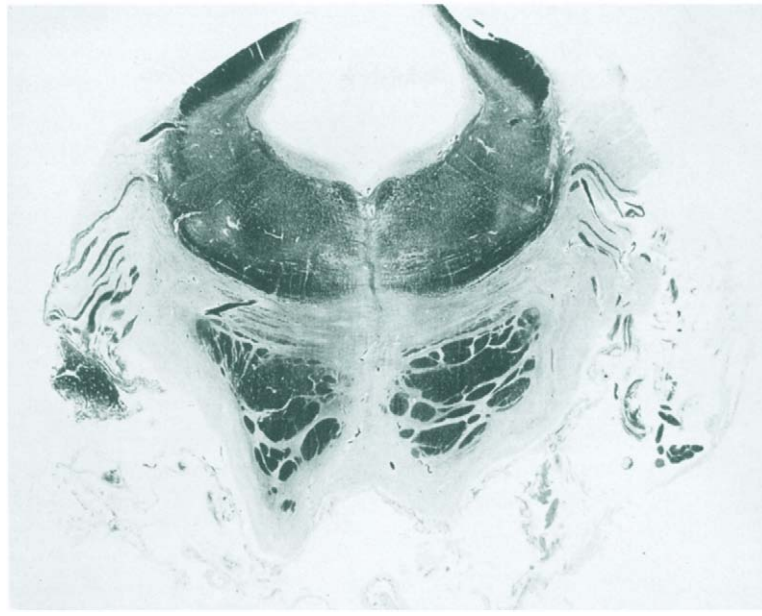


Fig. 277 Same case shown in Fig. 275. A loss of myelin in the brachium pontis. Heidenhain–Wölcke stain.

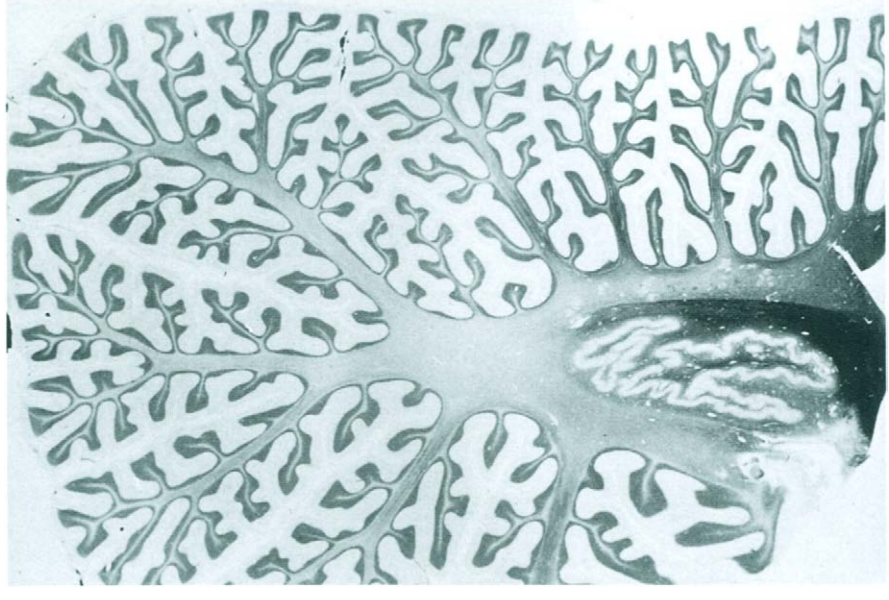


Fig. 278 Same case shown in Fig. 275. An extensive loss of myelin in the cerebellum, with partial preservation of the myelinated fibers in the fleece of the dentate nucleus.

functions and of autonomic control of the circulatory system frequently appear after a few years (Mitake and Mizutani, 1987). A parkinsonian syndrome with rigidity often supervenes and may mask the cerebellar symptomatology. Peripheral nervous symptoms may develop in cases of long duration. Psychiatric manifestations may precede the ataxia by several years (Thierauf *et al.*, 1985). Dementia frequently supervenes in late stages of the disease. The average course of the disease is 5–9 years from the onset of symptoms. A fulminating course leading to death within months, both in older and in younger patients, has been described by Barontini *et al.* (1983).

Neuropathology *Gross appearances.* The striking features are atrophy of the basis pontis and a reduction in the size of the medulla with prominent bulging of the normal pyramids. The cerebellum is small (Fig. 279). Other systems may be involved, particularly the putamen (Fig. 280) and the substantia nigra (Fig. 281A,B) (Oppenheimer, 1984), the lesions being those of striatonigral degeneration.

Light microscopy. Neuronal loss is severe in the nuclei pontis and the inferior olives.

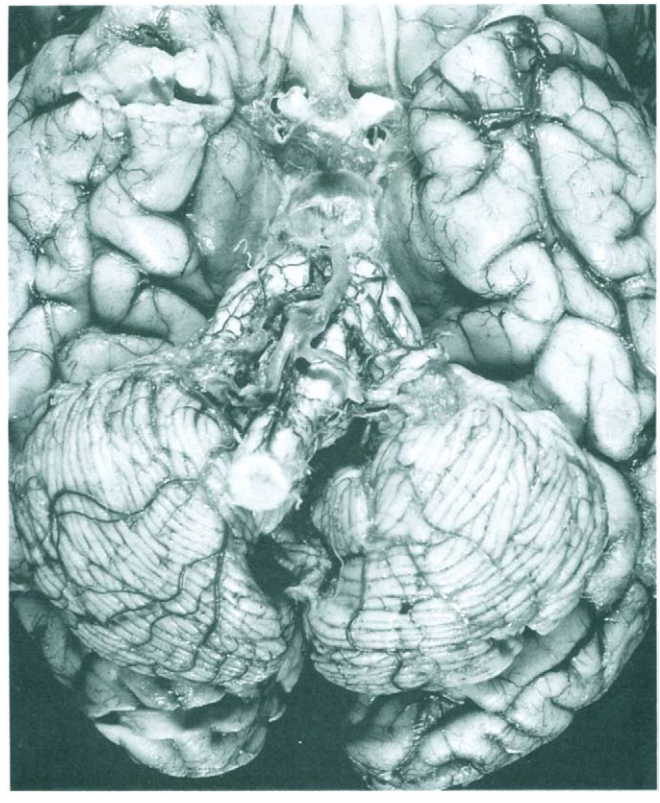


Fig. 279 Déjerine–Thomas type of olivopontocerebellar atrophy. Moderate atrophy of the cerebellum.

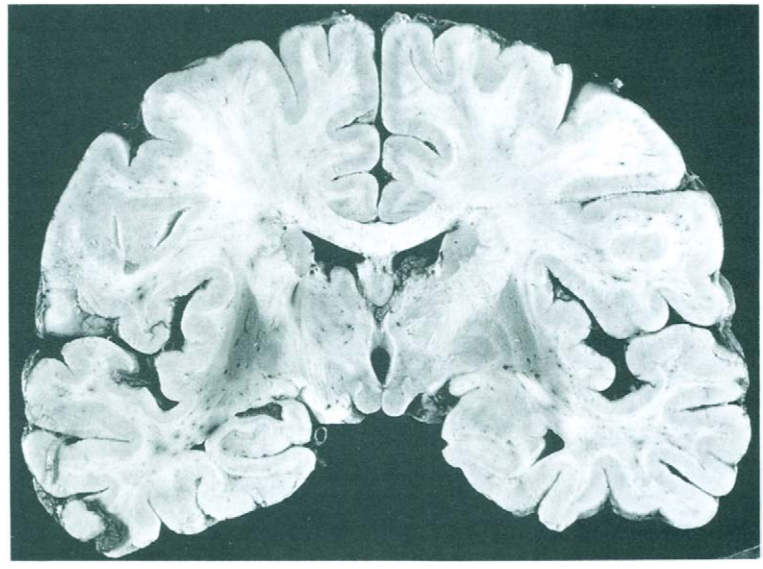


Fig. 280 Same case shown in Fig. 279. Atrophy of the putamen.

A loss of neurons has also been observed in the locus coeruleus (Mitake and Mizutani, 1987), the thalamus, and the intermediolateral nucleus of the spinal cord. In preparations stained for myelin, both the hilum and the fleece of the inferior olives (Fig. 282A) as well as the ventral and dorsal olivocerebellar fibers appear pale. The intact fascicles of the pyramidal tracts stand out in the atrophic basis pontis (Fig. 283). The middle cerebellar peduncle is shrunken and devoid of myelin. A loss of fibers is also reflected in an appreciable reduction in the size of the inferior cerebellar peduncle. Degeneration of the corticopontine tracts was reported by Yagishita *et al.* (1991). Degeneration of the vestibular nuclei and the vestibulocerebellar tracts is rare.

The loss of cerebellipetal fibers leads to an absence of myelin in the cerebellar hemispheres, particularly in the caudal parts. A characteristic pattern is formed by the preservation of the dentate nuclei and the superior cerebellar peduncles as well as of the fleece formed by Purkinje cell axons (Fig. 282A). The loss of myelin may occasionally be patchy. The flocculi, tonsils, and vermis are generally spared, but morphometric studies by Kume *et al.* (1991) revealed a more severe loss of Purkinje cells in the vermis than in the hemispheres.

In rare cases, interpreted as incomplete forms of OPCA, the inferior olives may be preserved. Guillain *et al.* (1933) reported pseudohypertrophy of the olives with enlargement of the nucleus, swelling, and vacuolation of individual neurons.

A unique case of unilateral OPCA was reported by Davison and Wechsler (1938). Jellinger and Tarnowska-Dzidusko (1971) drew attention to the fibrillary gliosis that appears early and seems excessive for the amount of fiber loss. This is particularly striking in the periphery of the folia and their branches (Fig. 282B). It has also been found in the motor cortex (Fujita *et al.*, 1993). Occasionally, pigment is found in the glial cells, as well

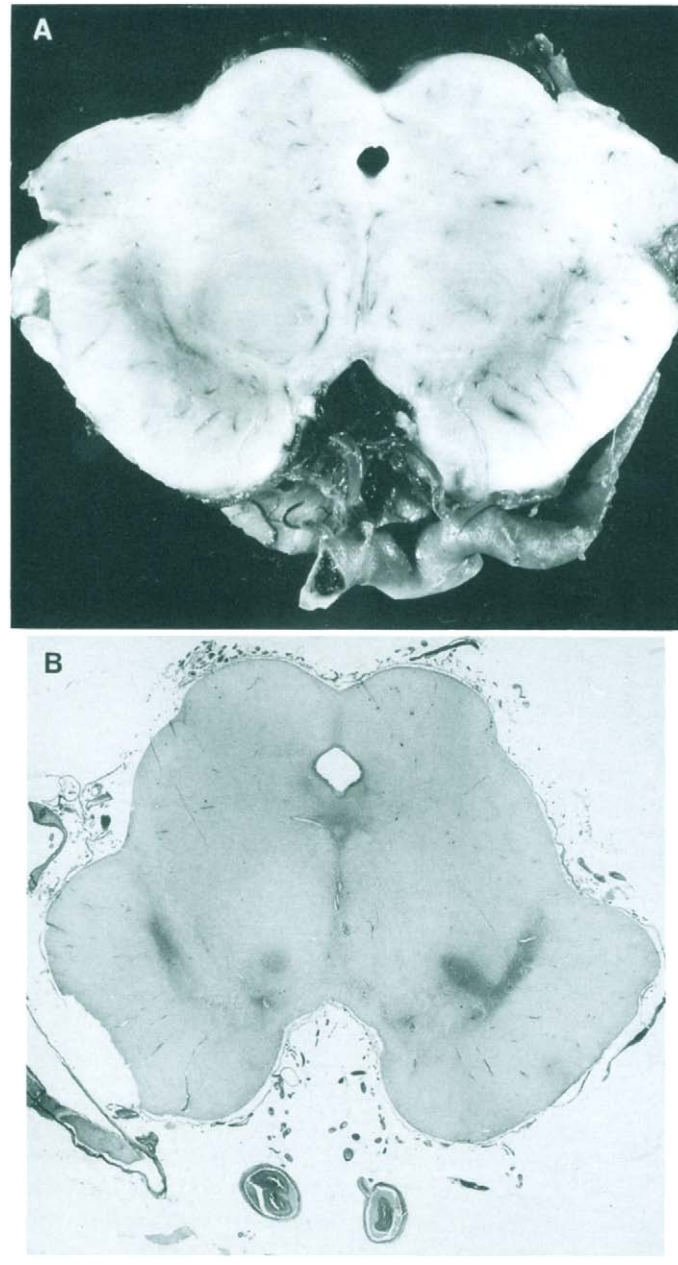


Fig. 281 Same case shown in Fig. 279. (A) Depigmentation of the substantia nigra with (B) a glial reaction. Holzer stain.

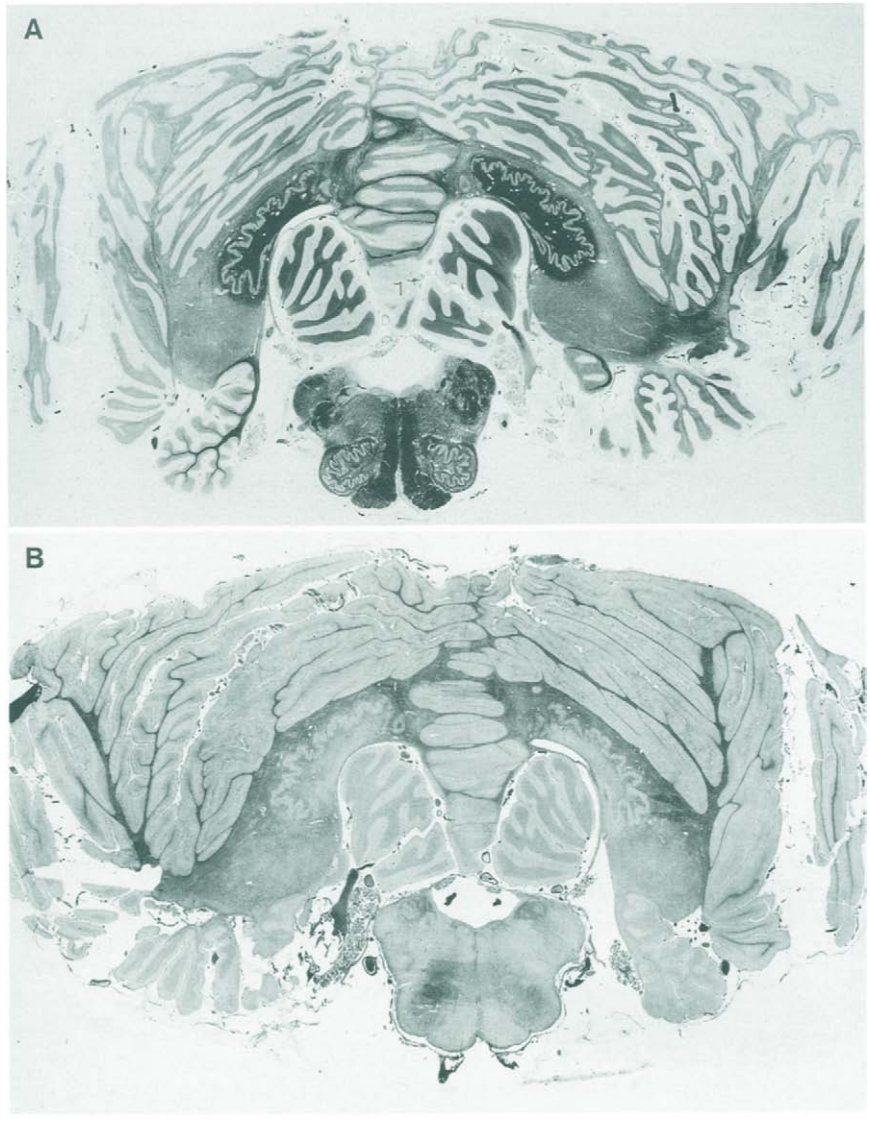


Fig. 282 Same case shown in Fig. 279. (A) A loss of myelin in the hilum of the inferior olives and in the white matter of the cerebral hemispheres, with sparing of the dentate nuclei and the brachium conjunctivum. Heidenhain–Wölcke stain. (B) Gliosis of the olives and the cerebellar white matter. Holzer stain.

as fat droplets in acute cases. In later stages a remarkable number of astrocytic cells is found beside the fibrillary gliosis, suggestive of a continuous proliferation of these cells. Microglial proliferation also appears to be excessive for the very slow and limited tissue disintegration.

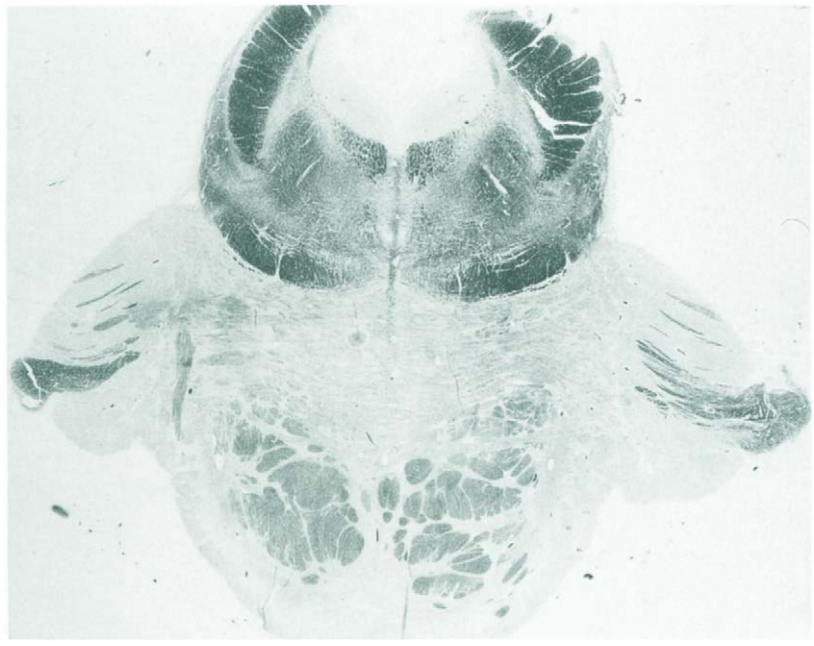


Fig. 283 Olivopontocerebellar atrophy. Atrophy of the basis pontis and the middle cerebellar peduncles.

The density of α_2-receptors and β-adrenoreceptors is reduced in the cerebellar cortex of the OPCA cases (Figols *et al.*, 1993). By contrast, the density of β-receptors in the cerebellar white matter is clearly increased, probably due to the subcortical reactive gliosis.

Intracytoplasmic argyrophilic inclusions have been found in both neurons (Kato and Nakamura, 1990) and oligodendrocytes (Papp *et al.*, 1989), and this was subsequently confirmed by several authors (Nakazato *et al.*, 1990; Kato *et al.*, 1991; Abe *et al.*, 1992; Arai *et al.*, 1992c; Horoupian, 1992; Kobayashi *et al.*, 1992; Mochizuki *et al.*, 1992; Papp and Lantos, 1992, 1994; Costa and Duyckaerts, 1993). The "atypical Pick bodies" of Horoupian and Dickson (1991) probably represent similar inclusions. Neuronal inclusions tend to be scanty and are found most commonly in surviving cells of the nuclei pontis. Oligodendroglial inclusions, on the other hand, are numerous and widespread in the entire motor system: pyramidal, extrapyramidal, and cerebellar (Papp and Lantos, 1994). Although they are morphologically similar, the neuronal and oligodendroglial inclusions differ antigenically. The neuronal inclusions are ubiquitinated (Kato *et al.*, 1991), but do not react with any antibodies to cytoskeletal elements. By contrast, oligodendroglial inclusions react with antibodies to α- and β-tubulin and τ (Nakazato *et al.*, 1990), as well as to *MAP5* (Arai *et al.*, 1992b). In addition, Kobayashi *et al.* (1992) obtained a reaction with an antibody to paired helical filaments. All inclusions are ubiquitinated.

Both the neuronal and oligodendroglial inclusions are ultrastructurally similar. They consist of filaments with a circular profile, 20–30 nm (Nakazato *et al.*, 1990; Papp and

Lantos, 1992) or 24–40 nm (Kato *et al.*, 1991) in diameter. They are coated with a finely granular electron-dense material that confers a fuzzy appearance to the fibers, both in longitudinal and transverse sections.

Pathogenesis Of the five types of genetic OPCA identified by Königsmark and Weiner (1970), four are inherited as autosomal dominants and one (type II), as an autosomal recessive. While the latter is evidently genetically different, doubts may be expressed as to whether the dominant types represent distinct genetic entities or the different phenotypic expression of one or more genes. Linkage studies in several phenotypically different families have placed the gene locus on chromosome 6 ("the 6p OPCAs"). Yakura *et al.* (1974) were the first to suggest a linkage of hereditary ataxias with the HLA gene on chromosome 6. Subsequent studies have confirmed this linkage (Jackson *et al.*, 1977; Haines *et al.*, 1984). The ataxia locus was identified in a large dominant OPCA family at 12-cM distance from the HLA complex with a lod score of 3.15 (Jackson *et al.*, 1977).

Various biochemical abnormalities have been discovered in genetic OPCA. Perry *et al.* (1977) reported an aspartate–taurine imbalance in dominantly inherited OPCA. In a further study Perry (1984) identified four different patterns of imbalance in four families. These are type I, reductions in aspartate, glutamate, and GABA with an increase in taurine in the cerebellar cortex; type II, similar reductions in aspartate, glutamate, and GABA with normal taurine; type III, reductions in aspartate and glutamate with normal taurine and GABA in the cerebellar cortex and a slight reduction in GABA in the dentate nucleus; and type IV, severe reductions in aspartate and glutamate in the cortex with a severe reduction in GABA in the dentate nucleus (Bebin *et al.*, 1990). The levels of other neurotransmitters may also be affected. Kish *et al.* (1992a) studied the level of monoamines in the striatum of end-stage cases of dominant OPCA and found a variable loss of dopamine, while serotonin was normal and its metabolite, 5-hydroxylindoleacetic acid, was increased. In another study Kish *et al.* (1992b) found similar changes in the levels of serotonin and 5-hydroxyindoleacetic acid in the cerebellar cortex. Kish *et al.* (1991a) demonstrated increased catabolism of the excitotoxin quinolinic acid (QA) in the cerebellar cortex. Of the two enzymes involved in the breakdown of QA, phosphoribosyltransferase was markedly increased, while 3-hydroxyanthranilate oxygenase was normal.

The neurotransmitter receptors were studied in two cases of OPCA by Albin *et al.* (1990). Benzodiazepine and GABA receptors were decreased in the granule cells and molecular layers, *N*-methyl-D-aspartate (NMDA) were depleted in the granule cell layer, while quisqualate receptors and non-NMDA/non-QA glutamate binding sites were depleted in the molecular layer. On the other hand, GABA, benzodiazepine, and metabotropic binding sites are increased in the dentate nuclei (Price *et al.*, 1993). Other abnormalities include disturbances in phospholipid metabolism (Nitsch *et al.*, 1993), elevated stimulatory and reduced inhibitory G proteins (guanine nucleotide-binding proteins) in the cerebellar cortex (Kish *et al.*, 1993a), reduced levels of somatostatin-like activity in the cerebral cortex with increased activity in the striatum (Kish *et al.*, 1993b), and decreased activity of the thiamine pyrophosphate-dependent α-ketoglutaric dehydrogenase complex (Mastrogiacomo and Kish, 1994). The course of the patient reported on by Kageyama *et al.* (1991) suggests that mitochondrial disease could underlie some cases of OPCA.

A deficiency of glutamate dehydrogenase in leukocytes, originally described in a subgroup of autosomal-recessive OPCA (Huang and Plaitakis, 1984), has been found to be nonspecific, as it also occurs in some dominant and sporadic cases (Kaakkola *et al.*, 1990a, b).

The significance of all of these findings is debatable. While some may be involved in the pathogenetic mechanism, others may simply be an expression of neuronal loss (Harding, 1986).

Most cases of sporadic OPCA are a part of multiple system atrophy consisting of the triad OPCA, striatonigral degeneration, and Shy–Drager syndrome, with one or the other component predominating. Even in clinically "pure" cases, minor lesions are present in other sites. The link between the components is further reinforced by the presence of oligodendroglial, and, to a lesser extent, neuronal, argyrophilic inclusions, present in all manifestations of the syndrome and absent in normal and pathological controls. While their significance in the pathogenesis remains obscure, they form a useful hallmark of the disease (Costa and Duyckaerts, 1993; Papp and Lantos, 1994).

Infantile Olivopontoneocerebellar Atrophy (Carbohydrate-Deficient Glycoprotein Syndrome Type I)

While most forms of OPCA, both genetic and sporadic, manifest themselves in adulthood, a severe variant of the syndrome occurring in early infancy has been described in several families (Agamanolis, 1986; Harding et al., 1988; Horslen et al., 1991; Strømme et al., 1991; Chang et al., 1993), and in several others [reviewed by Jaeken and Carchon (1993)] it has been demonstrated that this condition was a manifestation of the carbohydrate-deficient glycoprotein syndrome (see p. 80). However, the variously reported cases differ clinically, in their inheritance, and in their associated lesions, indicating that this is a heterogeneous group of disorders (Albrecht et al., 1993).

Clinical Picture From the neonatal period through early and late infancy, the predominant symptoms are failure to thrive, floppiness, growth retardation, severe development delay, and, in not a few cases, alarming episodic failure of multiple organ systems: liver insufficiency, pericardial effusions, heart tamponade, and stuporous states and/or strokelike attacks. There is also mild to moderate hepatomegaly at this early stage and all patients have elevated transaminase levels (Peterson *et al.*, 1993). In the preschool and school stage mental and motor impairments are the predominant clinical manifestations, while the previous internal organ symptomatology gradually fades away. The neurology of the patients becomes dominated by signs of ataxia and dysequilibrium. The neurological manifestations evolve toward a dominant and quite severe weakness and atrophy of a lower motor neuron type affecting both legs, combined with cerebellar ataxia and coordination difficulties. RP may be present. In the puberty and adulthood stage the patients show progeria and hypogonadism. Cerebellar atrophy of the olivopontocerebellar type is found on CT in the majority of the patients (Jaeken *et al.*, 1991). Most patients die before the age of 6 years.

Pathology Hepatic portal fibrosis, hepatomegaly, and steatosis are present early in the course of the disease, progressing to a cirrhosis-like pattern at a later stage (Chang

et al., 1993). Cystic dilatation of the distal renal tubules, pulmonary edema, and pericardial effusions can be observed.

Neuropathology *Gross appearances.* Brains were reduced in size and weight. The cerebellum in each case was very small and shrunken with prominent hard folia. The anterior vermis was most severely affected. The pons and the inferior olives were slightly smaller than normal.

Light microscopy. The cerebellar cortex is devastated. The loss of Purkinje and granule cells was especially accentuated in the cases with long-term survival. A few Purkinje cells remain, with abnormal dendritic expansions displaying "cacti" and "stellate bodies." A severe neuronal loss and gliosis in the nuclei pontis, virtual disappearance of the transverse pontine fibers, and an almost total neuronal loss in the olives with heavy gliosis are constant findings in cases with longer survival (Albrecht *et al.*, 1993). No neuronal or oligodendroglial inclusions have been demonstrated (Chang *et al.*, 1993). The retina is very thin and shows marked degeneration and loss of photoreceptors and their cell nuclei in the outer nuclear layer.

In the patients who died in the neonatal period or in early infancy, the pontine nuclei in the brain stem showed a moderate loss of neurons with gliosis. The inferior olives showed nerve cell loss in the rostral parts that are known to project onto the anterior vermis.

Electron microscopy. Densely packed membranous cytoplasmic body-like inclusions were seen in the expanded arborizations of the Purkinje dendrites in the case reported by Chang *et al.* (1993).

Pathogenesis The strange association of abnormalities in two very different glycoproteins, and the subsequent finding of pathological transferrin heterogeneity, led to the hypothesis of a defect in their common carbohydrate portion. This was confirmed by the demonstration of a partial deficiency of sialic acid as well as of galactose and *N*-acetylglucosamine in serum transferrin and total serum glycoproteins. Many other serum glycoproteins were found to be abnormal, probably due to the same carbohydrate defect (see p. 80).

Variants of Spinocerebellar Atrophies

Aside from the common spread of the degenerative process onto other systems, there are some isolated observations on unusual associations that belong to the group of OPCAs and may be separated from other multisystem atrophies.

Olivocerebellar Atrophy (Myoclonic Epilepsy of the Baltic Type; Progressive Degenerative Myoclonic Epilepsy)

Koskiniemi *et al.* (1974) described a syndrome of myoclonic epilepsy with histopathological findings of a system degeneration. In view of its geographic distribution, it was called the Baltic type of myoclonic epilepsy. A similar case, however, was first reported by Dimitri (1932).

Clinical Picture The disease manifests itself around the age of 10 years, most commonly with myoclonus, followed after some years by epileptic seizures. Only in the case documented by Dimitri (1932) did epilepsy precede the myoclonus. Mental changes are less pronounced than in Lafora's disease (see p. 98). Some patients died before the age of 20 years (Dimitri 1932; Habib *et al.*, 1985); most others, after the age of 25 (Haltia *et al.*, 1969). Patients treated with phenylhydantoin died within a few years after the onset of symptoms. An autosomal-recessive inheritance could be demonstrated in most cases.

Neuropathology *Light microscopy.* The principal lesion is neuronal loss in the inferior olives, affecting predominantly the ventral and lateral cell bands (Habib *et al.*, 1985). In most cases this is associated with gliosis. The cerebellar changes range from a slight to a subtotal loss of Purkinje cells (Haltia *et al.*, 1969).

Cerebellar atrophy was absent in only one case. Additional lesions may include a slight neuronal loss in the dentate nucleus, thalamus, red nucleus, globus pallidus, and striatum (Haltia *et al.*, 1969). The lesions are symmetrical and affect the lateral cell groups.

Pathogenesis The topography of the lesions in the lateral parts of the inferior olives and the neocerebellum, which receives the climbing fibers as olivary afferents, points to the olives as the primary site of the system degeneration. This is in contrast with the Holmes type of spinocerebellar degeneration, in which cerebellar atrophy of the Purkinje cell type is the primary lesion (Habib *et al.*, 1985).

Atrophy of the Dentate Nucleus and the Brachium Conjunctivum

The involvement of the dentate nucleus and the superior cerebellar peduncle may occur in all forms of spinopontocerebellar atrophies as well as in atrophies of other systems as a secondary phenomenon (Fig. 284). On the other hand, an isolated primary atrophy of this nucleus and its efferent pathway is a rarity. The apparently "pure" case of Bostroem and Spatz (1928), presenting clinically with athetosis and epilepsy, was, nevertheless, associated with lesions in other parts of the brain. There was considerable shrinkage of the basis pontis, and upon reexamination of the case Vogt and Vogt (1942) found diffuse damage to the globus pallidus. Whether the case examined by Grinker (1944) was indeed pure remains uncertain, as no information is available on the spinal cord.

Olivopontocerebellar Atrophy with Tapetoretinal and Macular Degeneration

The first case of OPCA with amyotrophy and tapetoretinal degeneration, confirmed by autopsy, was that of Lelong et al. (1941). In spite of the absence of pontine atrophy, this case was included among the variants of OPCA. Other authors have confirmed this association in both familial and sporadic cases (François, 1974). The association of OPCA with pure macular degeneration is rare (Harada et al., 1984).

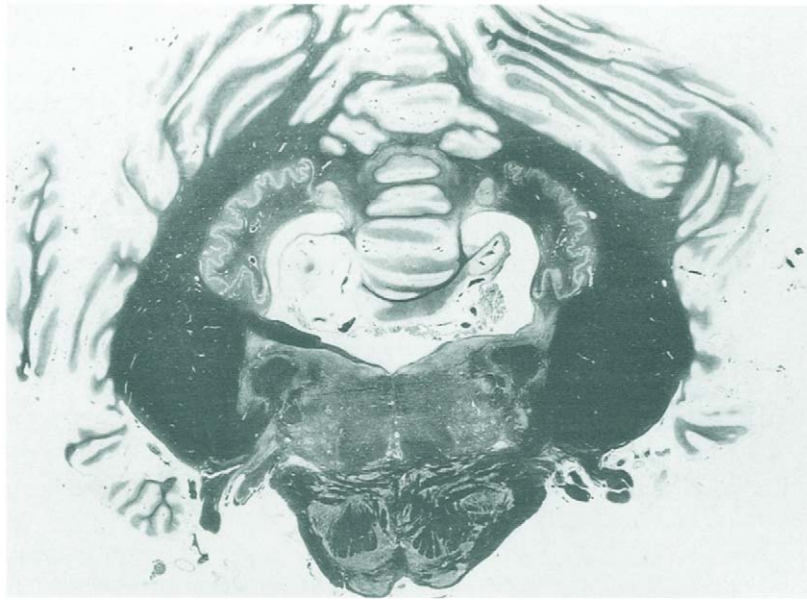


Fig. 284 Spinopontocerebellar atrophy with atrophy of the dentate nucleus and the brachium conjunctivum. Pallor of the myelin in the hilum and the fleece of the dentate nucleus.

Multisystem Atrophy and Related Conditions

The main group of spinocerebellar atrophies is formed by diseases affecting cerebellar connections with the basal ganglia, midbrain, and cranial nerve nuclei, with a considerable degree of variability, even among members of the same family. As reports of involvement of other systems in the degenerative process multiplied, Verhaart (1958) introduced the concept of "heterogeneous system degeneration," later replaced by the term *multisystem atrophy* (Graham and Oppenheimer, 1969).

In common present-day usage this term has been confined to the triad of striatonigral degeneration, OPCA, and Shy–Drager syndrome, each of which is presented in the appropriate section (see pp. 563, 588, and 668, respectively). This restriction has the advantage of conferring a specific meaning to the term, rather loosely used in the past. It does, however, exclude a number of "orphan" entities left outside the classification. We propose to cover them provisionally under the blanket term *disorders related to multiple system atrophy*, without implying any pathogenetic relationship. The allocation of syndromes to this group is arbitrary, as different authors would make a different selection.

The basic criterion in the definition of this concept is the involvement of systems that, physiologically, are not directly related to each other. This includes syndromes that cannot be allocated to any of the well-known clinical entities, as well as defined system atrophies in which the process encroaches on other systems. In chronic conditions secondary,

tertiary, and even quaternary transneuronal atrophies may account for the involvement of remote centers. In these situations it is important to try to identify the primary lesions. This may be of significance in elucidating the etiology and pathogenesis of several degenerative processes, which may be expected in the near future. Murayama *et al.* (1992) considered the oligodendroglial cytoplasmic inclusions (see p. 598) to be a common finding of multisystem atrophy. However, its presence has not yet been established in most of the conditions we deal with in this section.

At present we limit the concept of *multisystem atrophy* to conditions—some of which may not be sharply defined—whose main characteristic is the apparently synchronous involvement of several neuronal systems.

Infantile Multisystem Atrophies

In congenital multisystem atrophies among the diverse affected structures a pontoneocerebellar hypoplasia (see p. 575) is almost always present. Pathogenetically, a process is postulated, starting *in utero*, inherited as an autosomal-recessive trait, and operating in various stages of development.

Infantile multisystem atrophies are very rare diseases, classified into various morphological syndromes. Dentato-rubro-pallido-luysial atrophy has been described only once in early infancy (Bergmann *et al.*, 1990). In rare cases OPCA begins in early infancy with ataxia, myoclonus, and epileptic seizures. Infantile OPCA was implied, but not designated as such, by Norman and Urich in 1958. Retinal changes in infantile multisystem atrophies mostly corresponded to RP (Nishimura *et al.*, 1987). Boylan *et al.* reported a childhood-onset system degeneration with features of progressive supranuclear palsy in three siblings. Bergmann *et al.* (1993) reported a case of infantile multisystem atrophy with probably autosomal-recessive inheritance. Neuropathological examination showed degeneration of the cerebellum, inferior olives, medial thalamus, Clarke's nucleus, anterior horn cells, corticospinal and spinocerebellar tracts, and posterior columns. Immunohistochemically, many neurons contained intranuclear and intracytoplasmic ubiquitin-positive inclusions.

Progressive Supranuclear Palsy (Steele–Richardson–Olszewski Syndrome; Oculofacial Dystonia; Subcortical Argyrophilic Dystrophy; Subcortical Alzheimer's Syndrome)

The first case of this condition was reported by Chavany *et al.* (1951) as an atypical variant of PD. The condition was defined by Steele *et al.* (1964) as an independent entity.

Clinical Picture The condition affects predominantly, but not exclusively, males, mainly in the age group between 50 and 70 years. The main symptoms are progressive paralysis of the vertical gaze, equally affecting upgaze and downgaze (Friedman *et al.*, 1992), dysarthria, and a parkinsonian syndrome with rigidity affecting predominantly the neck muscles. Mild dementia is frequently present and may precede the onset of ocular manifestations (Kleinschmmidt-De Masters, 1986). The combination of severely slowed information processing and marked executive dysfunction are characteristic of progres-

sive supranuclear palsy (Litvan, 1994). The auditory startle response is reduced or absent (Rothwell *et al.*, 1994). In the early stages diagnostic problems are often due to the variable clinical presentation and in those atypical cases in which gaze palsy does not develop (Tolosa *et al.*, 1994). Autonomic dysfunction can also be a feature of progressive supranuclear palsy (Gert Van Dijk *et al.*, 1991). Neuroimaging studies show characteristic anatomical alterations only late in the disease course (Duvoisin, 1994). Definite atrophy of the midbrain and of the region around the third ventricle is seen in slightly more than half of the cases (Savoiardo *et al.*, 1994). Death occurs 5–6 years after the onset of symptoms.

Neuropathology Lantos (1994) suggested a new classification into typical cases, which conform to the original definition; atypical ones, in which either the distribution or the intensity differs from that of typical cases; and combined cases, in which lesions of other degenerative (Gearing *et al.*, 1994) or vascular diseases are present (Dubinsky and Jankovic, 1987).

Gross appearances. The brain is moderately atrophic, particularly in the region of the basal ganglia. The substantia nigra is poorly pigmented or totally depigmented. The red nuclei, superior colliculi, and pontine tegmentum are discolored a grayish brown (Fig. 285) and are severely atrophic (Fig. 286A,B).

Light microscopy. Moderate to severe neuronal loss is apparent in the globus pallidus, subthalamic and red nuclei, substantia nigra, tectum, and dentate nucleus with accompa-

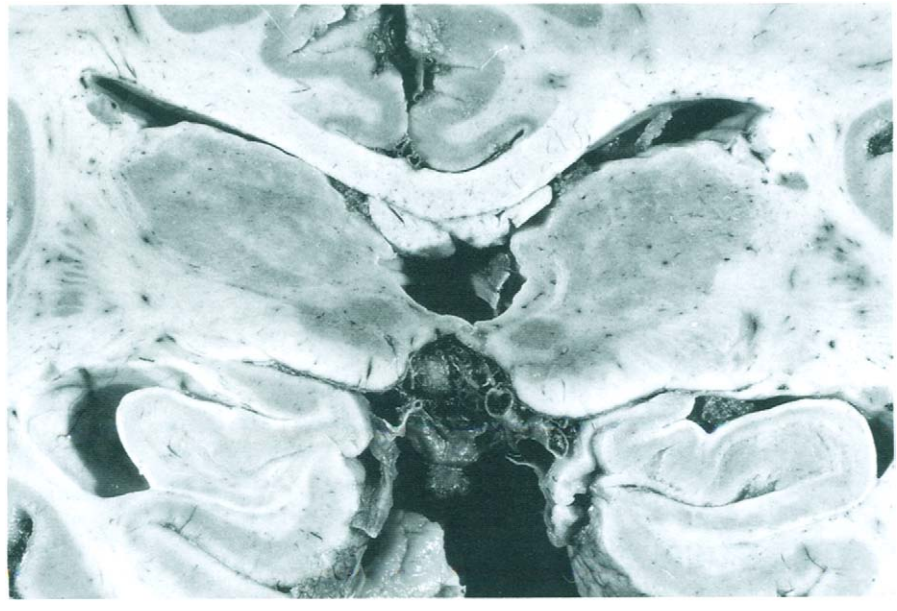


Fig. 285 Steele–Richardson–Olszewski syndrome. Moderate cerebral atrophy with brownish discoloration of the red and subthalamic nuclei.

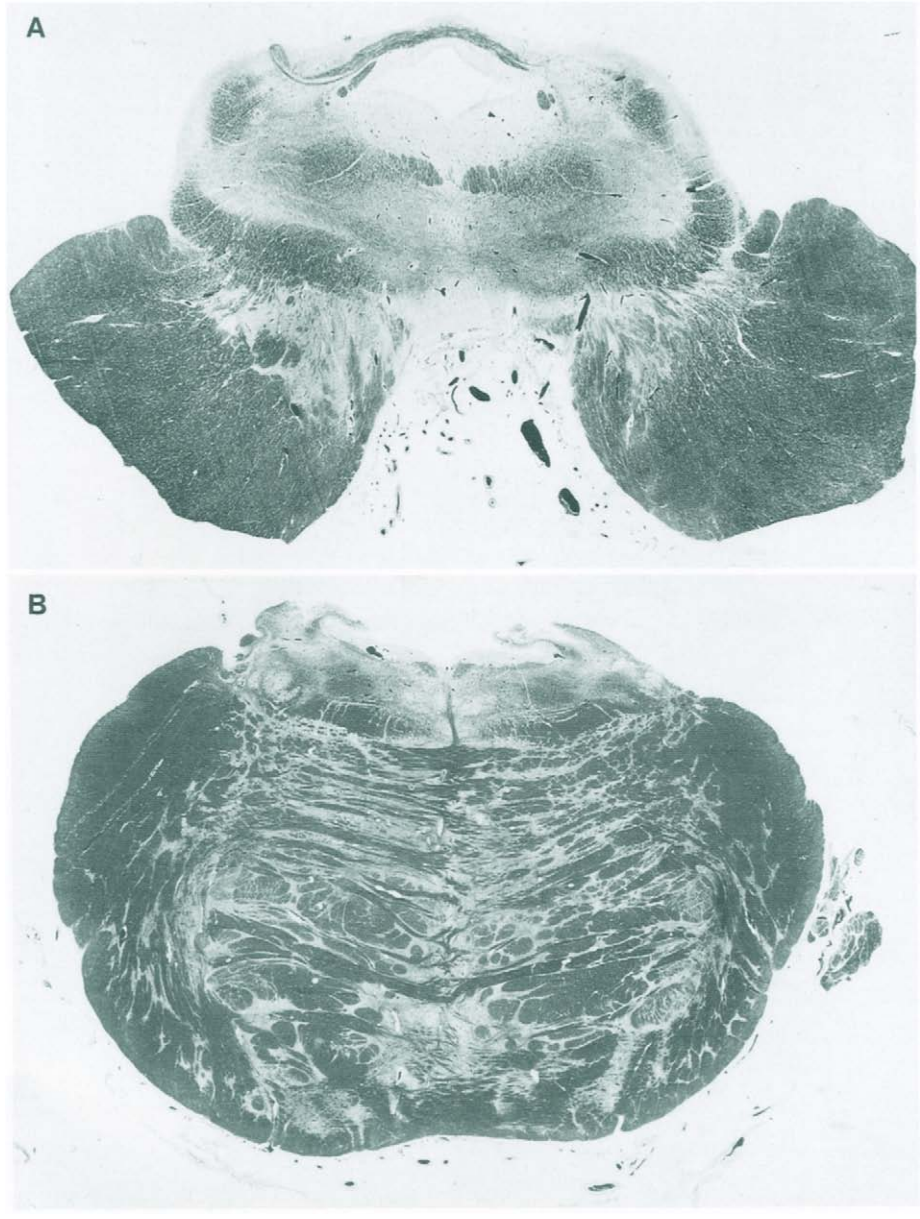


Fig. 286 Same case shown in Fig. 285. (A) The tectum and (B) the pontine tegmentum are severely atrophic. Heidenhain–Wölcke stain.

nying fibrillary gliosis, which extends onto the corresponding fiber tracts. Some of the surviving neurons show simple pigmentary atrophy. A 52% loss of neurons was discovered in the basal nucleus (Tagliavini *et al.*, 1984). Occasional involvement of the oculomotor nuclei and the anterior horns of the spinal cord has been reported. NFTs ("globoid" tangles) are found in the nuclei of the III, IV, V, VI, VII, and XII cranial nerves (Kleinschmidt-De Masters, 1989). NFTs are also present in the cerebral cortex without or with SPs (Hauw *et al.*, 1990; Hof *et al.*, 1992), in the anterior and lateral horns of the spinal cord (Kato *et al.*, 1986), and in the spinal dorsal root ganglia (Nishimura *et al.*, 1993). With a few exceptions (Ishino *et al.*, 1987), tangles are sparse or absent in Ammon's horn. The NFTs are basophilic and argyrophilic (Fig. 287A–C) and generally Congo red negative.

It has been generally accepted that "senile plaques" were not present in the cerebral cortex. However, many SPs in the cerebral cortex and even, to a lesser extent, in the cerebellar cortex of the same patients have been observed by Sasaki *et al.* (1991). Takeuchi *et al.* (1992) found widespread cerebral lesions, consisting of nerve cell loss and NFTs in the frontal, parietal, and occipital cortices and demyelination and gliosis in the frontal, parietal, and occipital subcortical white matter, in addition to the typical pathological findings of progressive supranuclear palsy.

Differences in the molecular composition of progressive supranuclear palsy and AD were highlighted by immunochemical studies (Cruz-Sanchez, 1994). In the former τ accumulated heavily in a set of sites different from those of age-matched controls and patients with AD (Shin *et al.*, 1991). Abnormal τ-proteins can be detected in all cortical areas (Vermersch *et al.*, 1994). GVD was seen in several subcortical neurons (Tomonaga, 1977); grumous degeneration, in the nucleus dentatus (Mizusawa *et al.*, 1989). Neuronophagia is commonly present (Fig. 288). The amorphous material surrounding swollen or normal neurons is strongly positive for neurofilament subunits (Cruz-Sanchez *et al.*, 1992b).

A reduction in dopamine receptors was demonstrated both in postmortem material and *in vivo* by PET (Baron *et al.*, 1986). A reduction in choline acetyltransferase was found both in the substantia innominata and in the frontal cortex and a loss of cholinergic neurons was seen in the pontine reticular formation (Malessa *et al.*, 1991).

Electron microscopy. The NFTs here differ from those of AD. They consist predominantly of straight filaments, 15 nm in diameter (Fig. 289). They can also be observed in the cortex (Fig. 290). Under light microscopy they are seldom detected (Takahashi *et al.*, 1989). Occasional helical filaments, 10 to 12 nm in diameter with a periodicity ranging from 150 to 300 nm (Fig. 291), also differ from the paired helical filaments of AD (Ghatak *et al.*, 1980; Yamamoto *et al.*, 1990). In spite of these ultrastructural differences, the neurofibrils share immunohistochemical characteristics with those of AD.

A correlation has been found between the degree of neuronal loss and the presence of NFTs (Cervós-Navarro and Schumacher, 1994).

Pathogenesis The hypothesis that progressive supranuclear palsy is linked to an environmental toxin is supported by cases in which this condition is associated with the use of organic solvents (McCrank and Rabheru, 1989). The relatively high frequency of a multiinfarct state in patients with clinically diagnosed progressive supranuclear palsy (Dubin-

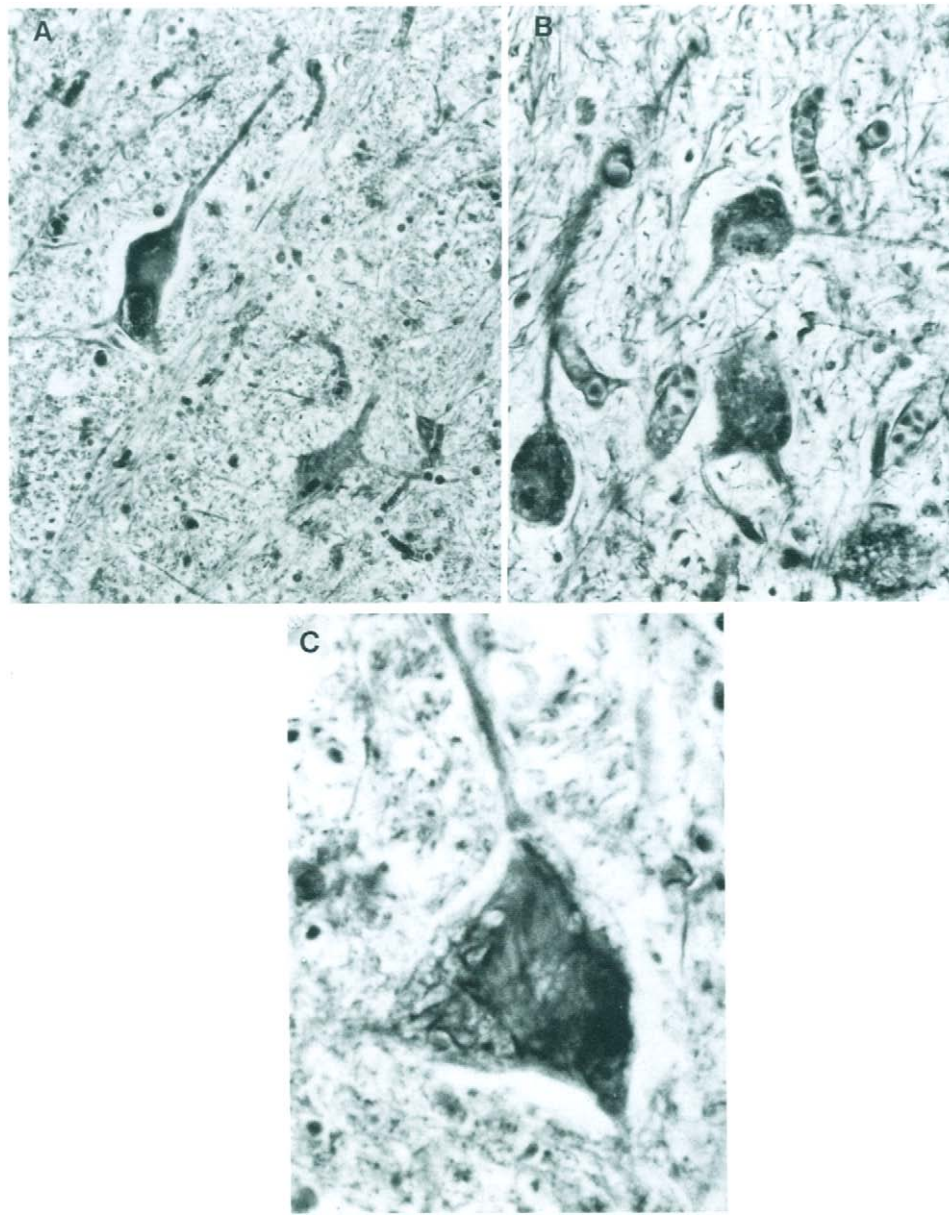


Fig. 287 Same case shown in Fig. 285. Neurofibrillary tangles in (A) the oculomotor nucleus, (B) the hypoglossal nucleus, and (C) the anterior horn of the spinal cord. von Braunmühl stain, (A) ×300, (B) ×450, and (C) ×800.

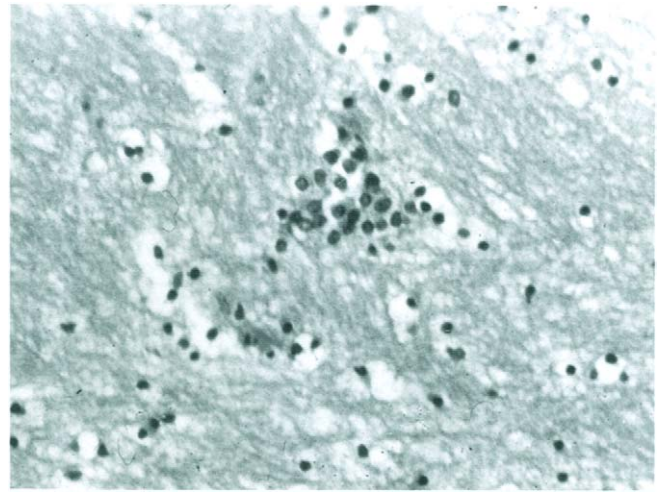


Fig. 288 Same case shown in Fig. 285. Neuronophagia in the hypoglossal nucleus. Hematoxylin–eosin stain, ×300.

sky, 1987; Moses and Zee, 1987; Tanner, 1987) suggests that a subtype of this disease may be due to vascular causes (Winikates and Jankovic, 1994). Juncos *et al.* (1991) found a significant decrease in the number of neurons with detectable immunoreactivity for choline acetyltransferase in the nucleus of Edinger–Westphal (69%), the rostral interstitial nucleus of the medial longitudinal fasciculus (97%), and the interstitial nucleus of Cajal (78%). They concluded that there is a regionally selective destruction of cholinergic neurons.

Dentato-rubro-pallido-luysial Atrophy (Hereditary Dentato-rubro-pallido-luysial Atrophy)

The first reported case of this disease appears to be that of the atrophy of the dentate nucleus and the brachium conjunctivum of Bostroem and Spatz (1928), in which diffuse neuronal loss in the globus pallidus and the substantia nigra was subsequently demonstrated by Vogt and Vogt (1942). The first full description of the syndrome is that by Titeca and Van Bogaert (1946). The pallido-dentato-rubral atrophy of Hunt (1917), in which myoclonus epilepsy was ascribed to cerebellofugal atrophy centered on the dentate nucleus, may also belong to this group.

Clinical Picture Iizuka *et al.* (1984) recognized three clinical forms of the disease: (1) one characterized by ataxia and choreoathetosis, corresponding to the classical descriptions: (2) a pseudo-Huntington form prevalent in Japan; and (3) a myoclonic–epileptic form described by Naito and Oyanagi (1982), Pfeiffer and McComb (1985), and Suzuki *et al.* (1985). Transitional forms are common, and the range of variation of the neurological disturbances is considerable.

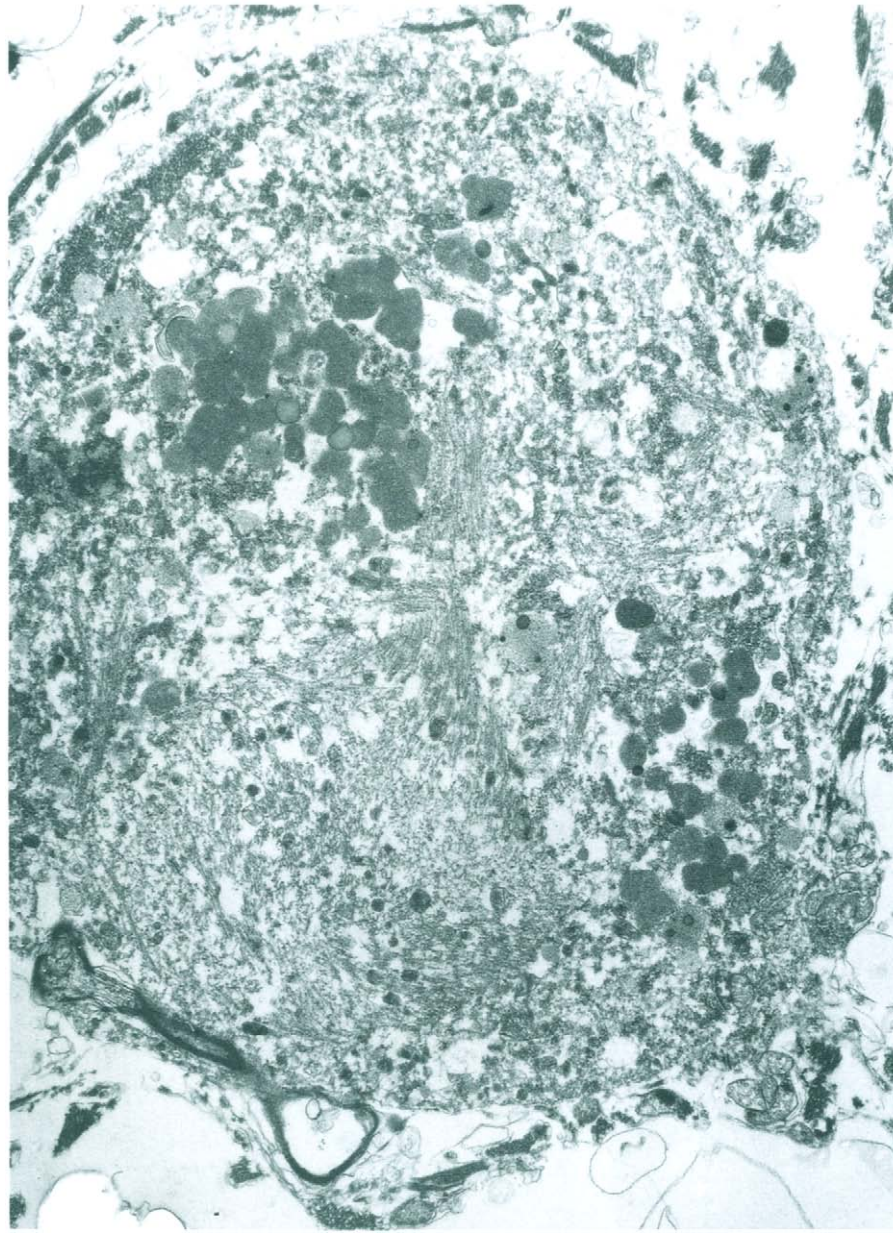


Fig. 289 Fine structure of a progressive supranuclear palsy type in neurofibrillary tangles (NFTs) in the inferior olivary nucleus. A periodic acid–Schiff-type NFT penetrates through the lipofuscin and other cell organelles. It consists of fine filamentous structures that run in a near-parallel fashion and form loose bundles. (Reproduced from Arima *et al.*, 1992.)

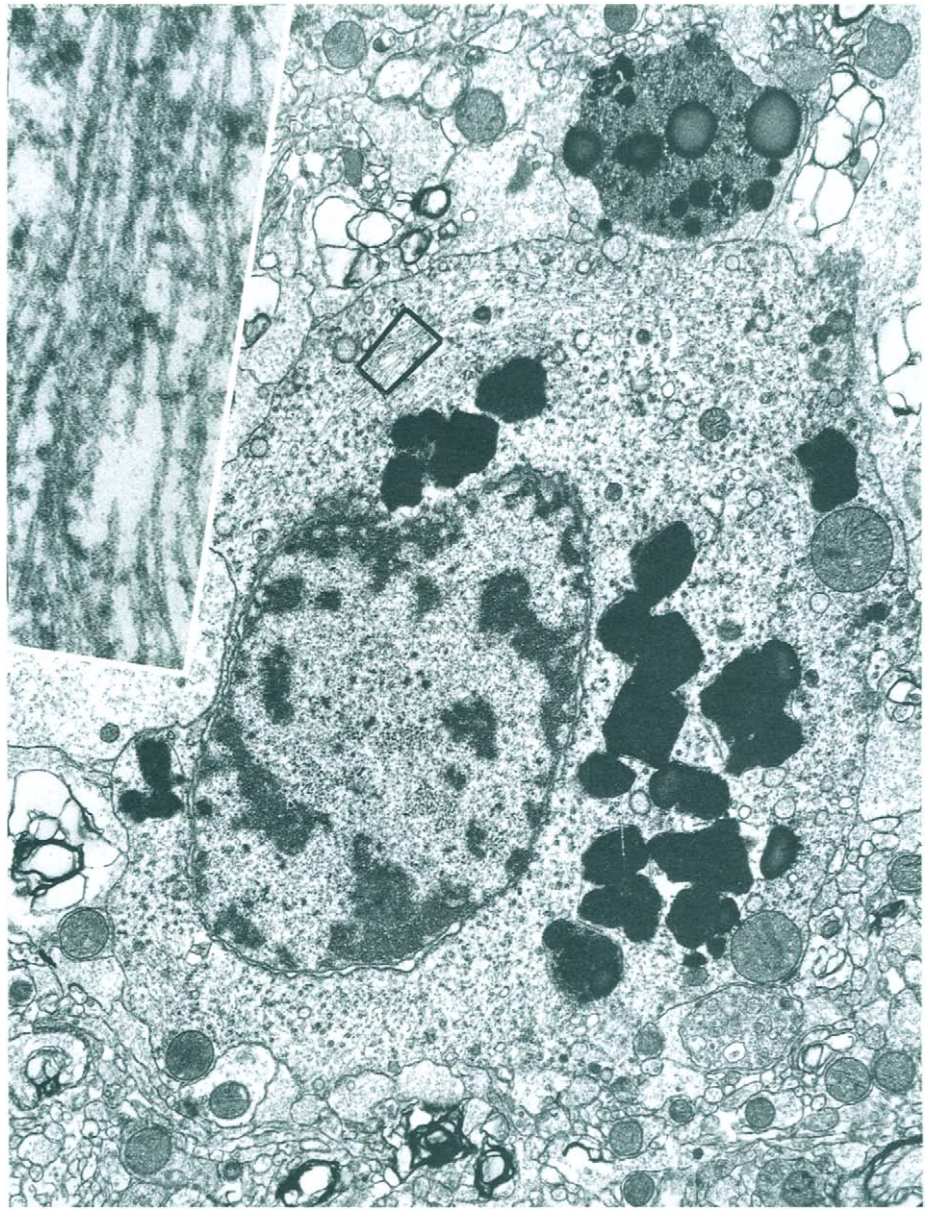


Fig. 290 Electron micrographs. Small neurons in the superior frontal gyrus, containing sparsely distributed abnormal filaments, ×33,000. (Inset) A higher-magnification view of the area shows 15-nm-wide straight tubules identical to those seen in the nucleus basalis of Meynert, ×100,000.

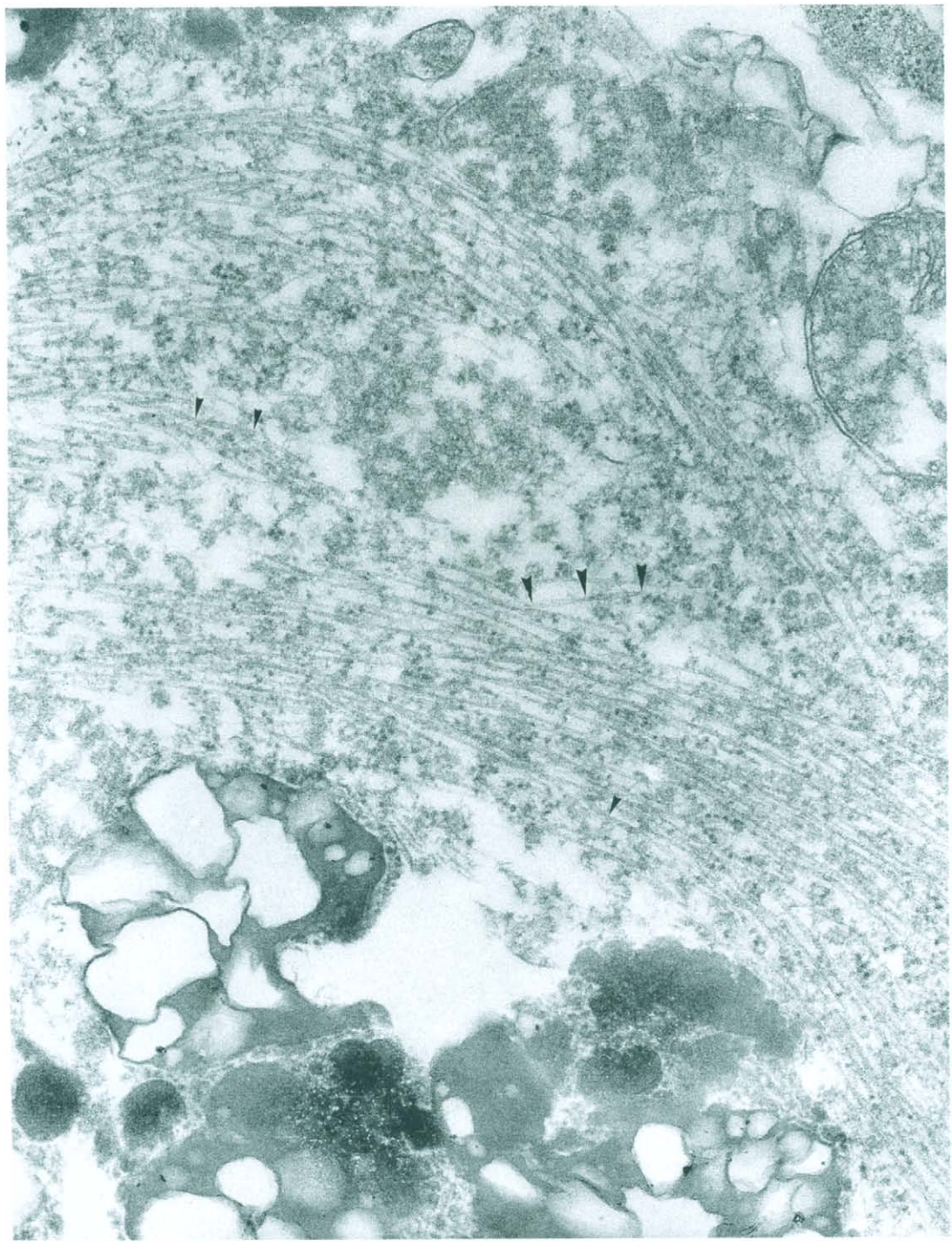


Fig. 291 A neurofibrillary tangle in a cerebellar dentate neuron, showing 15-nm straight tubules and a few twisted tubules with a long periodicity of about 200 nm (arrowheads). (Reproduced from Yamamoto *et al.*, 1992.)

In the ataxic–choreoathetotic form the disease generally presents in adulthood, or occasionally in adolescence, with cerebellar symptoms, followed 6–10 years later by hyperkinetic manifestations that may take the form of chorea. In the pseudo-Huntington form extrapyramidal disturbances and dementia are the main symptoms. In this and the myoclonic–epileptic forms diffuse high-signal areas on T_2-weighted MRI are frequently observed in the cerebral white matter (Arai *et al.*, 1994). An absent auditory brain stem response has been reported in cases of presumptive dentato-rubro-pallido-luysial atrophy (Kaga *et al.*, 1990). In some cases mental changes may be slight and the chorea predominates. An early onset after birth in two siblings who died at 5 and 6 months of age, respectively, was discussed by Bergmann *et al.* (1990). The myoclonic–epileptic form is familial, the inheritance being autosomal dominant.

Neuropathology *Gross appearances.* Atrophy of the dentate nucleus, of variable severity, is present in all cases, in addition to atrophy of the external nucleus of the globus pallidus and the pontine tegmentum. The atrophic areas show a brownish discoloration.

Light microscopy. Neuronal loss is always severe in the dentate nucleus and the globus pallidus and frequently also in the subthalamic nucleus, but less pronounced in the red nucleus. The Purkinje cells are only minimally affected in most cases. The inferior olives, superior colliculi, and thalamus are involved occasionally (Martin, 1970). Neuronal changes are rare in the cerebral cortex. Axonal degeneration and a loss of myelin are seen in the hilum of the dentate nucleus, the superior cerebellar peduncle, and the ansa lenticularis. All affected nuclei and fiber tracts show a reactive gliosis. The enzymes related to catecholamine and GABA metabolism show a different pattern of abnormality from that seen in OPCA (Iizuka and Hirayama, 1986). A degeneration of the pallidonigral system, as well as of the substantia reticularis, has been reported.

Dyssynergia Cerebellaris Myoclonica (Malignant Familial Myoclonus; Ramsay Hunt Syndrome)

The clinical picture of this disorder, associated with Friedreich's ataxia, was described by Hunt (1921). Several authors have cast doubt on its identity as a nosological entity, while others recognize it only as a clinical syndrome. One of Hunt's patients turned out instead to have Wilson's disease, and only one case with tremor and cerebellar symptoms was confirmed neuropathologically. The clinical syndrome is often a manifestation of ceroid lipofuscinosis.

Some authors consider the syndrome synonymous with MERRF (see p. 54) (Berkovic *et al.*, 1987). However, Roger *et al.* (1982) considered the two syndromes to be separate entities. Kobayashi *et al.* (1994) excluded in their case the presence of RRFs as well as Lafora's bodies and stressed its degenerative character.

Clinical Picture Myoclonus is the predominant symptom. Others include epilepsy and disturbances of gait and deep sensation. In some families epilepsy was absent, and the clinical picture was defined as "familial myoclonus with ataxia." Kobayashi *et al.* (1994) reported a progressive intellectual decline. Its connection with the "dyssynergia cerebellaris progressiva" of Hunt (1914) is uncertain.

Neuropathology The degeneration of the dentate nucleus and the brachium conjunctivum described by Hunt (1921) as the principal lesion has been confirmed in several neuropathologically examined cases (Kobayashi *et al.*, 1994). The degenerative changes encroached, in all of these cases, on other parts of the cerebrum and the cerebellum, including the thalamus (Martin, 1970) as well as the brain stem and the spinal cord. The cerebral cortex was also involved in some cases. The atrophy of the affected nuclei and the degeneration of the fiber tracts were accompanied by gliosis. In some clinically typical cases no lesions were found in the dentate nucleus. In one the lesions were confined to the posterior and, to a lesser extent, the lateral columns of the spinal cord. In the other two OPCA was found, with involvement of spinal fiber tracts.

Pathogenesis Combination of a grumous degeneration of the dentate nucleus with a clinical Ramsay Hunt syndrome was described in neurotoxic conditions. Doubt has been cast on the existence of an isolated atrophy of the dentate nucleus and on its relevance to the causation of myoclonus or other neurological symptoms, and in many cases detailed examination revealed involvement of other parts of the CNS. In some cases no lesions were found in the dentate nucleus. The possibility that a spinal myoclonus is responsible for the clinical picture (Silverskjöld, 1986) must be taken into consideration. The observation of therapeutic successes from oral administration of 5-hydroxytryptophan prompted the conclusion that a disturbance of serotonin metabolism may be a common pathogenetic factor.

Optico-cochleo-dentatal Degeneration (Dégénérescence Systematisée Optico-cochléo-dentelée)

Since the description of this syndrome by Nyssen and Van Bogaert (1933), barely a dozen further cases have been reported. This may be ascribed to the difficulty in making a clinical diagnosis as well as to inadequate neuropathological examinations (Ferrer *et al.*, 1987).

Clinical Picture The patient's age at onset of symptoms is variable and ranges from early infancy to late childhood. A considerable variation of the clinical manifestations may be present in some families. Nevertheless, the basic pattern consisting of blindness, deafness, and motor retardation is fairly constant. Other motor disturbances such as ataxia, tremor, spasticity, reduced reflexes, myoclonus, and choreoathetosis may also be present. Patients with disease of early onset may be mentally retarded, while those with a later onset may suffer from affective disorders. The course of the disease is slowly progressive and the patients survive up to the age of 30 years. All cases described to date have been familial and suggest an autosomal-recessive mode of inheritance.

Neuropathology *Gross appearances.* Both the cerebrum and the cerebellum are atrophic; in the latter the superior vermis is particularly affected. The optic nerves and chiasm are also atrophic, as a rule.

Light microscopy. A severe loss of neurons and gliosis are present in the dentate nucleus. The Purkinje and granule cells are somewhat rarefied, particularly in the rostral vermis (Ferrer *et al.*, 1987). The proximal segments of the Purkinje cell axons frequently

show ballooning (torpedoes). The hilum of the dentate nucleus and the brachium conjunctivum undergo degeneration with a loss of myelin and gliosis. SPs were found in the severely atrophic parts of the dentate nucleus in two children aged 4–7 years. The inferior olives show neuronal loss and gliosis in the dorsal cell band.

The optic nerves and chiasm show a severe loss of axons and the lateral geniculate bodies exhibit transneuronal atrophy, while the optic radiation and the visual cortex show only minor changes. Neuronal loss and gliosis are also seen in the dorsal and ventral cochlear nuclei and in the superior olives. Atrophy of the axons and a loss of myelin are found in the proximal parts of nerve VIII and in the lateral lemniscus. A loss of neurons, gliosis, and SPs are seen in the medial geniculate bodies and the inferior colliculi. Aside from the three principal systems, lesions may also be present in the medial lemniscus, pyramidal tracts, thalamus, and cerebral cortex (Martin, 1970), and occasionally also in the striatum. The loss of neurons and gliosis in the cerebral and cerebellar cortices and in the hippocampus (Ferrer *et al.*, 1987) were interpreted as postictal.

Electron microscopy. Donahue *et al.* (1967) found thickening and multiplication of the basement membranes in the cerebral capillaries.

Machado–Joseph Disease (Azorean Disease; Nigrospinodentatal Degeneration with Ophthalmoplegia)

Nakao *et al.* (1972) reported a progressive cerebellar ataxia and other neurological symptoms in several members of a family of Portuguese origin. Woods and Schaumburg (1972) published a report on several members of a Portuguese family who, aside from ataxia, had pyramidal and extrapyramidal symptoms. They defined the syndrome as a nigrospinodentatal degeneration with nuclear ophthalmoplegia. A third family was described as having autosomal-dominant striatonigral degeneration. Subsequently, the disease was also reported in families from Japan, India, China, Brazil, Australia, and Israel (Goldberg-Stern *et al.*, 1994). The eponymous designation is derived from the names of the first reported families.

Clinical Picture The striking feature of Machado–Joseph disease is that, in spite of the relatively monotonous pathological findings, there is considerable variability in the individual clinical expression, and thus this disease has been classified into many phenotypes (Rosenberg, 1992).

One form begins around the age of 25 years and is dominated by extrapyramidal and pyramidal signs (Woods and Schaumburg, 1972). Apnea and dyspnea in both awake and asleep states have been observed for a long period (Furuzono *et al.*, 1991). Japanese patients from different families developed sleep disturbances followed by delirium at the middle end stage (Fukutani *et al.*, 1993). An earlier variant, starting about the age of 8, was described by Coutinho *et al.* (1982). Another form, characterized by pyramidal and cerebellar disturbances, and occasionally also by parkinsonism (Teive *et al.*, 1991), appears between the ages of 35 and 50 years. A third form begins later, between 40 and 60 years, with ataxia, peripheral neuropathy, and symmetrical distal atrophy of the skeletal muscles. All forms are associated with progressive external ophthalmoplegia with

bulging eyes. On MRI the dorsolateral part of the putamen showed decreased signal intensity (Muramatsu *et al.*, 1990). Somatosensory evoked potentials revealed abnormal findings in all and an auditory brain stem response in only half of the patients (Kondo *et al.*, 1990). The activity of glutamate dehydrogenase in leukocytes has been found to be significantly decreased (Goncalves *et al.*, 1993). PET revealed reductions in the cerebral blood flow and the cerebral metabolic rate of oxygen not only in the cerebellum but also in the cerebral cortex, different from typical PET findings of spinocerebellar degeneration (Yamazaki *et al.*, 1992).

Variable phenotypes may appear in individual families, which are, however, expressions of a single genetic mutation (Rosenberg, 1992).

Pathology Neurogenic atrophy of the skeletal muscles, including the tongue, of variable severity, is found, as a rule (Coutinho *et al.*, 1982). Group atrophy is particularly prominent in the extraocular muscles.

Neuropathology *Gross appearances.* The main features are mild to severe atrophy of the basis pontis, brachium pontis, and dentate nucleus, as well as depigmentation of the substantia nigra. The dentate nucleus is often slightly discolored. Atrophy of the anterior spinal roots may also occur (Woods and Schaumburg, 1972).

Light microscopy. Nonspecific multisystem degenerations of the CNS spreading from the brain stem to the cerebellum and the spinal cord are the common neuropathological findings. A loss of neurons and gliosis are prominent in the subthalamic nuclei and particularly in the zona compacta of the substantia nigra (Fig. 292) as well as in the cranial nerve nuclei (Fig. 293A,B) and occasionally in the periaqueductal gray, but rarely in the putamen. In the Japanese type a marked neuronal loss is present in the oculomotor nucleus, with preservation of the Edinger–Westphal nucleus, demyelination, and cellular and fibrous gliosis in the pallidum, cranial and spinal motor nuclei, spinocerebellar tracts, and Clarke's column (Kogure *et al.*, 1990; Shimizu *et al.*, 1990). With increasing duration of the disease, the neuronal loss becomes severe in the pontine nucleus, hypoglossal nucleus, and anterior horn of the cervical cord. On the other hand, neuronal loss in the dentate nucleus and Clarke's column (Fig. 294) is severe irrespective of the duration of the disease (Tsuchiya *et al.*, 1994). The inferior olivary nuclei are normal, thus separating this disease from OPCA. Argyrophilic intracytoplasmic inclusions in the oligodendrocytes are also present (Abe *et al.*, 1992).

Ubiquitin-immunoreactive filamentous inclusions in the spinal anterior horn cells and the hypoglossal neurons, similar to the findings described in ALS, were present in a case documented by Suenaga *et al.* (1993).

There is a moderate loss of myelin in the posterior columns of the spinal cord and in the spinocerebellar tracts (Fig. 295) (Pou *et al.*, 1986). The pyramidal tracts show either no atrophy or mild atrophy in the lumbosacral segments. The spinal and gasserian ganglia show a loss of neurons and a proliferation of capsule cells (Coutinho *et al.*, 1982). A loss of myelinated fibers may be seen in the peripheral nerves (Fig. 296).

Pathogenesis Clinically, it is difficult to distinguish Machado–Joseph disease from other autosomal-dominantly inherited ataxias, and it was suggested that it may be caused

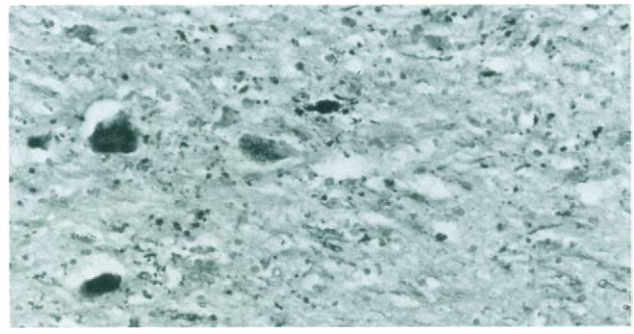


Fig. 292 Machado–Joseph disease. The substantia nigra, showing an extraneuronal accumulation of melanin and gliosis. Hematoxylin–eosin stain, ×160. (Reproduced from Pou *et al.*, 1986.)

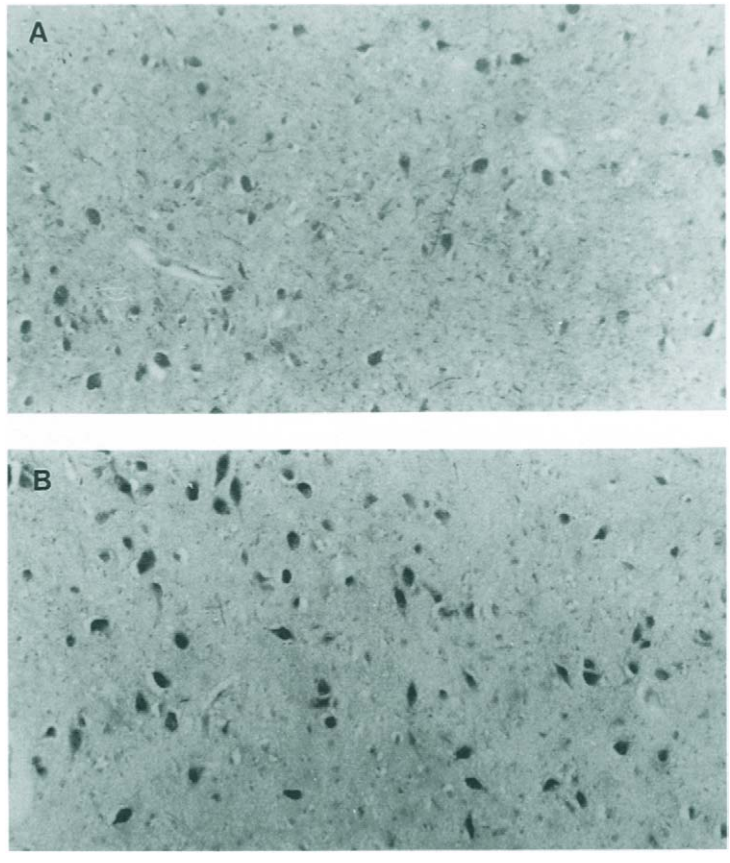


Fig. 293 Same case shown in Fig. 292. (A) A loss of neurons and mild gliosis in the oculomotor nucleus. (B) A normal control. Klüver–Barrera stain, ×63.

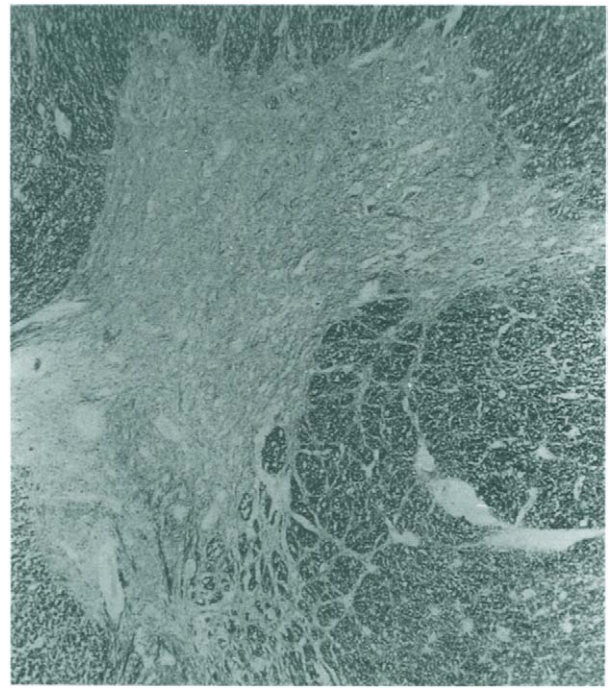


Fig. 294 Same case shown in Fig. 292. A severe loss of neurons in the anterior horn and Clarke's column. Klüver–Barrera stain, ×20.

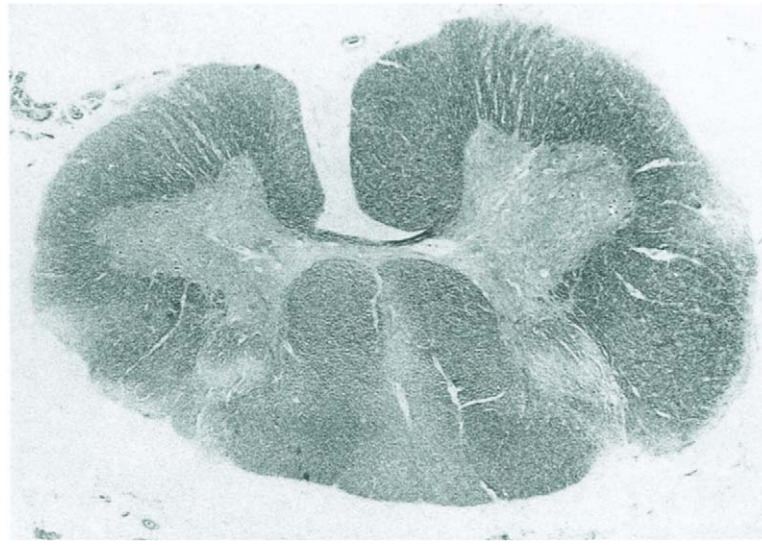


Fig. 295 Same case shown in Fig. 292. A moderate loss of myelinated fibers in the posterior columns and the spinocerebellar tracts. Klüver–Barrera stain.

Fig. 296 Same case shown in Fig. 292. Segmental demyelination and osmiophilic spheroids in a nerve root of the cauda equina. Osmium tetroxide stain, ×160.

by an allelic variant of spinocerebellar ataxia. Exclusion from the spinocerebellar ataxia locus on chromosome 6p and from the second locus for spinocerebellar ataxia on chromosome 12q demonstrated that both multisystem atrophies are genetically distinct, despite similarities in the disease phenotypes (Twist *et al.*, 1994).

Takiyama *et al.* (1993) mapped the gene for Machado–Joseph disease to the long arm of chromosome 14 (14q24.3–q32) in five pedigrees of Japanese descent. St. George-Hyslop *et al.* (1994) provided evidence that in patients of Azorean pedigrees mutations arose at the same locus.

Ataxia–Telangiectasia (Louis-Bar Syndrome)

This disease was described by Syllaba and Henner (1926) and independently by Louis-Bar (1941). Boder and Sedgwick (1958) defined it as a clinicopathological entity under the name *ataxia–telangiectasia*. Some authors considered the disease a phakomatosis; others, an immunodeficiency. Morphologically, it belongs to the spinocerebellar degenerations or the multisystem atrophies (Kwast and Ignatowicz, 1990). From a pathogenetic point of view, it should be included among the disorders of DNA repair.

Clinical Picture The disease is inherited as an autosomal-recessive trait and manifests itself in childhood, usually at the time when the children learn to walk. The children adapt themselves to their dysmetric gait, but the ataxia becomes incapacitating by the end of the first decade. Disturbances of speech and disorders of ocular movements appear at the same time. Choreoathetotic movements may be superimposed on the ataxia. Atrophy of the skeletal muscles with fasciculation resembling spinal muscular atrophy appears in patients with long-term survival. Mental retardation and spasticity are rare (Meshram *et al.*, 1986). On MRI cerebral white matter changes suggesting leukodystrophy have been reported (Chung *et al.*, 1994).

Telangiectases appear between the ages of 3 and 6 years, first in the conjunctivae and later spreading over the face, ears, and neck. They are particularly common in areas exposed to light or friction. Hypo- or hyperpigmentation, atrophy, and premature senescence appear later (Paterson and Smith, 1979). Cases with onset in adulthood have been reported (Serizawa *et al.*, 1994).

The patients show an abnormal sensitivity to radiation, a deficiency of IgA and occasionally also IgM, elevated serum α-fetoprotein levels, and an extreme resistance to insulin (Chung *et al.*, 1994). There is a high incidence of malignancy, particularly of leukemias and Hodgkin's disease. In all patients with multiple cancers, ataxia–telangiectasia should be considered in the differential diagnosis (Scott *et al.*, 1993b). Gliomas or medulloblastomas were observed in four of every 1000 patients. Recurrent infections, particularly of the respiratory tract, may lead to death in childhood, with malignancy presenting another common cause of death. Survival to the fourth (Boder, 1985) or fifth decade has been recorded, as well as early death before the age of 2 years (Tsukahara *et al.*, 1986).

Variants of the syndrome have also been described. Seemanova (1990) reported several cases presenting with microcephaly, normal intelligence, growth retardation, dysmorphic facies, immunodeficiency, and chromosomal instability. Fifty percent of the probands died of lymphoreticular malignancies in early childhood. There was also a significantly increased incidence of malignant tumors in heterozygote blood relatives. Cases resembling Louis-Bar syndrome but without telangiectasias and with atypical neurological symptoms were described by Lanzi *et al.* (1992).

Pathology The thymus is absent or underdeveloped, with absent Hassall's corpuscles. The lymphoid tissue is hypoplastic, with a loss of lymphoid follicles in the tonsils, lymph nodes, and spleen. The gonads, particularly the ovaries, are hypoplastic. Large cells with abnormal nuclei are seen in the anterior lobe of the pituitary. The telangiectasias in the skin and the conjunctivae consist of dilated and tortuous venules. They have also been found in the liver. Changes in the cytoskeleton were seen in fibroblast cultures (McKinnon and Burgoyne, 1985). Neurogenic atrophy is often found in the skeletal muscles (Agamanolis and Greenstein, 1979).

Neuropathology *Light microscopy.* A severe loss of Purkinje cells with empty baskets and some rarefaction of the granular layer are seen in the cerebellar cortex, particularly in patients who survived beyond the second or third decade. The surviving Purkinje cells may show abnormal orientation of their dendrites (Vinters *et al.*, 1985) as well as intracytoplasmic eosinophilic inclusions. Changes in the locus coeruleus, inferior olives, and dentate nuclei may also occur. A reduction in GABA concentration and GABA receptors was found in the cerebellar cortex, dentate nucleus, and inferior olives (Perry *et al.*, 1984). Aside from degenerative changes, neuronal inclusions of the Lewy body type were seen in the substantia nigra (Agamanolis and Greenstein, 1979). Two cortical tubers, resembling those of tuberous sclerosis, were described by Gotoff *et al.* (1967). Filamentous inclusions and axonal spheroids in the brain stem nuclei strongly reacted with monoclonal antibodies against neurofilament subunits (Monaco *et al.*, 1988). A loss of anterior horn cells, with chromatolysis or shrinkage of the surviving cells, is seen in the spinal cord. Axonal swellings are present in the anterior horns and the spinal nerve roots. Degeneration of the posterior columns with a loss of myelinated fibers and gliosis, particularly in the tracts of Goll, is seen in cases with long-term survival. In younger patients with a less pronounced loss of myelin, proliferation of microglia may be observed. Chromatolysis and a loss of neurons occur in the posterior root ganglia, where the satellite

cells contain large bizarre nuclei. A loss of large fibers, swelling of the paranodal myelin, and segmental demyelination have been observed on sural nerve biopsies (Barbieri *et al.*, 1986), in addition to storage material and bizarre nuclei in the Schwann cells (Malandrini *et al.*, 1990). Both sensory and motor nerves are affected (Kwast and Ignatowicz, 1990).

Telangiectasias are frequently present in the leptomeninges, particularly over the cerebellum (Thieffry *et al.*, 1966). Vascular malformations ranging from tortuosity to fully formed telangiectasias have been repeatedly observed in the white matter, thalamus, brain stem, cerebellum, and spinal cord (Agamanolis and Greenstein, 1979). The vascular lesions are surrounded by hemosiderin, tissue atrophy, and glial scars containing bizarre astrocytes with large hyperchromatic nuclei (Amromin *et al.*, 1979). Telangiectasias are also found in the posterior nerve roots.

Occasional perivascular inflammatory infiltrates have been described as a complication of intercurrent infections, such as pneumonia and otitis media.

Electron microscopy. Inclusions in the Schwann cells were seen on sural nerve biopsies (Barbieri *et al.*, 1986).

Pathogenesis The disease is inherited as an autosomal-recessive trait and the gene has been located on chromosome 11q22–23 (Taylor *et al.*, 1994). Its product appears to be involved directly or indirectly in some form of DNA recombination. It seems to be fairly widespread in the general population and may be responsible for the reduced tolerance to radiation in some cancer patients (Gatti *et al.*, 1991). Although there is a marked variation in disease findings, siblings were always similar. The heterogeneity seen seems at odds with the unilocus linkage of ataxia–telangiectasia (Woods and Taylor, 1992).

The impaired DNA repair is responsible for the increased sensitivity to ionizing radiation (Cornforth and Bredford, 1985; Cox *et al.*, 1986). The presence of bizarre nuclei in the Schwann cells and satellite cells of the dorsal root ganglia, and occasionally also in the astrocytes, suggests an accumulation of unrepaired DNA fragments and may be due to the same mechanism.

Animal Models The mouse mutant *wasted* was proposed as a model of ataxia–telangiectasia on the basis of neurological abnormalities, chromosomal aberrations, and early death. This model differs from the human disease in essential features, particularly immunological abnormalities (Kaiserlian *et al.*, 1986) and sensitivity to ultraviolet and γ-radiation (Inose *et al.*, 1986).

Sjögren–Larsson Syndrome

The first reported case of this syndrome was described by Pardo-Castello and Faz (1932) as "Little's disease with ichthyosis." Sjögren and Larsson (1957) published a detailed study of this syndrome, now known by their names.

Clinical Picture The principal features are ichthyosis, psychomotor retardation, and spasticity. The symptoms appear early, usually during the first few months after birth. The pyramidal disturbances progress slowly until puberty. The spastic quadriparesis is particularly pronounced in the legs, causing abnormalities of gait up to complete abasia. Hypo-

density of the white matter was seen on CT (Mulder *et al.*, 1987). Bony and dental dysplasias are common. Epileptic seizures are rare. In an adult form ichthyosis appears in the third decade and a slowly progressive paraparesis follows up to 10 years later (Bravaccio *et al.*, 1976). The mode of inheritance is autosomal recessive.

Pathology Skin biopsies show thickening of the keratinized epithelium, moderate acanthosis of the epidermis, thinning of the granular layer, and abnormalities in the sebaceous and sweat glands. Electron microscopically, abnormal lamellar or membranous inclusions are present in the cytoplasm of horny cells of the epidermis and in the spinous and granular cells (Ito *et al.*, 1991). These abnormalities may also be seen on biopsies of patients in whom the ichthyosis is not clinically apparent.

Neuropathology *Gross appearances.* Atrophy of the pons, olives, and cerebellum has been observed (Yamamoto *et al.*, 1971).

Light microscopy. A cortical neuronal loss with mild gliosis affected particularly Betz's cells. Dystrophic neurons were also present in the basal ganglia, and a severe decline in the dopaminergic system in the putamen has been demonstrated (Wester *et al.*, 1991). A loss of myelinated fibers was seen in the centrum ovale and the pyramidal, vestibulospinal, and cerebellar tracts. The cerebellum showed a loss of Purkinje cells with a patchy loss of granule cells. A peripheral neuropathy with hypoplasia of the axons and a proliferation of Schwann cells ("onion bulbs") was described by Origuchi *et al.* (1974).

Pathogenesis Rizzo and Craft (1991) found a disturbance of fatty alcohol oxidation due to defective activity of NAD oxidoreductase. However, patients with normal fatty alcohol metabolism have also been described (Scalais *et al.*, 1992).

Pallidonigroluysial Atrophy

Contamin *et al.* (1971) found neuronal loss in the globus pallidus, substantia nigra, and subthalamic nucleus in a patient aged 54 years with progressive akinesia and nuchal rigidity. Two additional cases in elderly patients were reported by Takahashi *et al.* (1977). An earlier onset of the disease was noted in cases associated with ALS (Gray *et al.*, 1985). A parkinsonian patient whose main clinical feature was akinesia showed neuropathological findings corresponding to pallidonigroluysial atrophy and progressive supranuclear palsy (Yamamoto *et al.*, 1991).

Neuropathology Kawai *et al.* (1993) reported, in three autopsy cases, severe astrogliosis and neuronal loss in the pallidum, Luys' body, and nigra. They found granular deposits of brown pigments in the neuropil, microglia, oligodendrocytes, and astrocytes in three such the nuclei and the striatum. The brown pigments proved histochemically to be iron. Bergmann *et al.* (1993) found a motoneuron loss at all spinal cord levels, with sparing of the nucleus of Onufrowicz and slight demyelination of the lateral tracts.

Pallidonigrospinal Degeneration

Serratrice *et al.* (1983) reported a case of a 64-year-old woman who, after 11 years of weakness, atrophy, and fasciculation in the lower limbs, developed tremor, akinesia, and

rigidity. Autopsy revealed a loss of nerve cells in the anterior horns, globus pallidus, and substantia nigra. The pyramidal tracts were intact.

Pyramido-thalamo-spinocerebellar Degeneration with Leukodystrophy

Poser *et al.* (1957) reported two cases of an atypical cerebellar degeneration with leukodystrophy in one family. Martin *et al.* (1974) described the same syndrome in another family.

Clinical Picture The disease manifests itself in early childhood with prominent bilateral pyramidal symptoms and slight cerebellar and extrapyramidal disturbances that progress slowly in the course of the disease. Optic atrophy and pseudobulbar symptoms develop later. Most patients die during the third decade.

Neuropathology *Gross appearances.* A variable degree of cerebral atrophy is associated with ventricular dilatation.

Light microscopy. Neuronal loss was constantly present in the thalamus, dentate nucleus, inferior olives, nuclei pontis, and vestibular nuclei. In patients who reached the age of 30 years, a loss of nerve cells was also present in the cerebellar cortex and in the anterior horns of the spinal cord. The optic, pyramidal, spinothalamic, and spinocerebellar tracts, as well as the posterior columns, showed a loss of myelin. Diffuse demyelination with astrocytic proliferation and isomorphic gliosis was present throughout the cerebral and the cerebellar white matter. The accumulation of lipofuscin in the astrocytes was considered nonspecific (Martin *et al.*, 1974).

Degeneration of the Reticular Substance (Dyshomeostasis of the Neuraxis)

Varela (1969) separated his observations on three cases with primary atrophy of the entire reticular substance from those in which a partial atrophy formed part of a complex multisystem atrophy or was a sequela of encephalitis lethargica. The characteristic feature was a global involvement of the reticular substance, although some other systems were also affected. The onset, clinical symptomatology, and course of the disease were different in the three patients, but common features included disturbances of sucking, hyperkinesia, mental deterioration, and a pyramido-cerebello-extrapyramidal syndrome.

Neuropathology Neuropathology revealed degeneration of the entire reticular substance and the reticulospinal tracts throughout the length of the spinal cord. The reticular components of the pons, medulla, and thalamus were affected as well as the pallidosubthalamic system.

Spinopontine Degeneration

Boller and Segarra (1969) described a family with progressive ataxia originating in adulthood, in whom the anatomopathological findings did not correspond to any known form of hereditary cerebellar ataxia. Another such family was reported by Taniguchi and Königsmark (1971).

Neuropathology A prominent neuronal loss was present in the basis pontis. The spinocerebellar tracts—and, less so, the posterior columns—showed a loss of myelin. The cerebellar cortex and the dentate nuclei were intact, or were minimally affected. All three pairs of cerebellar peduncles were atrophic and showed moderate gliosis. Some loss of nerve cells was also observed in the red and subthalamic nuclei.

Multisystem Atrophy with Intranuclear Hyaline Inclusions

Sung (1980) described a patient who developed a progressive neurological illness at the age of 3 years and died at the age of 21. At autopsy ubiquitous intranuclear inclusions were found in neurons of the CNS and the peripheral nervous system. The author called the condition "neuronal intranuclear inclusion disease." Similar cases had previously been reported by Janota (1979) as familial degeneration with Marinesco bodies. Michaud and Gilbert (1981) described an additional case with similar inclusions, but with a different clinical picture and distribution of affected neurons. They interpreted their case and those of Sung (1980) and Janota (1979) as different degenerative diseases sharing the common feature of intranuclear inclusions.

Clinical Picture The clinical features have been variable, although symptoms usually began in infancy or childhood and the course was progressively downhill (Ruszkiewicz *et al.*, 1994). Other reported cases also showed variable clinical features and distribution of lesions (Soffer, 1985).

Light microscopy. The intranuclear inclusions are found in nerve cells of all types. They may be found in the cerebral cortex, thalamus, substantia nigra, locus coeruleus, inferior olives, hypoglossal nucleus, anterior horn cells, and myenteric plexus (Funata *et al.*, 1990).

Their size is variable, up to 15 μm, and generally parallels the size of the affected neurons. Two or more inclusions may be present in a single nucleus. They are spherical and are surrounded by a halo. Occasionally, they may contain a dense core. They appear hyaline and eosinophilic in H&E stains. They are unstained by fat stains or by Congo red, cresyl violet, Masson's trichrome, PAS, Bodian, or Bielschowsky's method. Under ultraviolet light, between 470 and 530 nm, they emit a yellowish green autofluorescence.

Although the inclusions are principally present in neuronal nuclei, similar inclusions have been found in the glia, Schwann cells, and muscle, pituitary, and other tissues in some cases (Muñoz-Garcia and Ludwin, 1986).

Electron microscopy. The inclusions consist of irregularly arranged straight filaments, 8–9 nm in diameter, of an undetermined length. The inclusions composed of fibrils less than 15 nm in diameter were reported to show strong autofluorescence and to be restricted to neuronal nuclei (Sung, 1980; Michaud and Gilbert, 1991; Haltia *et al.*, 1984; Soffer, 1985; Garen *et al.*, 1986). If fibrils over 15 nm in diameter were present, the inclusions did not show autofluorescence and were present in both neurons and glial cells.

Predominantly Spinal Atrophies

The most common of these system atrophies is Friedreich's ataxia, which affects primarily the dorsal roots and the posterior columns, but may encroach on the medulla oblongata and the cerebellum, and is therefore often classified among the spinocerebellar degenerations. To this disease may be added rare variants, some of which are considered to be incomplete manifestations of Friedreich's ataxia.

Friedreich's Disease (Friedreich's Ataxia; Hereditary Spinal Ataxia; Pierre-Marie's Disease)

This disease was described by Friedreich (1863) as a degenerative disorder of the posterior columns, which may also involve the cerebellum and the medulla oblongata. The late clinical and morphological variant is sometimes referred to in the literature as Pierre-Marie's disease. Early-onset cerebellar ataxia with retained tendon reflexes, progressive myoclonic ataxia, ataxia with hypogonadism, and ataxia with deafness are not specific entities, and each of them probably includes different diseases (Filla *et al.*, 1992). Cases associated with OPCA, Roussy–Lévy syndrome, or Charcot–Marie–Tooth disease may be also considered to be separate entities.

Clinical Picture The disease begins in some patients in later childhood; in others, around the age of 20 years. In the former group the mode of inheritance is autosomal recessive; in the latter, dominant. De Michele *et al.* (1989) found no clinical or laboratory differences between Friedreich's disease patients with onset up to the age of 20 and those with a later onset. However, analysis of frequency distribution and intrafamilial variation of onset age suggested that the later-onset form may be either a genetically distinct entity or the effect of secondary modifying genes in some families. In both groups the first symptoms include a sensory ataxia, muscular hypotonia, areflexia, paresthesias, reduced vibration sense, and other modalities of deep sensation. Cerebellar ataxia, pyramidal

signs, disturbances of speech, dysmetria, and nystagmus appear later (Filla *et al.*, 1990). A relationship between central motor conduction abnormalities and disease duration and clinical impairment can be found in these patients (Lanzillo *et al.*, 1994). Kyphoscoliosis and pes cavus are common (Tynan *et al.*, 1992). These skeletal abnormalities may appear in members of families with Friedreich's disease free from neurological symptoms and are interpreted by some authors as *"formes frustes"* of the disease. Signs of cardiomyopathy are common. Significantly lower CSF thiamine levels than in controls have been reported (Pedraza and Botez, 1992). Acanthocytosis has been reported, as well as a corneal dystrophy (Der Kaloustian *et al.*, 1985). The course of the disease is chronic, with an average duration of 16 years. Some patients reach the age of 40 years. A mild dementia may appear in the terminal stages.

Pathology Cardiac hypertrophy is present in most cases (Brumback *et al.*, 1986). The hypertrophic muscle fibers are separated by a diffuse network of fibrous tissue. Focal scarring resembling microinfarcts may also be present. The individual muscle fibers show some blurring of striation and lipid infiltration. In some cases additional acute changes have been reported in the form of deeply eosinophilic homogenous fibers, granular necrotic fibers, and infiltrations by polymorphs and macrophages.

Neuropathology *Gross appearances.* The spinal cord is severely atrophic and of a firm consistency. The severity of the atrophy is such that it was ascribed to a primary developmental hypoplasia. The dorsal roots are atrophic, as is the degeneration of the posterior columns, particularly the tracts of Goll. On transverse sections a grayish yellow discoloration may be seen in the posterior and lateral, and occasionally also the anterior, columns, all of which are firm. Occasionally, atrophy of the cerebellum may be apparent, with widening of the sulci or lesions of OPCA. Slight thickening and opacity of the spinal leptomeninges may be present, particularly on the dorsal aspect of the cord, in addition to histological evidence of inflammation.

Light microscopy. Loss of myelinated fibers in the posterior columns is a constant feature (Fig. 297A–C). It is most pronounced in the tracts of Goll, which are always affected, most severely in the cervical segments. The involvement of the tracts of Burdach is variable and reflects the duration and severity of the ataxia in the upper limbs. Some fibers adjacent to the gray matter are preserved, particularly in the cornuradicular zone of Marie. Lissauer's zone is relatively spared, sometimes even intact. The myelinated fibers of Clarke's column are rarefied or totally lost. The neurons of Clarke's column are shrunken and hyperchromatic, and reduced in number or totally absent. The spinocerebellar tracts are atrophic, the dorsal more so than the ventral. Slight atrophy of the posterior horns as well as the nuclei of the posterior columns may be present. Both the crossed and uncrossed pyramidal tracts may be involved, particularly in their distal parts (Fig. 298).

Cerebral lesions vary from case to case. Neuronal loss with gliosis has frequently been observed in the floor of the fourth ventricle, particularly in the dorsal nucleus of the vagus, the tractus solitarius, and its nucleus. Involvement of the hypoglossal nucleus may be present. Both the vestibular and the auditory parts of the eighth nerve and its pathway may be involved. Urich *et al.* (1957) found extensive destruction of

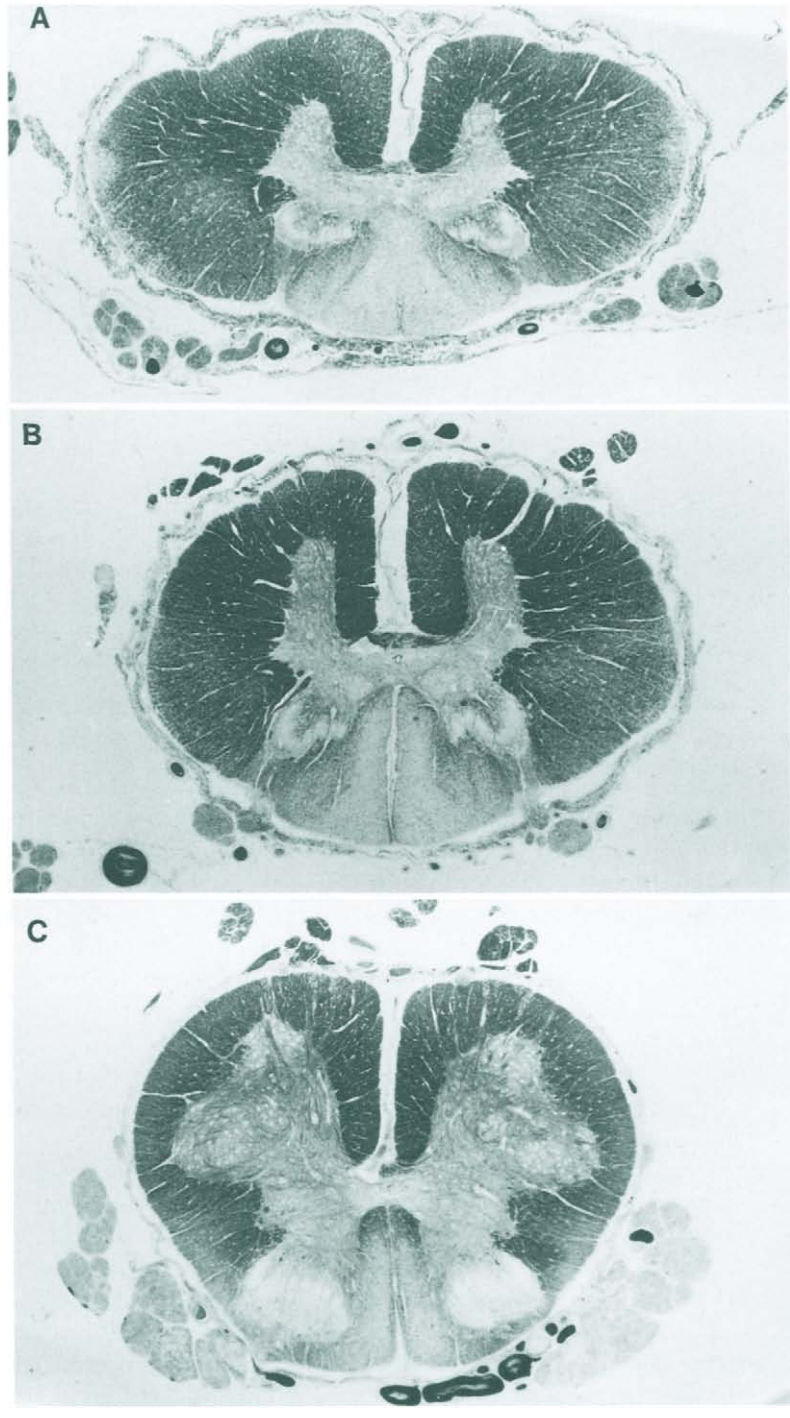


Fig. 297 Friedreich's ataxia. A loss of myelinated fibers in the posterior column of the spinal cord: (A) cervical, (B) thoracic, and (C) lumbar. Heidenhain–Wölcke stain.

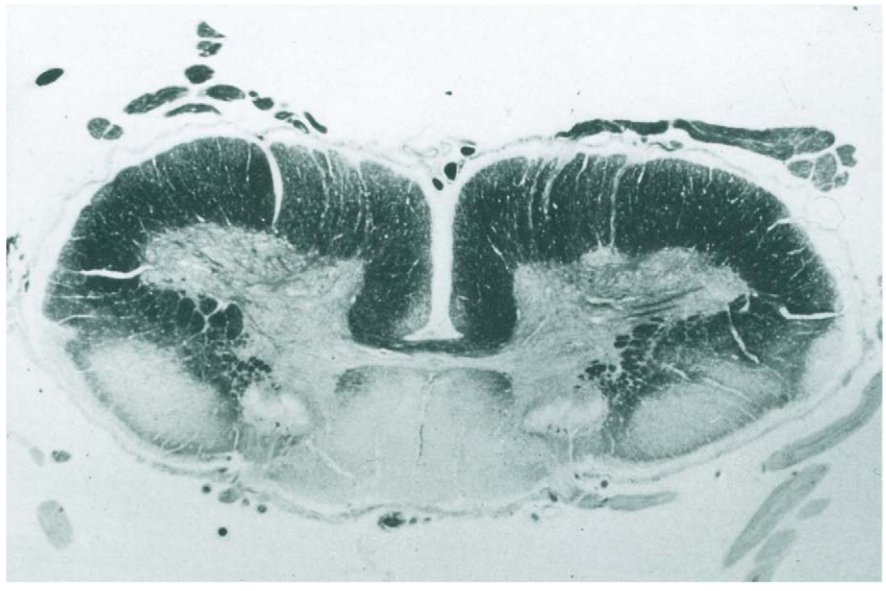


Fig. 298 Friedreich's ataxia. A loss of myelinated fibers in the posterior columns and the crossed pyramidal tracts. Heidenhain–Wölcke stain.

the lateral and superior vestibular nuclei, as well as of the ventral cochlear and superior olivary nuclei. The same authors observed neuronal loss and gliosis in the globus pallidus, subthalamic nucleus, and ventrolateral nucleus of the thalamus. Primary demyelination of the cerebral white matter has been reported. A loss of Purkinje cells with preservation of empty baskets is common. The surviving Purkinje cells show axonal swellings (torpedoes). Transneuronal degeneration may be responsible for rarefaction of the granular layer in advanced stages of the disease. The dentate nucleus may also be affected. Retinal degeneration may be severe in some cases, with a severe loss of ganglion cells. The surviving cells may be hyperchromatic or may form "ghost" cells. The optic nerves and tracts undergo atrophy, and also, transneuronally, the lateral geniculate body.

Considerable rarefaction of myelinated fibers is present in sensory nerves, where the remaining fibers show a greater than normal variation in diameter. The large fibers are particularly affected (Bennett *et al.*, 1984). Segmental demyelination was also seen in teased fibers. The large neurons are predominantly affected in the dorsal root ganglia. There is an increase in epineurial connective tissue.

Electron microscopy. The axons of the peripheral nerves show an accumulation of neurofilaments, vesicular profiles, and dense residual bodies. Thin myelin sheaths indicate remyelination of demyelinated axons. Muñoz-Garcia *et al.* (1986) found intramitochondrial inclusions resembling calcium apatite crystals in the peripheral neurons.

Pathogenesis The progressive skeletal deformities have been ascribed to the atrophy of paravertebral muscles secondary to the involvement of the spinal nerve roots. Biochemical abnormalities, such as a reduction in α-lipoprotein with normal values of cholesterol and triglycerides or disturbances in the glutamate dehydrogenase and pyruvate dehydrogenase complexes (Stumpf *et al.*, 1982), may be of pathogenetic significance. Insulin resistance is present in nondiabetic patients with Friedreich's ataxia, supporting the concept that a membrane abnormality that alters the binding function of the insulin receptor is present in these patients (Fantus *et al.*, 1993).

The slightly increased sensitivity to ionizing radiation points to a possible role of defective DNA repair in the pathogenesis of the disease (Chamberlain and Lewis, 1983), but this has not, to our knowledge, been confirmed.

The pathogenesis of the myocardial lesions has been the subject of controversy. Most French authors have ascribed them to a loss of parasympathetic (vagal) innervation and sympathetic overactivity. The acute lesions found in some cases closely resemble the lesions subsequently described in catecholamine excess.

The mutation causing Friedreich's ataxia maps on chromosome 9 in all patients who satisfy the strict diagnostic criteria (Chamberlain *et al.*, 1988). The inheritance form is autosomal recessive (Koeppen, 1991). The clinical variability does not imply genetic heterogeneity (Smeyers Dura *et al.*, 1993).

Hereditary Ataxia with Degeneration of the Posterior Columns and the Dorsal Roots (Biemond Syndrome; *Dégénérescence Radiculo-cordonnale Postérieure*)

This disease was first described by Biemond (1955). Only a few families have been recorded clinically, and in only one are autopsy observations available. Sporadic cases of severe degeneration of the posterior roots and columns have also been observed.

Clinical Picture The clinical picture is characterized by a very slowly progressive numbness in the hands and the feet, evolving toward a total loss of posterior column sensation. Ataxia affects the arms and the legs, particularly with the eyes closed. The tendon reflexes are absent; the sensory loss also involves the mouth. Some patients develop optic atrophy.

The spinal cord is atrophic. Under light microscopy the posterior columns are degenerated and the posterior roots are partially so. The thin fibers of the posterior roots and Lissauer's zone are intact. The trigeminal root is similarly affected. There is a minimal loss of Purkinje cells.

Arts *et al.* (1993) described an X-linked recessive disease with, in almost all patients, a fatal course in early childhood, occurring in a five-generation family. The affected boys had early-onset floppiness, ataxia, liability to infections (especially of the upper respiratory tract), deafness, and later, a flaccid tetraplegia and areflexia. Most of these patients died before the age of 5 years. At autopsy an almost complete absence of myelin in the posterior columns of the spinal cord was found. Some carriers developed a hearing impairment in early adulthood.

Xeroderma Pigmentosum (De Sanctis–Cacchione Syndrome; Xerodermic Idiocy)

Xeroderma pigmentosum has been known as a skin condition for over 100 years (Kaposi, 1872), but attention to the neurological manifestations was drawn only 60 years later (De Sanctis and Cacchione, 1932). It has now been established that neurological symptoms occur in 15–20% of cases of this disease.

Clinical Picture The disease is particularly prevalent among Jews and Arabs. Skin abnormalities occur already in childhood and appear in areas exposed to light. They consist of erythema, brownish pigmentation, circumscribed atrophy, ulceration, papules, and frequently also malignant tumors (Norris *et al.*, 1990). Ocular lesions have also been observed (Robbins *et al.*, 1993).

Neurological manifestations include microcephaly, progressive mental deterioration, epilepsy, spastic paresis, and extrapyramidal and cerebellar symptoms (often resembling Friedreich's ataxia). Deafness and peripheral neuropathy have also been reported. Rarely, neurological symptoms may develop later in life, when they are generally less severe (Robbins *et al.*, 1991, 1993).

The EEG shows intermittent spindles of grouped θ-waves with abnormally slow background activity, suggesting thalamic dysfunction as well as diffuse cortical hypofunction. CT and MRI examination revealed diffuse brain atrophy with ventricular dilatation and cranial bone thickening (Mimaki *et al.*, 1988).

Pathology The skin changes cover a wide range (Scott *et al.*, 1993a). In the extremely attenuated epidermis, foci of follicular hyperkeratosis with cellular atypia may be found and may progress to basal cell carcinomas. Angiomas and hamartomas may also be present.

Neuropathology *Gross appearances.* Cerebral and cerebellar atrophy ranges from moderate to severe.

Light microscopy. A diffuse neuronal loss has been observed in the entire cerebral cortex with a temporo-occipital predilection. A loss of nerve cells is also prominent in the midbrain, locus coeruleus, and substantia nigra. Rarefaction of Purkinje cells has been observed in the cerebellum. A variable degree of gliosis may be present in the white matter (Frias, 1982).

Degeneration of the posterior and, less commonly, the lateral, columns, with a loss of myelinated fibers is found in the spinal cord. A loss of nerve cells is seen in the posterior and lateral horns, as well as in the dorsal root ganglia (Lewis *et al.*, 1978). Some loss of both myelinated fibers and U-fibers is found in the peripheral and autonomic nerves (Kanda *et al.*, 1990).

Electron microscopy. Occasional fibers undergoing axonal degeneration have been seen on sural nerve biopsies (Fukuhara *et al.*, 1982).

Pathogenesis Xeroderma pigmentosum is a genetically heterogeneous disease. Seven different complementation groups have been identified, designated by the letters *A–G* (Vermeulen *et al.*, 1991). Neurological involvement occurs regularly in group A and in a proportion of the cases in group D (Kondo *et al.*, 1992; Johnson and Squires, 1992). A group F case with neurological abnormalities was reported by Moriwaki *et al.* (1993).

Cleaver (1968) observed reduced or absent DNA replication in fibroblast cultures exposed to ultraviolet light from patients with xeroderma pigmentosum. It was assumed that the fault lay in a deficiency of an endonuclease responsible for the splitting of thymine dimers of the damaged DNA. Later, it was shown that the photoreactivation, independent of enzyme activity, was the most important repair mechanism for the degradation of dimers, and that the postreplication repair was defective (Sutherland *et al.*, 1985). The neurological lesions have been explained by disturbances of cell division and development of the neural tube. Reduced natural killer cell activity may contribute to the greatly increased susceptibility to skin cancer. The genetic instability induced by faulty DNA repair may involve genes other than those responsible for the basic condition.

The genetic alteration in xeroderma pigmentosum group A consists of a mutation at the splicing junction of intron 3 and exon 4 (Mimaki *et al.*, 1992). Patients having this mutation at intron 3 in the homozygous state develop severe skin manifestations in early infancy and severe progressive neurological abnormalities. Among patients heterozygous for the splicing mutation in intron 3, many showed milder skin symptoms and milder neurological abnormalities than patients with the homozygous splicing mutation (Nishigori *et al.*, 1994).

Degeneration of the Posterior Columns and the Substantia Nigra

Patients affected simultaneously by familial Friedreich's ataxia and parkinsonism have been described (Weir and Fan, 1981). They differ clinically and morphologically from the more common association of OPCA with parkinsonism.

Clinical Picture The disease manifests itself in the second decade with ataxia as well as rigidity and tremor of variable intensity. Epileptic seizures may occur. The course of the disease is progressive, leading to death within a few years.

Neuropathology *Gross appearances.* The main features are atrophy of the posterior columns and pallor of the substantia nigra.

Light microscopy. There is a total loss of axons and myelin sheaths in the posterior columns. A moderate loss of nerve cells and gliosis are seen in the nucleus dorsalis and Clarke's column. A severe reduction in the number of pigmented neurons with prominent gliosis is conspicuous in the substantia nigra. A slight loss of Purkinje cells and neurons in the dentate nucleus was interpreted as postictal (Weir and Fan, 1981).

Roussy–Lévy Syndrome (Hereditary Areflexic Astasia; Posterior Root and Column Form of Spinocerebellar Degeneration)

Roussy and Lévy (1926) described a heredodegenerative disease in seven members of a family that they attempted to differentiate from Friedreich's ataxia, on the one hand, and from neural muscular atrophy, on the other. They called the syndrome *"dystasie aréflexique héréditaire."*

In the available literature it is indeed difficult to differentiate Roussy–Lévy syndrome from Friedreich's ataxia or the neural form of Charcot–Marie–Tooth disease (see p. 664). Some authors deny the nosological entity of the syndrome and interpret it as Charcot–Marie–Tooth disease with essential tremor (Aksu *et al.*, 1986). Others recognize the independent entity of the syndrome, which may be inherited in a pure form mixed with other system degenerations (Lapresle, 1986).

Clinical Picture The disease manifests itself in childhood with locomotor and static ataxia, as well as reduced or absent reflexes. The disease is slowly progressive. Pes cavus, slight pareses and muscular atrophies, sphincter disturbances, and a form of essential tremor are other features. The inheritance is dominant, but irregular. Aksu *et al.* (1986) warned against making the diagnosis in childhood and advised waiting for further developments.

Neuropathology Lapresle (1986) examined case 1 of Roussy and Lévy's original family and found an extensive proliferation of Schwann cells with onion bulb formation. Nerve biopsies also revealed a hypertrophic neuropathy with onion bulb formation, segmental demyelination, and shortening of internodal length (Barbieri *et al.*, 1984).

Ataxia, Peripheral Neuropathy, Retinitis Pigmentosa, and Diabetes Mellitus

This syndrome was described in a Japanese family by Furukawa (1968). The onset of symptoms is in adolescence and the course of the disease is slowly progressive. Aside from experiencing ataxia, peripheral neuropathy, RP, and diabetes mellitus, some patients also suffer from facial palsy, external ophthalmoplegia, dementia, and epilepsy (Kondo, 1982). Clinically, this entity probably corresponds to the maternally inherited disease described by Holt *et al.* (1990) as the ataxia–RP–dementia complex (see p. 58) associated with a mitochondrial mutation.

An autopsy finding in one of the members of the family described by Furukawa were reported by Oguchi *et al.* (1977). Aside from a loss of myelin in the peripheral nerves and the spinal roots, there was also degeneration of the optic nerves and chiasm and of the posterior columns and spinocerebellar tracts in the spinal cord.

In other patients with autosomal-dominant cerebellar ataxia and retinal degeneration no mutations were found either in the two known loci for the autosomal-dominant ataxia or in the locus for RP (Benomar *et al.*, 1994).

Ataxia with Optic Atrophy, Pes Cavus, and Pyramidal Signs

A severe loss of Purkinje cells and slight rarefaction of the granule cells were seen in the cerebellum. A loss of myelin was found in the inferior olives and the spinal cord, particularly in the posterior columns (Lundberg, 1981).

Ataxia, Myoclonus, and Deafness (May and White Syndrome)

In 1968 May and White described a family with inherited deafness, myoclonus, and ataxia. Similar families have subsequently been reported (Melo and Ferro, 1989). Neuropathologically, a loss of cells in the dentate nuclei, decreased cerebellar white matter, and minor alterations of the gracile tracts in the spinal cord were present (Baraitser *et al.*, 1984).

Vaamonde *et al.* (1992) reported on a family with inherited deafness, myoclonus, and ataxia with mitochondrial pathology. A mother and two of her daughters had deafness, cortical reflex myoclonus, and mild truncated ataxia. Muscle and skin biopsy specimens revealed abundant RRFs and abnormal mitochondria. Some of the affected members of the family also had diabetes mellitus, hypertension, and cardiomyopathy.

Ataxia, Mental Deterioration, and Epilepsy with Tooth Enamel Hypoplasia (Kohlschütter's Syndrome)

Kohlschütter described in 1974 a syndrome characterized by associated familial hypoplasia of the tooth enamel and epilepsy, spasticity, and progressive mental deterioration.

Palmeri *et al.* (1993) reported familial amelogenesis imperfecta of an autosomal-dominant type in five subjects belonging to three generations, associated with a neurological syndrome of variable clinical expression. Brain MRI showed a thin layer of periventricular gliosis of the white substance as well as hypoplasia of the corpus callosum. Biopsy of the sural nerve showed a slight reduction in the thickness of the myelin sheath in a number of large fibers.

Ataxia, Mental Retardation, Cataracts, Deafness, and Polyneuropathy

Begeer *et al.* (1991) described two sisters with mental retardation and congenital cataracts. Progressive hearing loss, ataxia, and polyneuropathy became evident in the third decade. Cases of Sjögren–Larsson syndrome and Duchenne muscular dystrophy were reported in the pedigree. Inheritance is presumably autosomal recessive.

Atrophies of the Motor Neurons

The brunt of the damage in the motor neuron diseases falls on the upper and/or lower motor neurons, affecting the perikarya and the axons. Aside from ALS and bulbar palsy, the following diseases belong to this group: spinal spastic paralysis, progressive external ophthalmoplegia, and the spinal muscular atrophies. The concept of *motor neuron diseases* comprises the whole group. Some authors, however, use the term to replace that of *ALS*.

Amyotrophic Lateral Sclerosis (Myatrophic Lateral Sclerosis; Progressive Bulbar Paralysis)

This condition was defined by Charcot and Joffroy (1869) as a disease of the upper and lower motor neurons. It comprises sporadic, endemic, and familial forms, although some authors have rejected this division as not sufficiently justified. According to the order of involvement of the spinal and cranial nerves, the disease may be subdivided into ALS and progressive bulbar palsy. Duchenne (1890) considered the latter an independent nosological entity, but since the work of Déjerine (1914) it is accepted as a topographical variant of ALS by most authors. Only the familial infantile and juvenile bulbar paralysis is treated as an independent subentity of motor neuron disease. The disease also occurs in combination with thalamic and nigral atrophies, with pallidoluysionigral atrophy (Gray *et al.*, 1985), with Huntington's chorea, with Pick's disease, in association with dementia, and within the framework of multisystem atrophies (Rosenberg, 1982).

Sporadic Form

The majority of the patients with ALS belong to the sporadic group. Nishigaki (1970) attempted to make a correlation between clinical symptoms and morphology in three subtypes. Horoupian *et al.* (1984) described a variant with dementia, which is considered

separately. A motoneuron disease-like disorder after ganglioside therapy was reported by Yuki *et al.* (1991) and was subsequently confirmed.

Clinical Picture The disease appears between the ages of 40 and 70 years, with the median age at onset being 52 years. Males are more commonly affected. A juvenile form with onset in the second decade has been reported occasionally (Beauvais *et al.*, 1990). The presenting symptom is usually muscle weakness, and sometimes the patients complain of pain. According to the principal localization of lesions, weakness with muscular atrophy and fasciculation or spastic paresis may follow. Muscle tone is increased, tendon reflexes are exaggerated, and other pyramidal signs are present. Spinal symptoms predominate in some patients, while bulbar symptoms appear in others. All variations may occur. Ophthalmoplegia is rare, but detailed examination reveals subtle disturbances of ocular movements in over 60% of the patients (Ohki *et al.*, 1994).

Bulbar paralysis is characterized by atrophy, fasciculation, and paresis of the tongue and the pharyngeal muscles. Speech is nasal and indistinctly articulated. Difficulty in swallowing may cause malnutrition. The fully conscious patients lose weight and finally succumb to aspiration pneumonia or circulatory failure precipitated by a choking attack.

Most patients die 2–4 years after the onset of symptoms, but longer survival up to 15 years has been recorded. These patients may represent unrecognized familial cases (see p. 645). The juvenile form tends to run an acute course of 12–18 months.

CT and MRI may show involvement of much larger cortical areas than the motor cortex, particularly the frontotemporal and limbic cortices in some cases (Kato *et al.*, 1993). PET scanning shows reduced cerebral blood flow in the sensorimotor cortex, and sometimes in subsidiary motor areas as well (Kew *et al.*, 1994).

Neuropathology *Gross appearances.* Atrophy of the precentral gyrus and the paracentral lobule may be seen in some cases (Fig. 299). Atrophy of the anterior spinal roots may vary in severity, but is always present (Figs. 300 and 301). The hypoglossal nerve may also be attenuated. On transverse sections of the spinal cord, one observes shrinkage, firmness, and a grayish yellow discoloration of the anterior horns and the crossed pyramidal tracts. These changes are particularly prominent in the cervical segments.

Light microscopy. Neuronal loss affects predominantly the large motor cells of the spinal cord and the nuclei of cranial nerves. The most severe changes are found in the cervical segments (Fig. 302A and B), but the depletion of nerve cells is also evident in lumbosacral segments. The changes in thoracic segments vary from case to case. Of the cranial nerves the hypoglossal nerve is always affected in the bulbar form, and frequently also the glossopharyngeal and accessory nerves, while the third, fourth, and sixth nerves are spared, with rare exceptions. The changes affect the perikarya of the large—or, rarely, the small—motor cells of the anterior horns. In a morphometric study Terao *et al.* (1994) showed losses of both α- and γ-motor neurons with preservation of the small cells of the dorsomedial region of the anterior horn. All motor cells, both in the spinal cord and in the motor cortex, are significantly smaller than in normal controls (Kiernan and Hudson, 1991, 1993). Aside from cell loss, many ghost cells with pale swollen bodies are present (Fig. 303A). The surviving cells contain only 58% of the RNA compared with normal controls. Abnormal dendrites and atrophic axons can be demonstrated with

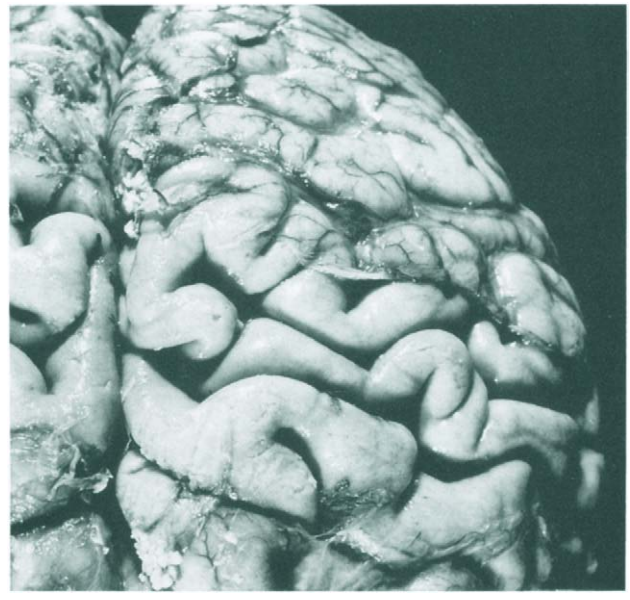


Fig. 299 Amyotrophic lateral sclerosis. Atrophy of the precentral gyrus.

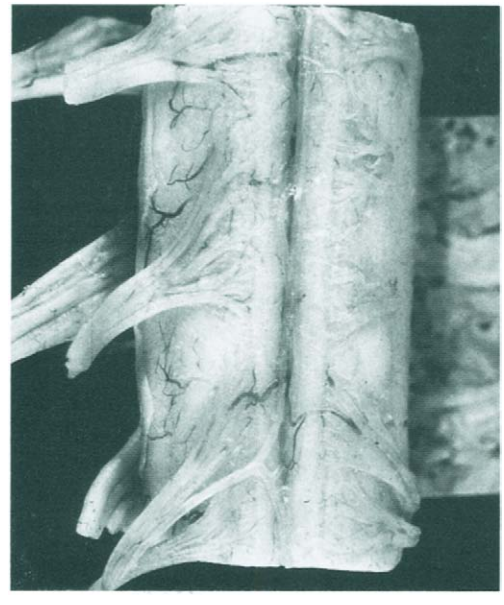


Fig. 300 Amyotrophic lateral sclerosis. Pronounced thinning of the anterior roots. (Courtesy of G. Kersting.)

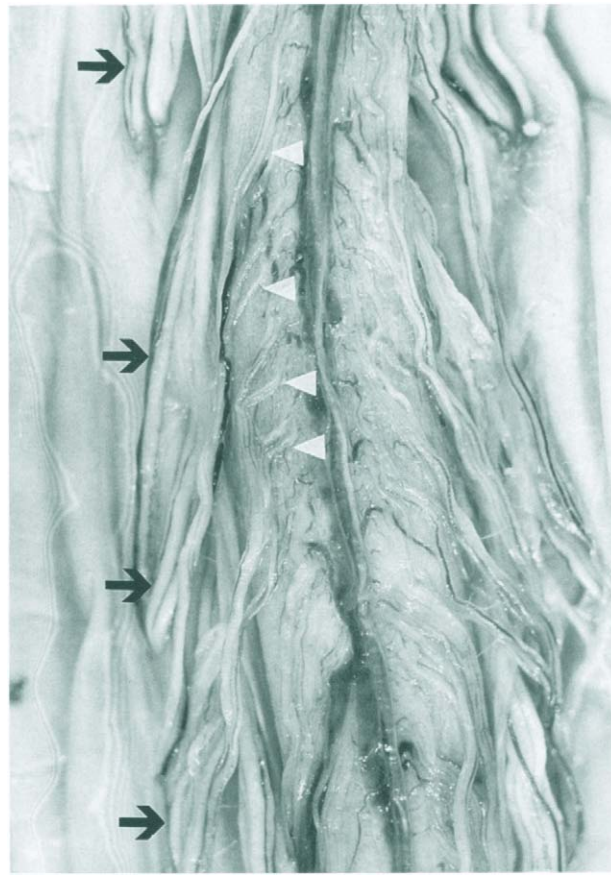


Fig. 301 Amyotrophic lateral sclerosis. The anterior roots (triangles) in the lumbar segments are attenuated and are much thinner than the posterior roots (arrows).

impregnation methods (Fig. 304). Only the cells innervating the bladder and the rectum in the medial parts of the anterior horns of the sacral segments are preserved (nucleus of Onufrowicz), in addition to the intermediolateral nucleus (Sung, 1982) and those of Clarke's column. The latter, however, may be partially depleted in thoracic segments (Averback and Crocker, 1982). In the intermediolateral nucleus the number of neurons is reduced at T_2, but well preserved at T_9 (Takahashi *et al.*, 1993). Shrunken cells (Fig. 303B) and cells containing lipofuscin (Fig. 303C) are also present, as are figures of neuronophagia.

Several types of inclusion bodies may be present in the perikarya of anterior cells, with variable frequency. These include Bunina bodies (Bunina, 1962; skeinlike inclusions (Leigh *et al.*, 1991); hyaline inclusions, also known as Lewy body-like inclusions (Mizusawa, 1992); and basophilic inclusions. Bunina bodies are small, round or oval, eosinophilic inclusions, often occurring in clusters and found in the cytoplasm and dendrites of both degenerating and apparently normal neurons in all subtypes of ALS. They

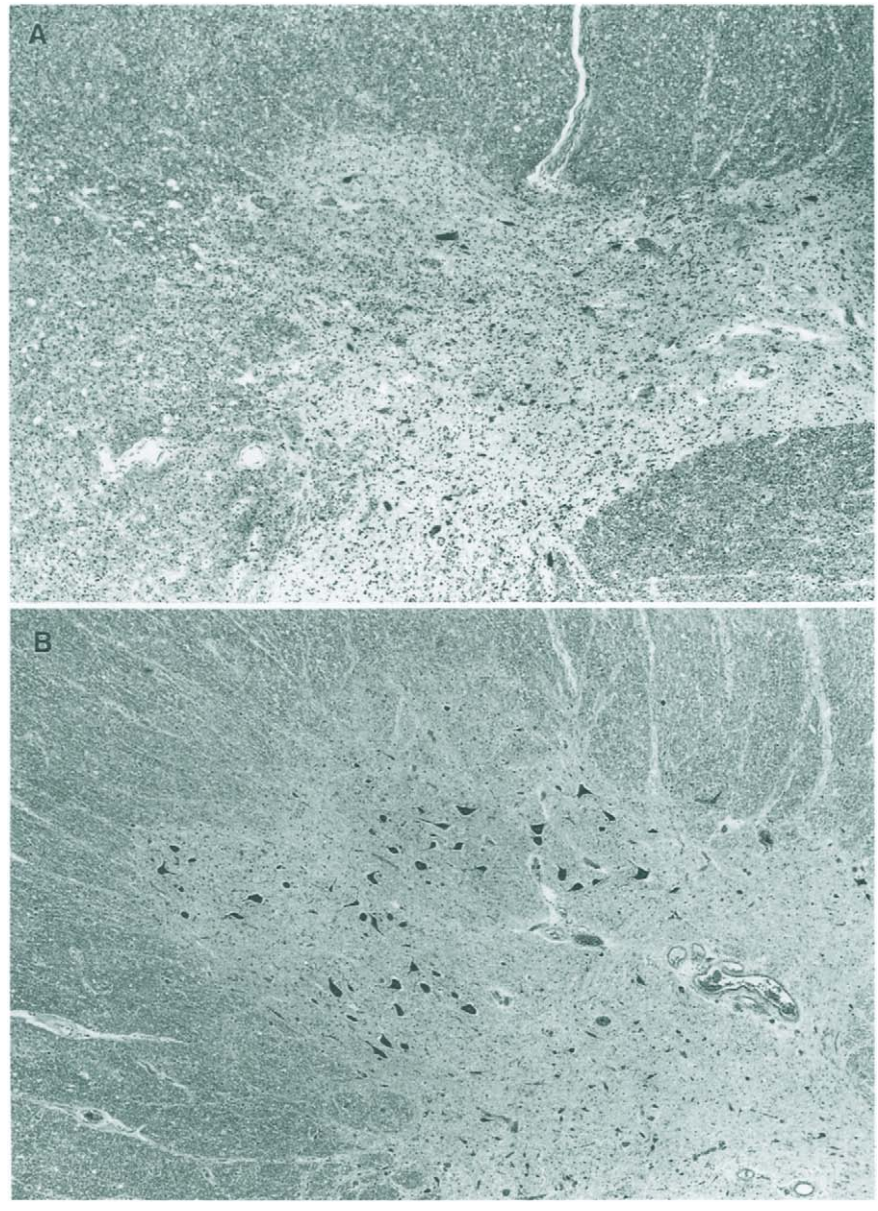


Fig. 302 Amyotrophic lateral sclerosis. (A) A loss of large motor neurons in the anterior horn of the spinal cord. (B) A normal control. Nissl stain, ×80.

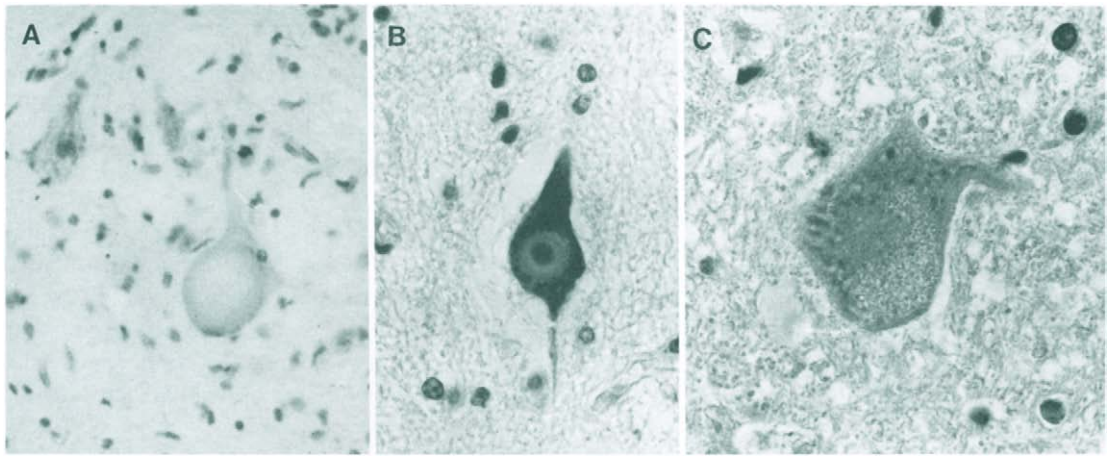


Fig. 303 Same case shown in Fig. 302. An anterior horn, showing (A) chromatolysis, (B) shrinkage, and (C) lipopigment accumulation in the neurons. Nissl stain, (A) ×300, (B) ×500, and (C) ×700.

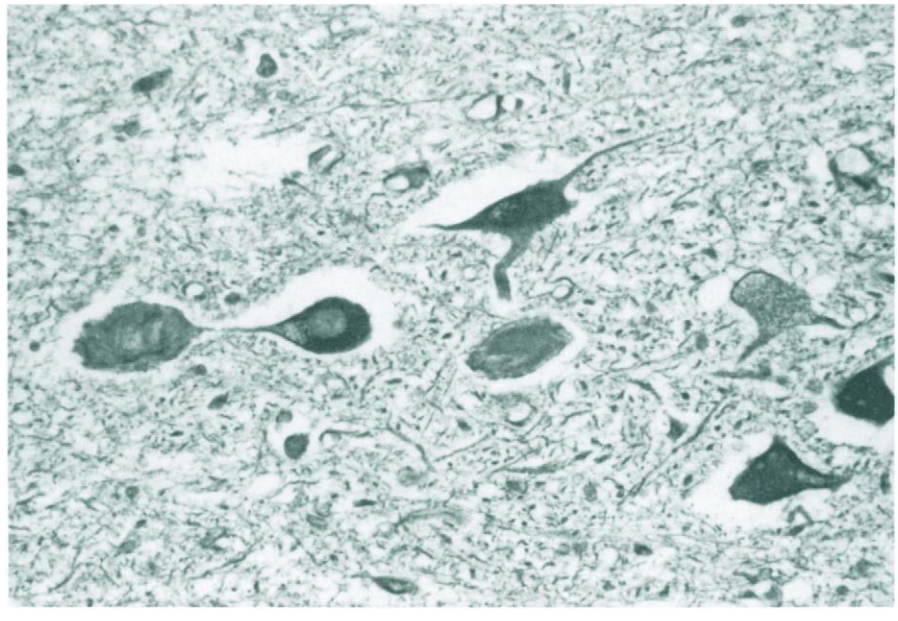


Fig. 304 Same case shown in Fig. 302. Swelling of the proximal axons. Kelemen stain, ×500.

are essentially confined to motor neurons, but are occasionally found in other neurons, particularly in atypical cases. They are also seen in Betz's cells and in otherwise intact cells of the nucleus of Onufrowicz and the oculomotor nuclei (Kihira *et al.*, 1991). They are not entirely specific for ALS, however, and may occur in other conditions. Skeinlike inclusions are almost invisible in H&E preparations (Leigh *et al.*, 1991) or may appear as faintly eosinophilic or amphophilic strands in the cytoplasm (Mizusawa *et al.*, 1991). Hyaline inclusions, originally described in familial cases, are found occasionally in sporadic ones. They are round eosinophilic bodies surrounded by a pale halo, resembling Lewy bodies. Basophilic bodies are pale, glassy, faintly basophilic, circumscribed areas in the cytoplasm of motor neurons, but are sometimes found outside the motor system. They are a characteristic feature of juvenile ALS, but can sometimes be found in adult cases (Kusaka *et al.*, 1993). Immunohistochemically, the skeinlike and hyaline inclusions are ubiquitinated (Mather *et al.*, 1993), while Bunina bodies and basophilic inclusions are not. A high proportion of ubiquitinated inclusions was seen in cases with an aggressive clinical behavior (Schiffer *et al.*, 1991). While most inclusions contain cytoskeletal elements, Bunina bodies are devoid of all normal neuronal antigens and are only stained positively by an anti-cystatin C serum (Okamoto *et al.*, 1994).

The main immunohistochemical abnormality is the accumulation of phosphorylated neurofilaments of the large (200-kDa) and medium-sized (160-kDa) components of neurofilament triplets in the perikarya and the proximal axons of motor cells (Muñoz-Garcia *et al.*, 1988). The expression of the small (68-kDa) component is controversial; while Chou (1994) found overexpression of this component, a considerable reduction was reported by Bergeron *et al.* (1994).

Proximal swellings of axons and spheroids are already present in early stages of the disease, but they are not confined to patients with ALS (Clark *et al.*, 1994). Axonal swellings also occur in the corticospinal tracts (Okamoto *et al.*, 1990). All spheroids react with various antibodies to neurofilaments (Nakazato *et al.*, 1984).

The loss of neurons is more difficult to demonstrate in the cerebral cortex. Peiffer (1984) recommends the following technique. After identification of the paracentral lobule, a thick coronal slice is obtained by cutting along the anterior and posterior margins of the lobule. A block is obtained from this slice by cutting at right angles to the oblique course of the precentral and postcentral gyri. Sections of this block present an optimal picture of the architecture of the central cortex. Laminar status spongiosus and gliosis between laminae I and II of the motor cortex are a frequent finding. With Golgi impregnations one finds a reduction in the dendrites and spines of the remaining Betz's cells. A loss of neurons in the substantia nigra is an occasional finding (Kato *et al.*, 1993). ALS patients showed significantly increased binding of glutathione in the dorsal and ventral gray horns compared to controls (Lanius *et al.*, 1993). A decrease in synaptophysin expression was observed in the anterior horn neuropil of all motor neuron disease patients and this reduction was correlated with the degree of degeneration or neuronal loss of the anterior horn cells (Sasaki and Maruyama, 1994). Neuropeptide Y neurons are less severely affected than parvalbumin neurons, which are severely depleted in the ALS cortex (Nihei and Kowall, 1993).

With the usual fat stains only scattered sudanophilic lipophages are seen in the pyramidal cell layer of the precentral cortex. They increase in number in the corticospinal tracts,

particularly in the basis pontis, the pyramids, and, above all, the crossed pyramidal tracts in the lateral columns. Cell loss is occasionally accompanied by neuronophagia (Troost *et al.*, 1993). Astrocytic proliferation, either in clumps or in a laminar distribution, may be more striking than neuronal loss (Murayama *et al.*, 1991). Gliosis may also be found outside the motor area (Kushner *et al.*, 1991). The degeneration of the fibers of the pyramidal cells may be followed through the cerebral white matter, internal capsule, and cerebral peduncles with the use of the Marchi method. The loss of myelinated fibers can be seen in the crossed and uncrossed pyramidal tracts in the spinal cord (Fig. 305B) or, less commonly, in the pons and the medulla (Fig. 305A). It is pronounced in the cervical cord and is sometimes asymmetrical (Swash *et al.*, 1986). Both the axons and the myelin sheaths of the thick fibers are affected, while the thin ones are generally spared. The loss of myelin need not be conspicuous in all cases of ALS. Now and again cases are seen with typical clinical symptomatology and a loss of anterior horn cells in which no myelin loss can be demonstrated in the pyramidal tracts.

The astrocytic reaction is distinct in the degenerated pyramidal tracts. Degeneration of the posterior columns is less common in sporadic than in familial cases (see p. 646) and, with rare exceptions (Moss and Campbell, 1987), was reported mainly in the earlier literature. Morphometrically, one finds increased vascularity in the anterior horns, exceeding that which can be ascribed to shrinkage of the tissue. Tangled and wavy vessels may also be seen (Fig. 306A,B).

As a result of neuronal loss, the anterior roots are atrophic (Fig. 307) with a predominant loss of large myelinated fibers. This is reflected in neurogenic atrophy with fiber grouping in skeletal muscles. Glial bundles resembling those seen in Werdnig–Hoffmann disease have been seen occasionally in the anterior roots (Ghatak and Nochlin, 1982). In the pseudoneuropathic form of the disease, it is assumed that the neurons of the dorsal root ganglia are involved in the degenerative process. Sural nerve biopsies revealed some axonal degeneration in most cases, increasing in severity with the duration of the disease (Heads *et al.*, 1991).

Electron microscopy. The substrate of axonal spheroids consists of an accumulation of neurofilaments, 10 nm in diameter (Hirano, 1991). Both the skeinlike and hyaline inclusions show a similar ultrastructure and consist of a mixture of neurofilaments and abnormally large fibrils (Nakano *et al.*, 1993). Immunoelectron microscopy showed that only the abnormal fibers were ubiquitinated (Lowe *et al.*, 1988; Schiffer *et al.*, 1991). Bunina bodies consist of amorphous electron-dense material interspersed with tubular and vesicular structures. Some of the larger bodies have an electron-lucent central area containing 10-nm filaments and other cellular organelles (Okamoto *et al.*, 1994). The basophilic inclusions consist of tangled microtubules, 15–25 nm in diameter, studded with granules (Oda *et al.*, 1978; Kusaka *et al.*, 1993).

An accumulation of neurofilaments, mitochondria, and vesicles, indicating a dying-back process, can be found on sural nerve biopsies. The sequence of events of the intracellular changes in the neurons can be tentatively reconstructed. Probably the earliest changes are those observed by Gonatas *et al.* (1992) and Mourelatos *et al.* (1993) in the Golgi apparatus, by both immunohistochemical and ultrastructural methods. The Golgi apparatus is involved in the transport and processing of several intracellular proteins. While the role of this organelle in human diseases has never been fully explored, protein

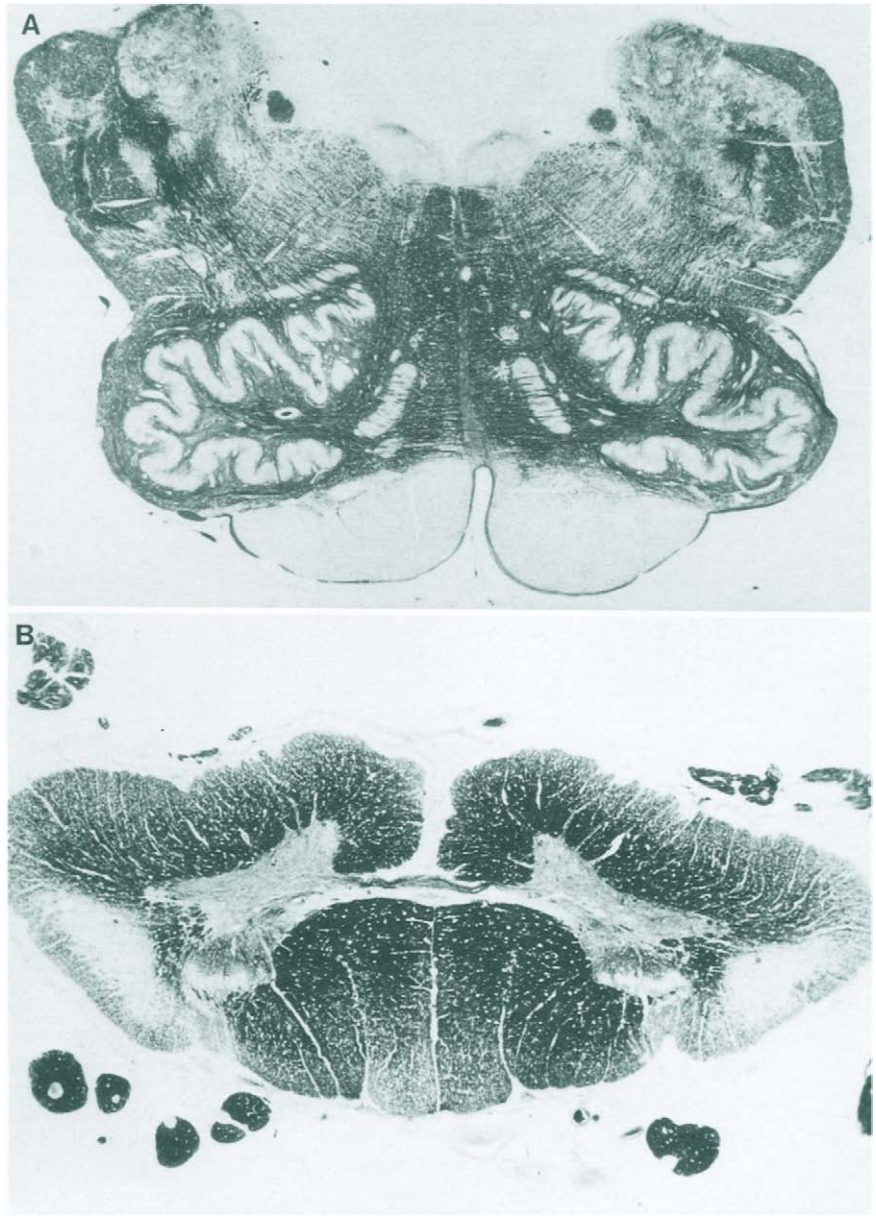


Fig. 305 Amyotrophic lateral sclerosis. A loss of myelin in the pyramidal tracts (A) in the medulla oblongata and (B) in the cervical cord. Heidenhain–Wölcke stain.

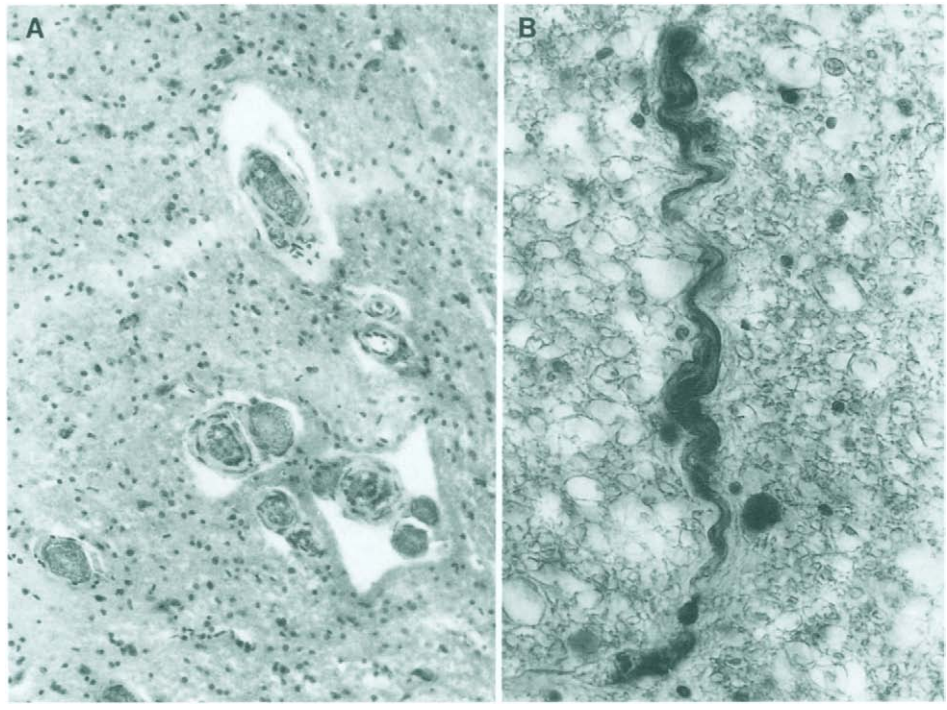


Fig. 306 Amyotrophic lateral sclerosis. (A) Tangled and (B) convoluted vessels in the anterior horn. van Gieson's stain, (A) ×380 and (B) ×500.

abnormalities are certainly present in the motor neurons in ALS. One of them manifests itself in the faulty assembly of neurofilaments (Chou, 1994), which, in turn, causes an inhibition of axoplasmic transport. This leads, on the one hand, to an accumulation of phosphorylated neurofilaments within the perikaryon and on the other, to deprivation in the terminal parts of the neuronal processes and their retraction or disintegration. Whatever the exact nature and cause of the cellular degeneration, the ultimate cell death is likely to be due to an excessive influx of calcium ions from the extracellular to the intracellular compartment (Appel *et al.*, 1994).

Pathogenesis The cause of sporadic ALS is unknown, but several theories have been advanced (Eisen and Krieger, 1993). The principal three are those of oxidative stress, excitotoxicity, and an immune mechanism. To these may be added element toxicity, apoptosis, and a deficiency or abnormality of growth factors.

The oxidative stress theory is an extrapolation of the finding of point mutations of the superoxide dismutase (SOD) 1 in a group of cases of familial ALS (see p. 646). Both the cytosolic SOD1 and the mitochondrial SOD2 are invariably normal in sporadic ALS, yet the protein carbonyl groups, a marker of oxidative damage, are significantly raised in the motor cortex (Bowling *et al.*, 1993).

Fig. 307 Amyotrophic lateral sclerosis. The anterior roots are largely devoid of myelin. Heidenhain–Wölcke stain.

The action of excitotoxins is based on analogy with the ALS–parkinsonism–dementia syndrome of Guam, in which the evidence in favor of excitotoxic factors is much stronger. Support for the theory is offered by evidence of disordered glutamate metabolism (Plaitakis, 1990; Munsat and Hollander, 1990; Malessa *et al.*, 1991) and high levels of excitotoxic amino acids in the CSF (Rothstein *et al.*, 1990, 1992), although these findings have been questioned (Perry *et al.*, 1990). Furthermore, human motor neurons that are susceptible in motor neuron disease do not contain parvalbumin or calbindin. Two proteins with calcium buffering properties are absent in the cells that selectively die in motor neuron disease (Ince *et al.*, 1993).

The results of immunohistochemical characterization of the inflammatory infiltrate in ALS suggest that an autoimmune process or an infectious agent may play a role in ALS (Troost *et al.*, 1990). Westarp *et al.* (1993) suggested a particular B-lymphocytic and retroviral involvement.

The role of immunological factors (Appel *et al.*, 1993) is suggested by the presence of

antibodies in the serum of patients with ALS, particularly those directed against a component of the calcium channel (Kimura *et al.*, 1994). An increased incidence of monoclonal gammopathies has been observed in patients with ALS and other motor neuron diseases (Sadiq and Latov, 1991).

The remaining theories have been less well documented. High dietary aluminum can induce motor neuron pathology in experimental animals (Garruto *et al.*, 1989). The motor neuron development depends on basic fibroblast growth factor and ciliary neurotrophic factor (Arakawa *et al.*, 1990), and abnormalities in these factors could lead to apoptosis. CSF glycine levels are significantly higher in motor neuron disease patients than in neurological controls. This is probably an epiphenomenon and suggests a defect of glycine "housekeeping" in the CNS in motor neuron disease (Lane *et al.*, 1993). The occasional occurrence of conjugal ALS in married couples strongly suggests the operation of an environmental factor (Cornblath *et al.*, 1993; Camu *et al.*, 1994).

It may be added that all therapeutic efforts aimed at counteracting the above mechanisms have yielded equivocal or totally negative results (Orrell *et al.*, 1994; Rowlands, 1994).

Our understanding of the pathogenesis of individual lesions is also incomplete. By using an antibody against a specific epitope of the Golgi apparatus, Gonatas and co-workers demonstrated fragmentation of this organelle in the motor neurons (Gonatas *et al.*, 1992; Mourelatos *et al.*, 1993). These authors considered this a primary lesion, as experimental deafferentation and deefferentation fail to produce a similar lesion (Mourelatos *et al.*, 1994). As the Golgi apparatus is involved in the production of secretory and membrane proteins, the connection between the damage to this organelle and the cytoskeletal abnormalities observed in ALS remains obscure.

The neurofibrillary imbalance may cause impairment of axoplasmic flow (Chou, 1994). On the other hand, the accumulation of phosphorylated neurofilaments in the perikaryon may be the result of defective axoplasmic flow. In either case the result is a dying-back process.

Kiernan and Hudson (1991) found no correlation between the numbers of surviving lower motor neurons and the mean sizes of pyramidal cells in layer V of the corresponding areas of the precentral gyri. The absence of such a correlation indicates that functionally related cortical and lower motor neurons probably degenerate independently, not from a transsynaptic effect.

Contrary to the widely held view that the process begins in the upper motor neuron, Chou and Norris (1993) maintained that the lower motor neuron is the primary site of damage, which is then transmitted to the upper motor neuron by retrograde axoplasmic flow.

Familial Forms (Hirano–Kurland–Sayre Type; Lou Gehrig Disease)

Familial incidence of ALS has been established in 5–12% of the patients. These must be differentiated from the endemic cases of Guam, in which a genetic etiology is open to doubt. Some of these familial cases represent variants with additional features besides the classical characteristics of ALS (Hirano *et al.*, 1967).

Clinical Picture In some patients the disease begins in childhood. The clinical symptomatology is characterized by sensory loss additional to the motor symptoms. Horton *et al.* (1976) distinguished families with an acute course of up to 2 years' duration from those with a more benign course with an average survival of 14 years.

In many families (Tanaka *et al.*, 1984) the onset of symptoms was later, around the fifth decade. Anticipation with earlier onset and a more rapid course in the second generation occurs. It is of interest that even in the same family cases may occur with a protracted course of up to 25 years and with a rapid course of 1–3 years, similar to the situation in sporadic cases. Families with a hereditary pure bulbar form are rare (Ben-Hamida *et al.*, 1990).

In several families ALS was associated with dementia (Schmitt *et al.*, 1984).

Neuropathology The neuropathological findings show a wide range of variation besides the usual features of ALS. The loss of upper motor neurons appears relatively slight compared with that of the lower motor neurons, including those of the lower cranial nerves. In two Canadian families, however, there was severe neuronal loss and gliosis in the precentral gyrus, as well as in the amygdalae, the insula, and the frontotemporal cortex. An asymmetry of lesions was noted by Kato *et al.* (1987).

In 70% of the familial cases, degenerative changes were observed in the posterior columns. Degeneration of the spinocerebellar tracts and of Clarke's column was found in several cases (Tanaka, 1984). Hyaline inclusions in neurons are more common in familial cases. They were present in the cerebral cortex, predominantly in the only moderately atrophic precentral gyrus, the inferior olives, the dentate nucleus, and the molecular layer of the cerebellar cortex. No inclusions were seen in the severely atrophic lower motor neurons. They differed from the myoclonus bodies in their histochemical and polarization–optical characteristics. Similar inclusions with analogous localization were also seen in sporadic cases (Barz *et al.*, 1976). Additional features may include a loss of neurons in the substantia nigra (Wolf *et al.*, 1991) and in the reticular formation (Kato and Hirano, 1992). Very extensive damage has been observed in a patient with long-term survival, the last 5 years with respiratory support (Takahashi *et al.*, 1993). Neuronal loss in this case was found in the brain stem tegmentum, cerebellar cortex, dentate and red nuclei, thalamus, and mamillary bodies.

Electron microscopy. On electron microscopy swollen synapses with an accumulation of microtubules and vesicles were found in the cerebral cortex of members of one Dutch family (Bots and Staal, 1973). Otherwise, the appearances of the lesions are identical to those seen in sporadic ALS.

Pathogenesis The condition is inherited, as a rule, as an autosomal-dominant trait with complete or incomplete penetrance (Amick *et al.*, 1971). In one family 18 cases were recorded in six generations (Veltema *et al.*, 1990). A recessive mode of inheritance was recorded in the cases of Orthner *et al.* (1973).

The condition is genetically heterogeneous. In one group of families, about 20% of the total, a defective gene has been discovered on chromosome 21, coding for the cytosolic Cu/Zn SOD1 (Rosen *et al.*, 1993, 1994). Eleven different point mutations have been found in 13 families. Additional mutations occurring in individual families have been reported by Elshafey *et al.* (1994), Nakano *et al.* (1994), and Rainero *et al.* (1994).

Inhibition of SOD1 by appropriate antagonists in an organotypic culture of the spinal cord resulted in apoptotic degeneration of the spinal neurons, including the motor neurons, over several weeks (Rothstein *et al.*, 1994). Introduction of human SOD containing a G-to-A substitution into transgenic mice caused a loss of motor neurons in the spinal cord, with resulting paralysis and death at the age of 5–6 months (Gurney *et al.*, 1994). These findings suggest that oxidative stress may play a part in the pathogenesis of some cases of familial ALS. Furthermore, SOD activity has secondary effects on glutathione, and it is of interest that in sporadic cases of ALS, binding on glutathione in the dorsal and ventral gray horns is enhanced. On the other hand, the mutated gene in ALS coincides with the gene of the glutamate receptor subunit (Eubanks *et al.*, 1993).

Endemic Form (ALS–Parkinsonism–Dementia Complex of Guam)

A high incidence of the ALS–parkinsonism–dementia complex was observed in the inhabitants of Guam, and also in immigrants to the island (Garruto *et al.*, 1980). The condition was found in western New Guinea (Gajdusek and Salazar, 1982) and in the Kii peninsula of Japan.

Clinical Picture The features of ALS are often associated with dementia, and occasionally with parkinsonism. The disease forms part of the ALS–parkinsonism–dementia complex (see p. 559), which probably constitutes a single nosological entity with variable expression in individual cases.

Neuropathology *Light microscopy.* NFTs and GVD are found in the cerebral cortex, basal ganglia, substantia nigra, and brain stem, in addition to the usual lesions of ALS. In the spinal cord NFTs are even more abundant in the posterior horns than in the anterior ones (Matsumoto *et al.*, 1990). They react with all antibodies against neurofibrils, as well as τ and ubiquitin. Ultrastructurally, they consist mainly of straight filaments, but also of constricted filaments, 15 nm in diameter, with a periodicity of 80 nm (Kato *et al.*, 1992).

An additional feature, uncommon in other types of ALS, is the presence of Hirano bodies. These are not specific for the condition, as they occur in a number of other degenerative disorders. They consist predominantly of actin, but also contain actin-associated proteins, τ, the middle-molecular-weight neurofilament subunit, and a carboxyl-terminal fragment of β-amyloid precursor protein (Hirano, 1994).

Pathogenesis The restriction of the condition to small territorially confined communities suggests the operation of an environmental factor (Garruto *et al.*, 1981). Attention has been drawn in particular to the consumption of cycad flour by the Chamorro people of Guam (Spencer *et al.*, 1987). Cycads contain the excitotoxin 2-amino-3-methylaminopropanoic acid, which is thought to be a pathogenetic agent in the condition. Duncan *et al.* (1990), however, pointed out that only negligible amounts of this substance remain in the standard preparation of cycad flour.

An alternative theory is that of element toxicity. Elevations of aluminum and iron, combined with depletions of zinc and calcium, have been observed by Yasui *et al.* (1993).

Hudson and Rice (1990) were struck by the similarities between the Guamanian ALS–parkinsonism–dementia complex and postencephalitic parkinsonism and suggested that a viral etiology should be investigated.

Whatever the cause of the condition, the fact is that it is disappearing rapidly, suggesting that the environmental factor has been removed, at least in Guam.

Spastic Spinal Paralysis (Familial Spastic Paraplegia; Primary Lateral Sclerosis; Strümpell–Lorrain Disease)

The first cases of this disease were reported by Seeligmüller (1876) and the disease was defined as a nosological entity by Strümpell (1880) and Lorrain (1898). Brown (1975) emphasized the differences between families suffering from familial spastic paraplegia and those affected by spinocerebellar degenerations, while Schoene (1985) included them in the latter group. The existence of a pure degeneration of the pyramidal tracts has often been questioned. Most authors consider it a variant of ALS in which the lesions are limited to the upper motor neuron. However, quantitative morphological data show that there is a clear difference between ALS and spastic spinal paralysis (Hudson *et al.*, 1993).

Clinical Picture The disease may appear in a pure or complicated form and affects several members of a family (Harding, 1983). The lower limbs are predominantly affected. In the dominant form, which includes 70% of the affected families, two types may be distinguished. In type I spasticity is the main feature. Symptoms appear before the age of 35, and two subtypes are recognized according to the patient's age at onset: one between the ages of 3 and 6 years, the other between 20 and 30 years. In type II the disease presents after the age of 5 years with muscular weakness, sensory loss, and urgency of micturition or incontinence (Klemm and Tackmann, 1991). The symptoms progress very slowly over several decades (Schneider *et al.*, 1990). Dementia, ataxia, and external ophthalmoplegia occur occasionally (Brown, 1975; Staal *et al.*, 1983). Transitional cases between the two types with late onset and slow progression and others with predominant spasticity point to genetic heterogeneity. Families of both types with an autosomal-recessive mode of inheritance have occasionally been reported (Staal *et al.*, 1983). Combinations with symptoms of spinocerebellar atrophies and other neurological manifestations are not uncommon. Involvement of the posterior columns, particularly a loss of vibration sense, is more common than in ALS. A combination with pseudoophthalmoplegia and extrapyramidal symptoms (Ferguson–Critchley syndrome) is rare. Pringle *et al.* (1992) reviewed eight patients with progressive symmetrical spinobulbar spasticity. Clinical features were those associated with dysfunction of the upper motor neuron and included spastic quadriparesis, pseudobulbar effect, spastic dysarthria, hyperreflexia, and bilateral Babinski's signs. Lower motor neurons signs were absent and higher cognitive function was preserved. MRI revealed atrophy of the prefrontal gyrus and PET scans showed diminished glucose uptake in the

pericentral cortex. Weller *et al.* (1990) described a patient with bulbar spasticity that preceded the onset of spastic tetraparesis by 6 years. There was no evidence of lower motor neuron involvement. Recently, the patient developed a complete inability to move the face and the tongue voluntarily, while automatic movements were preserved (Foix–Chavany–Marie syndrome).

Neuropathology *Gross appearances.* The precentral gyrus, and particularly the paracentral lobule, are atrophic. In "pure" cases no obvious changes can be seen externally in the spinal cord. On transverse section a reduction in the size of the lateral columns and discoloration of the areas of the crossed pyramidal tracts may be seen in longstanding cases.

Light microscopy. A loss of neurons in the motor cortex, particularly in laminae III and V, can be seen in some pure cases. Degenerative changes in the form of shrinkage or swelling may be seen in surviving cells. Silver impregnations may reveal a swelling of the dendrites. In the cerebellum, particularly in type II, there may be a severe loss of Purkinje cells, even in the absence of clinical ataxia (Staal *et al.*, 1983). Neuronal loss can also be seen in the inferior olives.

In preparations stained for myelin, the loss of myelinated fibers is conspicuous in the precentral gyrus, particularly in the stratum supraradiatum, while the stratum zonale is preserved. Rarefaction of myelin in the hemispheric white matter, the internal capsules, and the basis pontis may be apparent. The loss of axons and myelin sheaths is more pronounced in the medullary pyramids and the crossed pyramidal tracts, particularly in the thoracic segments. In fat stains the number of fat granule cells varies according to the patient's age and the intensity of the process. Reactive astrocytes are sparse, and fibrillary gliosis and glial scarring are seen in later stages.

The fasciculus gracilis, and, less commonly, the fasciculus cuneatus and the spinocerebellar tracts, may be involved in the degenerative process (Staal *et al.*, 1983). The olivocerebellar fibers may also undergo atrophy. In one autopsied case of Pringle *et al.* (1992), atrophy was confined to the motor cortex with a complete loss of Betz's cells and shrunken remaining pyramidal cells. Sural nerve biopsies show a loss of large fibers, confirmed by electron microscopy (Tredici and Minoli, 1979).

Pathogenesis Familial spastic paraparesis may represent a mitochondrial disorder (Beltran and Coker, 1990).

X-Linked Recessive Bulbospinal Neuronopathy (Kennedy–Alter–Sung Syndrome)

The first familly with this variant of motor neuron disease was described by Kennedy, Alter, and Sung in 1968. Subsequent families and some apparently sporadic cases have been reported by Harding *et al.* (1982), Wilde *et al.* (1987), Nagashima *et al.* (1988), Sobue *et al.* (1989), and Aminoff *et al.* (1994). The term *X-linked recessive bulbospinal neuronopathy* was suggested by Harding *et al.* (1982).

Clinical Picture The onset is insidious between the ages of 20–40 years. The principal symptoms are tremor, cramps, fasciculation, and motor weakness. The weakness, which becomes prominent some 5–10 years after the onset of symptoms, is usually most severe in the proximal limb girdles, but becomes widespread with time. Bulbar weakness usually develops 10 or more years after the onset of limb weakness. Wasting, fasciculation, and weakness of the tongue are usually present in the late stages of the disease. Dysarthria and dysphagia are usually mild. Sensory disturbances are minimal, usually limited to some loss of vibration sense.

The course of the disease is protracted and generally benign. Exceptionally, severe dysphagia may lead to aspiration pneumonia and premature death (Sobue *et al.*, 1989). Associated conditions include endocrine abnormalities, including gynecomastia, testicular atrophy, and reduced fertility. Diabetes mellitus develops in 20–30% of the affected males in some kinships.

Neuropathology There are losses of anterior horn cells in the spinal cord and of neurons in the motor nuclei of the brain stem (Kennedy *et al.*, 1968; Nagashima *et al.*, 1988; Sobue *et al.*, 1989). The nuclei of nerves III, IV, and VI are preserved. Morphometric studies revealed losses of α- and γ-motor neurons as well as a loss of small cells in the dorsomedial zone of the anterior horn (Terao *et al.*, 1994). In contrast with ALS, the upper motor neuron is not involved. The dorsal root ganglia are preserved, but there is some distal axonal degeneration of the sensory nerves (Sobue *et al.*, 1989).

Pathogenesis The disease is inherited as an X-linked recessive. There is strong evidence that the androgen receptor gene, localized on the long arm of the X chromosome (Fishbeck *et al.*, 1986), may be responsible for the neuronal damage. The abnormality consists of repeats of the GAC nucleotide triplet on the first exon of the gene (La Spada *et al.*, 1991; Nakamura *et al.*, 1994). Androgens are concentrated on bulbar and spinal motor neurons, except for those of cranial nerves III, IV, and VI (Sar and Stumpf, 1977). Experimental work has shown that androgens affect the growth, development, and regeneration of motor nerves (Kurz *et al.*, 1986; Yu, 1989). The association of the X-linked bulbospinal neuronopathy with gynecomastia, testicular atrophy, reduced fertility, and partial resistance to androgens (Arbizu *et al.*, 1983) suggests that all manifestations of the disease are due to a single defective gene.

Motor Neuron Disease and Dementia

Several cases of an association of motor neuron disease with dementia have been reported in the literature. This is probably a heterogeneous group, but a well-defined clinicopathological entity was presented by Horoupian *et al.* (1984). In the past some similar cases were labeled *the amyotrophic form of CJD*, until these cases were shown to be nontransmissible (Salazar *et al.*, 1983), Knopman *et al.* (1990) widened the concept by including otherwise similar cases devoid of lesions of the lower motor neuron ("dementia lacking distinctive histological features"). Additional cases were contributed by Neary *et al.* (1990).

Clinical Picture Onset of the disease is commonly in middle age. Dementia usually precedes the onset of motor symptoms, sometimes by as much as 2 years, but occasionally follows it. It is generally of a frontal lobe type. The motor symptoms are predominantly bulbar, or occasionally spinal. Even in pure spinal cases bulbar involvement appears terminally. In some cases the bulbar syndrome is supranuclear rather than nuclear. Parkinsonian features are uncommon. The duration of the disease is short, usually between 2 and 4 years. Death is commonly due to complications of the bulbar paralysis.

Neuropathology *Gross appearances.* The frontal, and occasionally the temporal, lobes are atrophic, with narrow gyri and gaping sulci. The basal ganglia, and particularly the caudate nucleus, may also show a variable degree of atrophy (Knopman *et al.*, 1990). The substantia nigra is frequently depigmented. The lower cranial motor nerves, particularly the hypoglossal nerve, are commonly atrophic, while the anterior spinal roots are less frequently affected.

Light microscopy. The loss of large pyramidal neurons, particularly in layer III of the frontal and, less commonly, the temporal cortices is accompanied by a superficial zone of coarse status spongiosus with gliosis. The remaining pyramidal cells show atrophy of their apical dendrites with a loss of branches and spines in Golgi preparations (Horoupian *et al.*, 1984). No NFTs, SPs, or Pick or Lewy bodies are present ("no distinctive histological features"; Knopman *et al.*, 1990). A variable degree of neuronal loss in the striatum and the thalamus was present in all cases documented by Knopman *et al.* (1990). A loss of pigmented neurons, ranging from slight to severe, is always seen in the substantia nigra. Atrophy of the hypoglossal nucleus was present in all cases reported by Horoupian *et al.* (1984), but in only some of those of Knopman *et al.* (1990). Only one case of Horoupian *et al.* (1984) showed an extensive loss of anterior horn cells in the spinal cord.

Hereditary Dystonic Paraplegia with Amyotrophy and Mental Retardation

Among the reported cases of familial spastic paraplegia, there are several families that do not conform to the clinical or morphological criteria defined by Strümpell. Gilman and Horenstein (1964) reported on a family in which several members suffered from a spastic paraplegia, amyotrophy, extrapyramidal disturbances, and mental retardation and called the syndrome "familial amyotrophic dystonic paraplegia." The syndromes reviewed by Gilman and Romanul (1975) included the cases of early authors, with pallidopyramidal degeneration, "holotopistic striatal necrosis," and spinocerebellar atrophy with dementia and extrapyramidal symptoms.

Neuropathology *Gross appearances.* Moderate atrophy of the cerebral cortex was observed, particularly of the frontal and temporal lobes, as well as marked atrophy of the caudate nucleus and depigmentation of the substantia nigra and the locus coeruleus.

Light microscopy. Neuronal loss and reactive gliosis were seen throughout the cerebral cortex, with accentuation in the precentral gyrus. The anterior commissure was atrophic, and in the basal ganglia slight to moderate neuronal loss was present in the caudate nu-

cleus, putamen, and globus pallidus. The red and subthalamic nuclei were also affected. A severe loss of neurons was seen in the substantia nigra. Mild gliosis was present in the ambiguus, hypoglossal, and pontine nuclei. A loss of myelinated fibers was seen in the crossed and uncrossed pyramidal tracts and the fasciculus gracilis. The dorsal root ganglia, particularly in the thoracic region, showed a reduction in the number of neurons (Gilman and Romanul, 1975).

Progressive External Ophthalmoplegic Amyotrophy

Marburg (1936) included acquired (i.e., noncongenital) progressive external ophthalmoplegia in the group of progressive nuclear amyotrophies together with bulbar paralysis and spinal muscular atrophy. These primary ophthalmoplegias must be distinguished from similar manifestations occurring in the context of system atrophies as an additional, nonobligatory, feature. Paralyses of the ocular muscles may also occur as an equivalent of the fully developed picture, such as sixth nerve palsies in families with spinopontocerebellar atrophies. All of these possibilities must be excluded before the diagnosis of primary external ophthalmoplegia can be entertained.

Neuropathology A reduction in the number of nerve cells becomes apparent in serial sections of the nuclei of cranial nerves III, IV, and VIa. The area of these nuclei also appears shrunken and the emerging nerves appear attenuated. Some of the cases, however, are not of a neural nature, but a myopathic one.

Laurence–Moon–Biedl Syndrome

Laurence–Moon–Biedl syndrome is characterized by retinal dystrophy, polydactyly, obesity, mental retardation, spastic paraparesis, and hypogonadism. An association with Hirschsprung's disease and multiple anterior pituitary hormone deficiencies were often described. The importance of endocrine assessment of such patients who show a disturbance of growth or puberty (Radetti *et al.*, 1988), and, occasionally, seizures (Chalvon Demersay *et al.*, 1993) is emphasized. The syndrome has for some time been confused with Bardet–Biedl syndrome. In Laurence–Moon–Biedl syndrome polydactyly is rare and spastic paraparesis dominates, whereas neurological complications are very unusual in Bardet–Biedl syndrome (Green *et al.*, 1990). The photoreceptor cells are primarily affected (Runge *et al.*, 1986). A patient with Laurence–Moon–Biedl syndrome associated with hypothalamic hamartoma was described by Diaz *et al.* (1991).

Benign Focal Amyotrophy

The monomelic type of muscle atrophy shows a mild progression of the amyotrophy during the first 2 years and thereafter remains stationary (Barontini *et al.*, 1991). The atrophy and weakness involve the distal upper extremities and follow a benign course. In some patients the atrophy progressed to involvement of the lower extremities, and hyper-

reflexia may be categorized in the clinical spectrum between the spinal muscular atrophies and ALS (Liu and Specht, 1993).

Degeneration of the Lower Cranial Nerve Nuclei

Two syndromes occur in children and adolescents in which the loss of motor neurons affects predominantly the lower cranial nerve nuclei. The two syndromes cannot always be distinguished from each other (Perticoni *et al.*, 1983).

Fazio–Londe Disease

Fazio (1892) reported the occurrence of a bulbar palsy in a mother and her son. Additional familial cases were described by Londe (1895). The first neuropathological examination was reported by Gomez *et al.* (1962).

Clinical Picture The paralysis of the cranial nerves begins in early life. Unilateral or bilateral facial palsy is often the first symptom. Dysphagia, dysarthria, dyspnea, and somnolence are other features. According to their clinical course, the patients may be divided into two groups (McShane *et al.*, 1992). Those with severe respiratory distress run a subacute course and die in infancy or early childhood, while some of those with disease of later onset may survive to adolescence and beyond. Some cases are sporadic; others are familial. A dominant inheritance was apparent in the family reported by Fazio (1892), but in most other families the inheritance was recessive.

Neuropathology In all autopsied cases a loss of neurons was found in the motor nuclei of cranial nerves III–VII, X, and XII (Gomez, 1975; Rosemberg *et al.*, 1982; McShane *et al.*, 1992). A loss of anterior horn cells limited to the cervical and occasionally the thoralic segments is common. Some neuronal loss has been observed in the cerebellum (Gomez *et al.*, 1962; McShane *et al.*, 1992). In one case reported by McShane *et al.*, the thalamus and the basal ganglia were also involved. Atrophy of the external ocular, neck, and intercostal muscles was seen in most cases. An 8-year-old patient with clinical features of a juvenile bulbar paralysis was found to suffer from a generalized giant axonal neuropathy (Larbrisseau *et al.*, 1979).

Brown–Vialetto–van Laere Syndrome (Pontobulbar Paralysis with Deafness)

A syndrome of deafness and lower cranial nerve palsies was first described by Brown (1894). The familial incidence was confirmed by Vialetto (1936), and the nosological entity was defined by van Laere (1966). Many subsequent cases have been reported (Davenport and Mumford, 1994).

Clinical Picture The clinical course of the disease is episodic, with the irregularly occurring episodes coming to a standstill, but without complete remission (Brucher *et al.*, 1981). The first symptom is usually a sudden deafness (Tavares *et al.*, 1985), followed by various paralyses of the lower cranial nerves. Occasionally, muscular weakness precedes

the onset of deafness (Summers *et al.*, 1987). The disease is often familial, inherited as an autosomal-recessive trait (Brown, 1894). Females predominate over males in a proportion of 2:1. The onset of symptoms is usually in the second decade, but may be in childhood or as late as the fourth decade. The progression of the disease is chronic and the patients survive for many years or decades. A motor neuron disease with deafness, resembling Brown–Vialetto–van Laere syndrome, occurs sporadically in juveniles in southern India (Sayeed *et al.*, 1975).

Neuropathology Autopsy studies include those of Brucher *et al.* (1981) and Francis *et al.* (1993). They revealed neuronal loss in cranial nerve nuclei V–XII, in the anterior and posterior horn cells of the spinal cord, and in Clarke's column with degeneration of the spinocerebellar and spinothalamic tracts. A loss of Purkinje cells was noted in the cerebellum and many of those that remain show degenerative changes and axonal torpedoes (Francis, 1993). A severe loss of nerve fibers is seen in the cochlear nerve, with pronounced gliosis in the ventral cochlear nucleus.

Spinal Muscular Atrophies

This is a group of diseases, variable in their clinical course, genetically conditioned, with primary atrophy of the motor cells in the anterior horns of the spinal cord as their common feature. They are subdivided into several types and subtypes, according to age incidence, clinical course, involvement of different muscle groups, and mode of inheritance. Pearn (1980) recognized seven different syndromes, which included variants of neuroaxonal dystrophy and of Friedreich's ataxia, while Pou Serradell (1988) divided the spinal atrophies into primary and secondary, generalized and localized, forms.

A clear separation of the various types is not always possible in view of the overlap of the defined criteria in individual patients. As many clinical observations were not followed up by neuropathological examinations, a simple classification into four types based on the patient's age at onset and the clinical course is the most useful, to which a congenital variant may be added.

Congenital Spinal Muscular Atrophy

The infants are hypotonic from birth ("floppy infants") and usually die within a few months. Some cases are associated with cerebellar hypoplasia (see p. 576). Many cases are associated with limb deformities (arthrogryposis multiplex congenita) and are indistinguishable from Pena–Shokeir syndrome type I (see p. 688).

Infantile Type (Werdnig–Hoffmann Disease; Infantile Acute Spinal Muscular Atrophy; Amyotonia Congenita of Oppenheim; Spinal Muscular Atrophy Type I; Infantile Neuronal Degeneration)

This disease was described by Werdnig (1891) and Hoffmann (1893). In a number of cases clinically diagnosed as Werdnig–Hoffmann disease, lesions were found transgress-

ing the motor system. Steinman *et al.* (1980) coined the term *infantile neuronal degeneration* for this group of cases, including 14 of their own. They are generally referred to as atypical cases or are included in the group of multisystem atrophies. Aside from the congenital and acute forms, a chronic form was identified as type II or an intermediate form of spinal muscular atrophy.

Clinical Picture The acute form begins within the first 6 months. The proximal limb muscles and those of the trunk are preferentially involved. Fasciculation of the tongue is observed occasionally, as well as a discrete tremor and paradoxical respiratory movements due to weakness of the intercostal muscles and preservation of the diaphragm. Death occurs before the age of 4 years, usually from ascending paralysis involving the bulbar nerves or from aspiration pneumonia.

Pathology *Gross appearances.* The affected muscles appear pale brown.

Light microscopy. The atrophy of the skeletal muscles is characterized by group atrophy, often of entire fascicles. The atrophic fibers, of both types I and II, alternate with isolated or grouped normal or abnormally large fibers, mainly of type I (Fig. 308). In early stages of the denervation process, the grouping of fibers may be barely recognizable.

Neuropathology *Gross appearances.* The striking features are the shrinkage, increased consistency, and yellowish brown discoloration of the anterior horns. The anterior

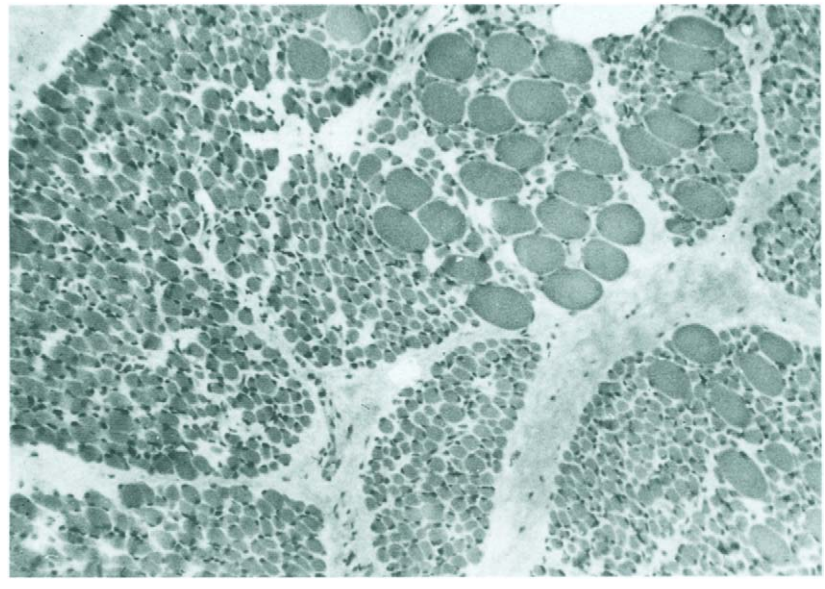


Fig. 308 Infantile form of spinal muscular atrophy. Pronounced atrophy of the muscle fibers, with preservation of the isolated abnormally large type I fibers. Hematoxylin–eosin stain, ×160.

roots share in the atrophy and are thinner than the normally more slender posterior roots (Fig. 309). The atrophy is particularly impressive in the regions of the cervical and lumbar enlargements.

Light microscopy. A severe loss of anterior horn cells is conspicuous in the affected parts of the spinal cord. The remaining neurons are often chromatolytic (Fig. 310). Aggregated ubiquitin granules are a characteristic feature in ballooned neurons (Matsumoto *et al.*, 1993). Neuronophagia (Fig. 310) and gliosis are common. Shrunken neurons are also frequently seen. The anterior horn cells in segment C3, supplying the phrenic nerve, are often spared, which accounts for the preservation of the diaphragm and the paradoxical respiratory movements. In the lumbar region Bandarenko *et al.* (1991) described giant neurofilamentous axonal spheroids, some approaching the size of the adjacent anterior horn cell. The long tracts of the spinal cord are affected occasionally. Aside from the pyramidal and spinocerebellar tracts (Fig. 311), the posterior columns may also be involved. The cells of Clarke's column may also be rarefied in the thoracic segments (Norman and Kay, 1965). Cerebellothalamic degeneration was reported by Norman and Kay (1965). This must be distinguished from cerebellar hypoplasia with congenital spinal muscular atrophy (see p. 578).

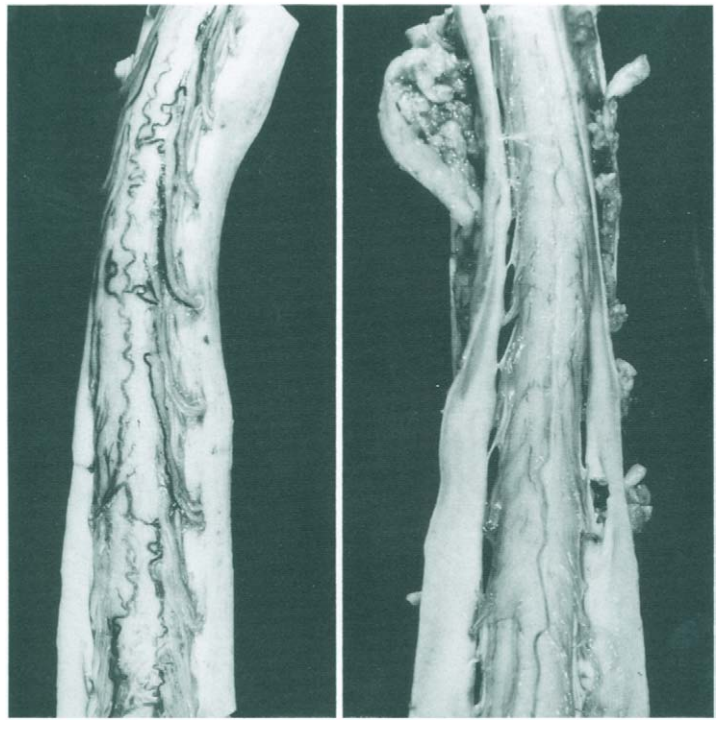


Fig. 309 Infantile form of spinal muscular atrophy. The anterior roots are thin, whereas the posterior roots are generally normal.

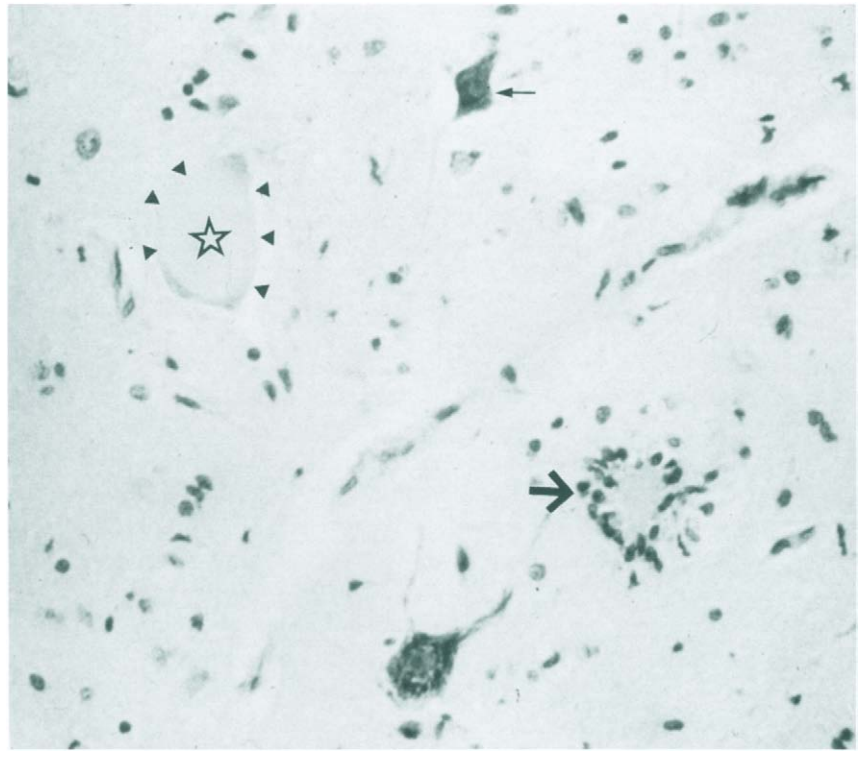


Fig. 310 Same case shown in Fig. 309. An anterior horn cell of the cervical cord, showing chromatolysis (star), neuronophagia (thick arrow), and shrinkage (thin arrow) of the neurons. Nissl stain, ×450.

Occasionally, degeneration may be present in the motor neurons of cranial nerves V–XII, as well as in the thalamus, basal ganglia, substantia nigra, dentatum, cerebellum (Fig. 312A), and dorsal root ganglia (Fig. 312B) (Sarnat *et al.*, 1989). Kato and Hirano (1990) showed in the oculomotor and trochlear nuclei several chromatolytic ballooned neurons. All contained epitopes of phosphorylated neurofilaments and ubiquitin. Phosphorylated neurofilaments were present mainly in the periphery of the cell in a ringlike shape, while the structures stained by the antibody to ubiquitin were small vesicles or granules and most of them were aggregated in the center of the cell. Neuronophagia and gliosis may also be seen. Some of the changes observed in the cerebrum and the cerebellum may be ascribed to terminal anoxia.

The large myelinated fibers have disappeared from the anterior roots. Large glial segments in the anterior roots have already been noted by Werdnig (1894). They also occur in the posterior roots. They are rarely observed in other diseases.

Electron microscopy. The glial bundles consist of astrocytic processes containing glial fibrils, and occasionally linked together by tight junctions. Each bundle is surrounded by a basal lamina and separated from neighboring bundles by an extracellular space containing collagen fibers. The chromatolytic cells, both motor and sensory (Peress *et al.*, 1986),

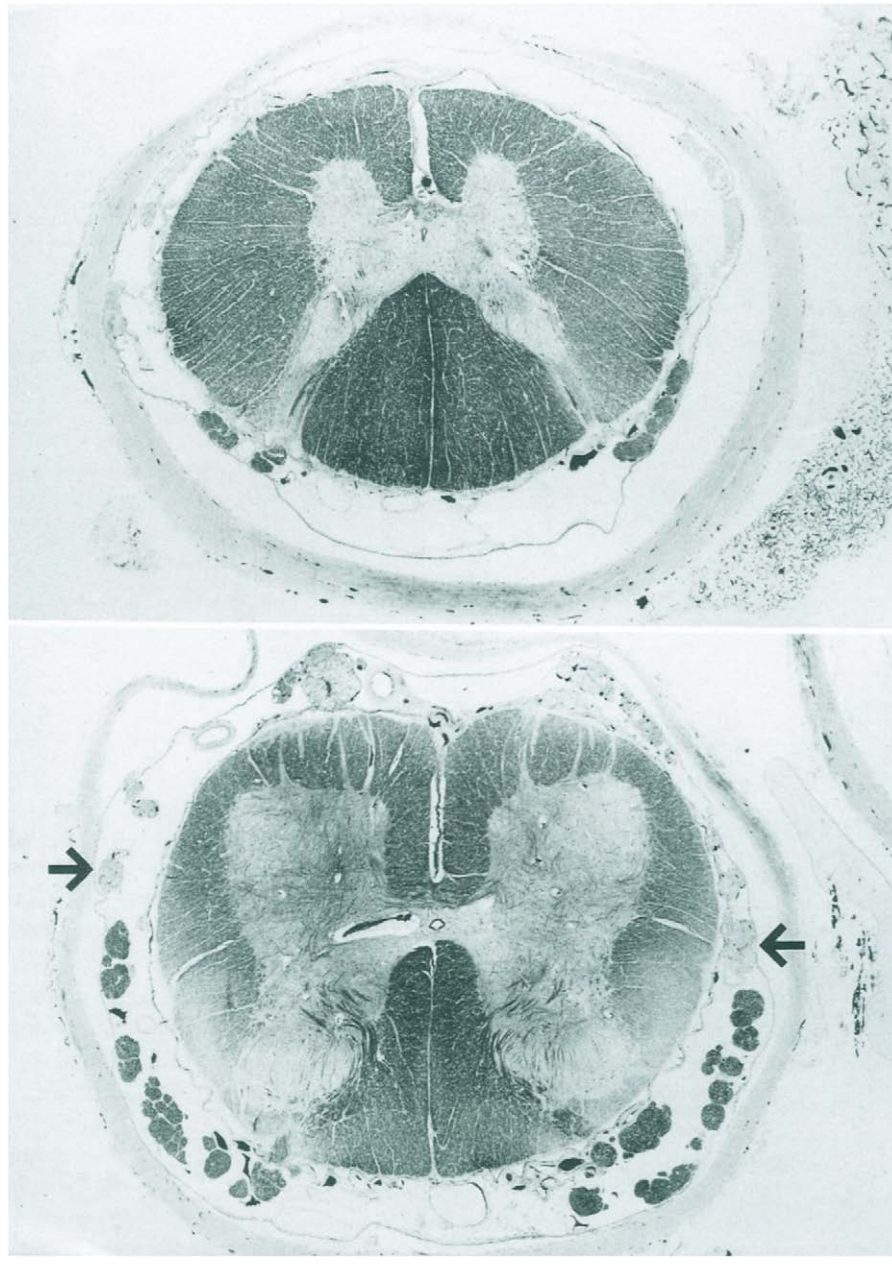


Fig. 311 Infantile form of spinal muscular atrophy. (Top) A loss of myelin in the pyramidal and spinocerebellar tracts. (Bottom) The anterior roots (arrows) are devoid of myelin. Heidenhain–Wölcke stain.

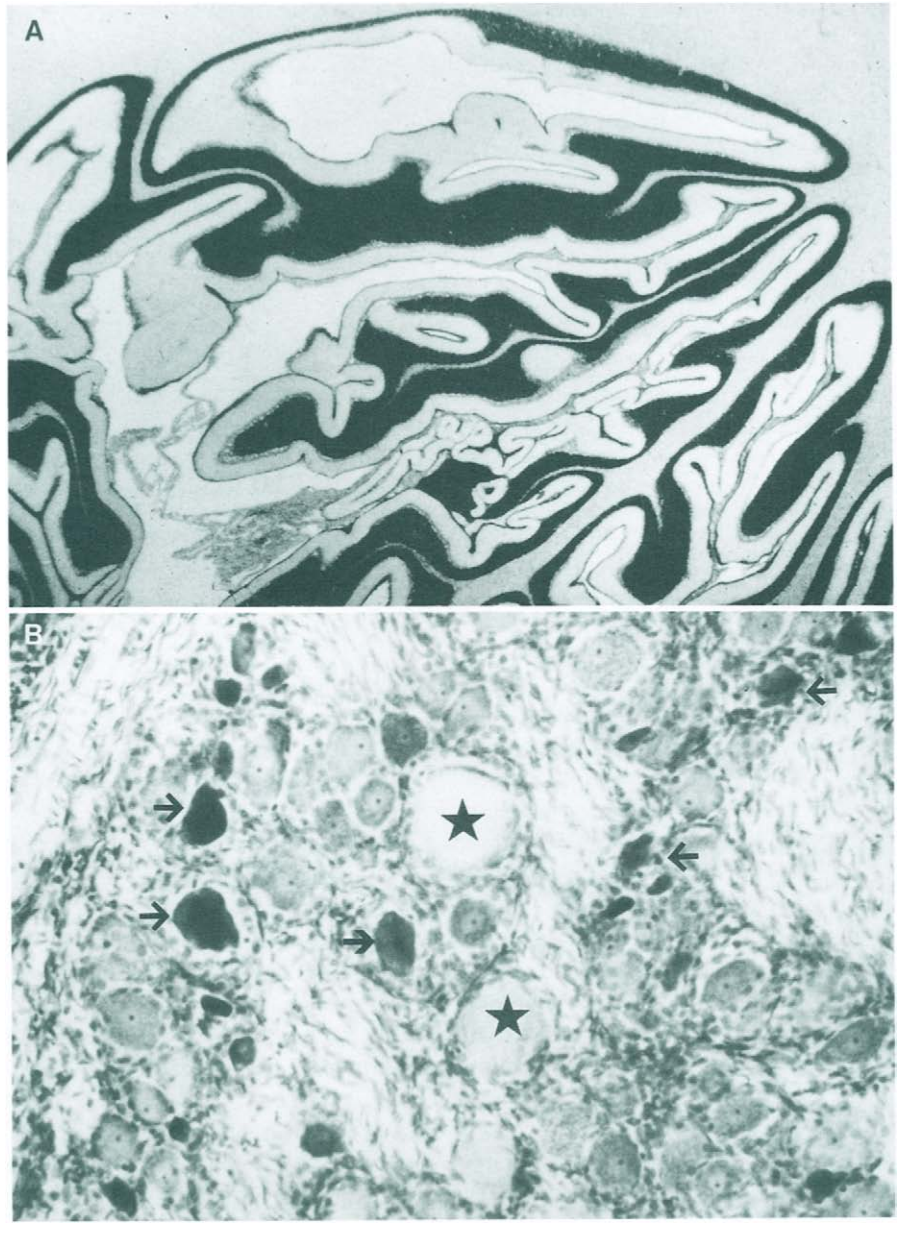


Fig. 312 Same case shown in Fig. 311. (A) A pronounced loss of Purkinje cells in the cerebellum. (B) Chromatolysis (stars) and shrinkage of the neurons in the posterior root ganglion. Nissl stain, (A) ×30 and (B) ×350.

show the ultrastructural features of axonal reaction. The anterior horn cells show features of immature neurons (Fidzianska *et al.*, 1984).

Chronic Infantile Form (Intermediate Spinal Muscular Atrophy; Spinal Muscular Atrophy Type II)

The chronic infantile form represents an intermediate type between the infantile and juvenile forms and is included by some authors in Wohlfart–Kugelberg–Welander disease (Pearn, 1980).

Clinical Picture The disease manifests itself during the first year of life and is characterized by proximal or generalized weakness. Scoliosis may develop in later stages. The occurrence of micropolymyoclonus has been reported. Death occurs in later childhood or adulthood after a protracted course of variable duration, but the disease process is never arrested (Russman *et al.*, 1983).

Juvenile Type (Wohlfart–Kugelberg–Welander Disease; Pseudomyopathic Spinal Muscular Atrophy; Chronic Proximal Spinal Muscular Atrophy; Spinal Muscular Atrophy Type III

This disease bears considerable similarity to juvenile muscular dystrophy of the limb girdle type. As a result, it was fairly late that it was recognized as an independent entity by Wohlfart *et al.* (1955) and by Kugelberg and Welander (1956). Some cases diagnosed as muscular dystrophy are, in fact, examples of this type of spinal muscular atrophy. This source of clinical confusion can now be resolved by the use of appropriate cDNA (Laing *et al.*, 1990). On the other hand, in patients who, in addition to having spinal muscular atrophy, exhibit other neurological and psychiatric manifestations, the possibility of hexosaminidase A deficiency should be considered (Parnes *et al.*, 1985).

Clinical Picture Several clinical variants may be distinguished (Harding, 1993). In the peroneal type the atrophy is predominantly distal. The pelvic girdle type, often associated with pseudohypertrophy of the calves, corresponds to the pattern described by Wohlfart and Kugelberg and Welander. In the scapulohumeral type the shoulder girdle is predominantly affected. The disease may be confined to the upper limbs and the shoulder girdle for many years before spreading to the lower limbs (Liu and Specht, 1993). All three types may manifest themselves only in adulthood and are compatible with long-term survival. The principal symptom is weakness in the legs and difficulty in walking, with a tendency to frequent falling. The muscular weakness may be precipitated by a nonspecific febrile illness.

The muscle atrophy usually begins proximally and is symmetrical. The average duration of the illness is 12 years, but in over 12% of the patients it is less than 5 years. On the other hand, prolonged survival up to 56 years has been reported.

Electromyography reveals denervation potentials and fasciculation suggestive of damage to the anterior horn cells. Fasciculation can be observed in the clinically affected muscles, and even more frequently in the tongue. Creatine kinase levels are normal, but

may be raised occasionally, which renders the differentiation from muscular dystrophy difficult. The diagnosis in these cases rests ultimately with a muscle biopsy. The Wohlfart–Kugelberg–Welander type may be inherited as an autosomal-recessive, autosomal-dominant, or X-linked recessive trait. The mode of inheritance of the scapulohumeral and peroneal types is autosomal dominant.

Pathology Aside from group atrophy and fiber type grouping, myopathic phenomena, such as fiber necrosis and phagocytosis (Fig. 313), may be present in muscles of the juvenile type of spinal muscular atrophy. The muscle fibers tend to be less rounded than in the infantile type.

Neuropathology The lesions in Kugelberg–Welander syndrome resemble those seen in Werdnig–Hoffmann disease (Kennedy *et al.*, 1968). A decrease in synaptophysin in the neuropil of the anterior horn was reported by Ikemoto *et al.* (1994).

Adult Type (Duchenne–Aran Disease; Vulpian–Bernhardt Disease; Scapuloperoneal Syndrome; Spinal Muscular Atrophy Type IV

Clinical Picture The adult type of spinal muscular atrophy with onset in the shoulder girdle is known as the Vulpian–Bernhardt type; that beginning in the hands and the fore-

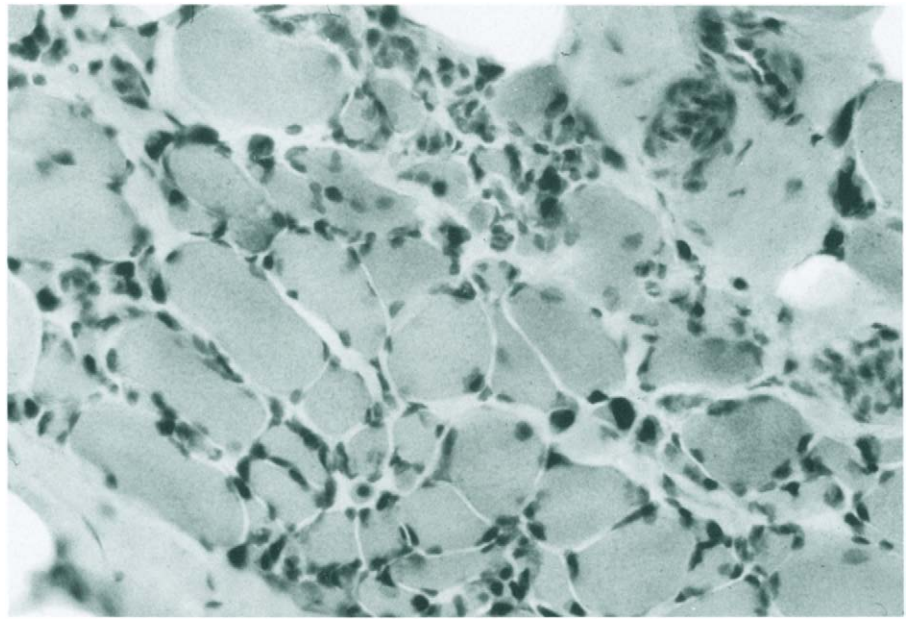


Fig. 313 Juvenile form of spinal muscular atrophy. Group atrophy of the muscle fibers, fiber necrosis, and phagocytosis. Hematoxylin–eosin stain, ×300.

arms is referred to as the Duchenne–Aran type. Both sporadic and familial cases occur in scapuloperoneal syndrome (Schröder, 1982). The onset of weakness in the distal musculature is at the age of around 30 years. The simultaneous appearance of myoclonus was reported in one family (Jankovic and Rivera, 1979). The course of the various types of the disease is slowly progressive and extends over several decades. The gradually extending atrophy leads ultimately to considerable disability. A few patients develop additional symptoms as well as mental retardation (Marsh and Munsat, 1974).

Neuropathology The findings resemble those seen in the infantile and juvenile forms and vary in extent and severity with the course of the disease. A loss of neurons and degenerative changes in surviving anterior horn cells are accompanied by slight gliosis of the anterior roots (Jankovic and Rivera, 1979). A variable loss of nerve fibers is seen in the peripheral nerves.

Although the pathological changes or the loss of neuronal cells was absent from the brains with classical histological techniques, an absence of dystrophin was found by Uchino *et al.* (1994). The authors postulated a relationship to the intellectual disturbance observed in some patients.

Pathogenesis The gene for spinal muscular atrophy was located by Brzustowicz *et al.* (1990) and independently by Melki *et al.* (1990) to the long arms of chromosome 5 (5q11.2–13.3). Initially, this was demonstrated only for the juvenile and adult types. The predominant locus for the chronic infantile form was mapped between *D5S6* and *MAP1B* (Brzustowicz *et al.*, 1993). Subsequently, it was shown that the same locus is shared by Werdnig–Hoffmann disease (Gilliam *et al.*, 1990), in which deletions in the 5q13 region have been found (Melki *et al.*, 1994) in a single locus mapped to a region between loci *D5S435* and *MPA1B* on chromosome 5q11.2–13.3 (Kleyn *et al.*, 1993). This accounts for the occasional occurrence of acute and chronic forms of the disease in the same family (Shaw *et al.*, 1992).

There remains a certain heterogeneity in the group of spinal atrophies. A small number of families (MacKenzie *et al.*, 1994), both typical and atypical, experience disease not caused by mutation in the 5q13 region. Ciofu *et al.* (1993) postulated X-linked inheritance for their family of congenital spinal muscular atrophy. The adult X-linked bulbospinal neuronopathy (Kennedy *et al.*, 1968) constitutes a distinct entity and is considered separately (see p. 649).

Motor Neuron Diseases in Animals Neurological disturbances caused by diseases of the motor neurons have been observed in a variety of young animals. These include the *wobbler* mutant of mice (Chamberlain *et al.*, 1988) and in zebras (Higgins *et al.*, 1977), cats (Vandervelde *et al.*, 1976), dogs (Tsai *et al.*, 1993), rabbits (Shields and Vandervelde, 1978), pigs (Higgins *et al.*, 1983), and horses (Cummings *et al.*, 1990). A genetic determination is presumed in most of these cases, and a definite hereditary pattern was demonstrated in dogs (Tsai *et al.*, 1993).

Under light microscopy vacuolation of the anterior horn cells was seen in the *wobbler* mouse (Mitsumoto *et al.*, 1987) and in horses (Cummings *et al.*, 1990). Other cell bodies were shrunken and undergoing neuronophagia. In the *wobbler* mouse the motor neurons

show an altered distribution of the neurofilaments. In dogs with hereditary muscular atrophy, neuronal loss was seen in the midbrain, medulla oblongata, and spinal cord. In addition, degenerating axons were found in the cerebellum, with retrograde changes in Purkinje cells. Chromatolytic neurons were also found in the dorsal root ganglia. Axonal swellings were present in the dorsal roots, in some cranial nerves, in the dorsal columns, and in the region of spinocerebellar tracts. On electron microscopy the axonal swellings contained an accumulation of neurofilaments, 10 nm in diameter. Concentric multilamellar inclusions were found in the ventral horn cells of dogs with hereditary neurogenic muscular atrophy.

Peripheral and Autonomic Neuropathies with Involvement of the Central Nervous System

This chapter deals with some disorders affecting primarily the peripheral and autonomic nervous systems, but which may be accompanied, regularly or occasionally, by lesions in the CNS.

Charcot–Marie–Tooth Disease (Progressive Peroneal Atrophy; Neurospinal Muscular Atrophy; Hereditary Motor and Sensory Neuropathy Types I and II)

Charcot and Marie (1886) separated from the progressive muscular atrophies a group of cases in which the atrophy began in childhood, affecting first the feet and then the lower legs, and sparing the arms. In the same year Tooth (1886) published his paper on the peroneal type of progressive muscular atrophy. Hoffmann (1889) proposed the term *progressive neuropathic atrophy*, while other authors preferred *neurospinal muscular atrophy. Peroneal muscular atrophy* is a clinical concept, based on the distribution of the muscular wasting. It is, in fact, a group of disorders heterogeneous both morphologically and genetically. Dyck and Lampert (1968a,b) subdivided the syndrome into a predominantly neuropathic form [hereditary motor and sensory neuropathy (HMSN) type I] and a neuronal form (HMSN type II). Lapresle (1980) included the latter in the group of spinocerebellar atrophies, while Harding (1992) considered it a variant of spinal muscular atrophy.

At least four subtypes are known to occur in the neuronal form: two autosomal domi-

nant (one with juvenile onset, the other with adult onset) and two autosomal recessive (a mild type and a severe juvenile type) (Harding, 1992).

Clinical Picture The disease may manifest itself in childhood around the age of 4 years, in adolescence around the age of 15 or 16 years, or, in two thirds of the cases, in adulthood up to the fifth decade. The first symptoms always involve the legs in children, while in adults occasionally the arms may be affected first. The muscular weakness leads to instability of gait in adults, while the children lose their ability to walk altogether. Muscular atrophy is a prominent feature, while sensory and autonomic symptoms are inconstant. A chronic progressive ophthalmoplegia has been repeatedly observed. Rantala *et al.* (1986) laid down the criteria for distinguishing the neuropathic and neuronal forms on the basis of symptomatology and clinical course.

In cases with disturbances of deep sensation, pyramidal signs, and cerebellar symptoms, it may be difficult to decide between Charcot–Marie–Tooth disease with central involvement and a form of spinocerebellar degeneration with amyotrophy.

The mode of inheritance may be autosomal dominant or recessive, or sex linked, which implies a considerable heterogeneity.

Pathology Both neurogenic and myopathic lesions have been described on muscle biopsies. Purely neurogenic changes are seen in the early stages; lesions of myopathic appearance may be superimposed later.

Neuropathology Early neuropathological observations were published by Marinesco (1894). The findings in most reports are difficult to evaluate, as the type of the neuropathy is rarely specified. The anterior horn cells in the spinal cord are always affected. Even if the number of neurons is not reduced (Dupuy *et al.*, 1983), central chromatolysis is present. The changes are particularly prominent in the lumbosacral region. Clarke's column is affected in about one half of the cases. In the white matter changes may be seen resembling those of spinocerebellar degenerations. The posterior columns are commonly affected; the pyramidal tracts, rarely. Gliosis is variable. The nuclei of Goll and Burdach may be atrophic, as well as the reticular substance in the medulla oblongata. Some cranial nerve nuclei can be atrophic. The substantia nigra may also be affected (Dupuy *et al.*, 1983).

In the dorsal root ganglia central chromatolysis can be seen as well as neuronal loss with a proliferation of satellite cells. The posterior roots show a severe loss of myelin with a proliferation of endoneurial connective tissue. In the peripheral nerves the differences between the two main types are distinct. The neuropathic form is a chronic demyelinating neuropathy with a proliferation of Schwann cells and formation of "onion-bulbs." In the neuronal group there is a loss of large myelinated fibers with a relative increase in the number of small U-fibers. Brooks (1980) described a giant axonal neuropathy in the myenteric plexus.

Pathogenesis Two autosomal-dominant variants have been identified, one with linkage to markers on the short arm of chromosome 17 (HMSN 1A), the other with linkage to

markers on the long arm of chromosome 1 (HMSN 1B) (Dyck *et al.*, 1992). Two different abnormalities have been identified in HMSN 1A: a duplication of 17p11.2 (Hallam *et al.*, 1992) and a point mutation of the gene *PMP22* in the same region, but without duplication (Gabreëls-Festen and Gabreëls, 1993). This region coincides with the locus of P_0, a major structural protein of peripheral myelin. In two pedigrees with the HMSN 1B genetic type, Hayasaka *et al.* (1993) found point mutations that are completely linked with the disease. The mutations are located in the extracellular domain, which plays a significant role in myelin membrane adhesions. Autosomal-recessive forms also occur, the gene of which has not been identified, as well as X-linked forms located on the long arm of the X chromosome (Dyck *et al.*, 1992).

Giant Axonal Disease (Giant Axonal Neuropathy)

Giant axonal neuropathy was described by Asbury *et al.* (1972) as a slowly progressive peripheral neuropathy. Involvement of the CNS has been repeatedly observed. The possibility of intermediate forms between infantile neuroaxonal and giant axonal dystrophy was discussed by Begeer *et al.* (1979).

Clinical Picture The disease begins between the ages of 2 and 6 years and progresses slowly over 15–20 years. Cases of later onset have occasionally been reported (Korves *et al.*, 1992). The first symptoms consist of hypotonia, areflexia, nystagmus, and unsteadiness of gait, followed by ataxia, typical peripheral neuropathy, optic atrophy, and dementia in the terminal stages. CT and MRI have been normal in some cases, but showed mostly changes in the white matter (Buissoniere *et al.*, 1989). The children often have very fair curly hair. An adult form, caused by a vitamin B_{12} deficiency, has also been reported. Axonal swellings, closely resembling those of giant axonal neuropathy, are also found in human toxic neuropathies produced by acrylamide and organic solvents.

Neuropathology The axons of the peripheral nerves, posterior columns, and cerebral cortex show swellings (Fig. 314) up to 30 μm and narrower spindle-shaped expansions. Onion bulb structures may also be present (Korves *et al.*, 1992). Many neurons show central chromatolysis. Abnormal neurofilament phosphorylation is suggested by heavy immunostaining of enlarged axons by a monoclonal antibody to neurofilament phosphorylated determinants and a lack of reaction with monoclonal antibodies with different phosphoepitope affinities (Taratuto *et al.*, 1990). Most enlarged axons are surrounded by a thin myelin sheath or are devoid of myelin. The number of myelinated fibers varied considerably among fascicles of the same nerve: some show a severe or moderate reduction, while others disclose a quite normal density. The number of giant axons is also clearly different among fascicles.

Electron microscopy. The swellings (Fig. 315) contain accumulations of intermediate filaments, 10–12 nm in diameter (Goebel *et al.*, 1986). Microtubules, tubulomitochondrial complexes, and smooth endoplasmic reticulum are compressed and displaced into spaces free from filaments. Filamentous inclusions are also found in endothelial cells,

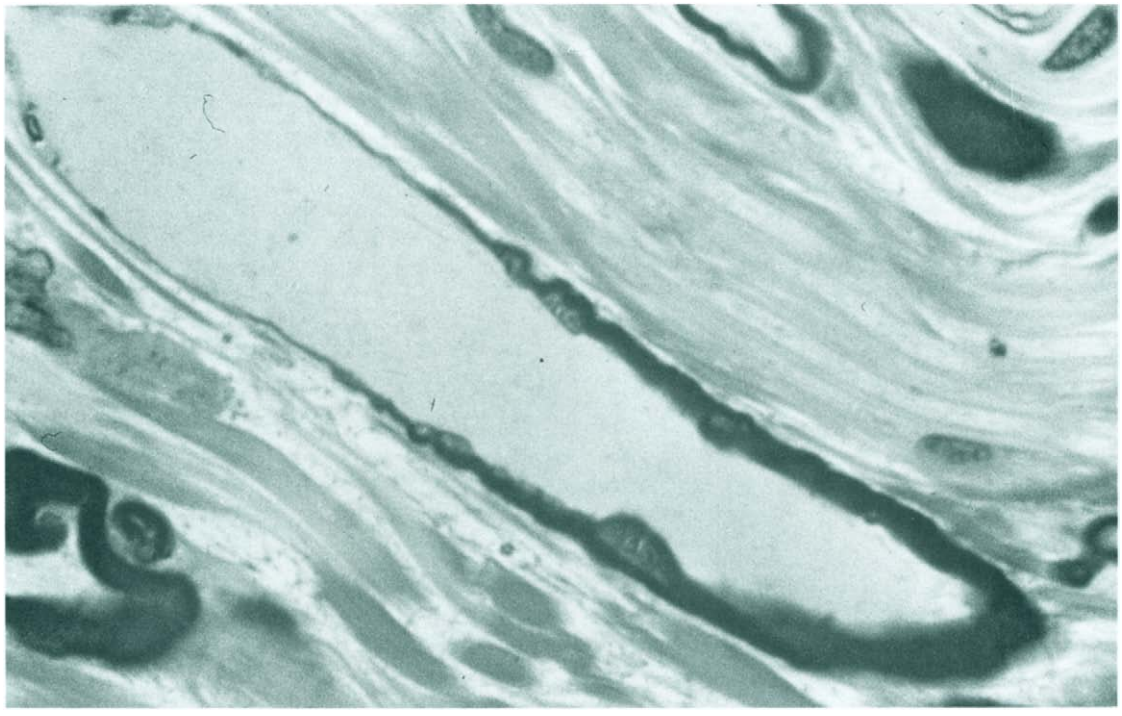


Fig. 314 Organic solvent neuropathy. The sural nerve, showing giant axonal swelling. Heidenhain–Wölcke stain, ×1000.

skin fibroblasts, perineurial cells, and Schwann cells (Sabatelli *et al.*, 1992). The inclusions in various cell types consist of at least three types of intermediate filaments: neurofilaments, glial filaments (GFAP), and mesenchymal (vimentin) filaments (Peña, 1982).

Pathogenesis Giant axonal disease is an autosomal-recessive inherited disorder. The autosomal-dominant cases of Goebel *et al.* (1983) probably represent a variant of type 2 of HMSN. Giant axonal swellings may be a consequence of flattening of the side arms of the neurofilaments against the axis of the filaments (King *et al.*, 1993).

Axonal enlargements also occur in rats that have been given 2,5-hexanedione (Stoltenburg-Didinger and Altenkirch, 1988) and in a hereditary neuropathy of rats (Janota, 1972). The generalized disorder of intracytoplasmic filaments may be ascribed to a genetic defect, probably of synthesis and spacial organization, of the intermediate filaments.

A number of cases reported in the literature have resulted from consanguineous marriages. This makes autosomal-recessive inheritance of giant axonal neuropathy highly probable (Donaghy *et al.*, 1988).

Close to the human giant axonal disease is the hereditary canine giant axonal neuropathy (King *et al.*, 1993).

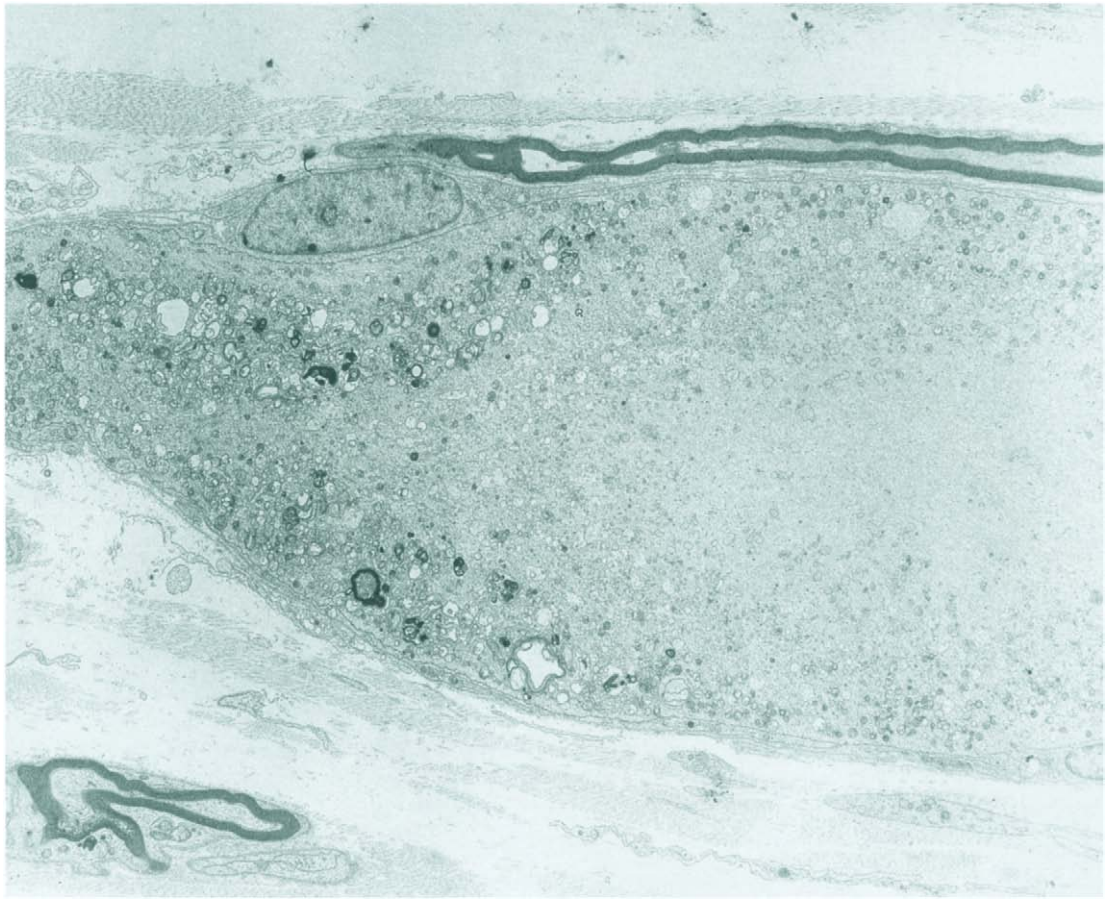


Fig. 315 Giant axonal neuropathy. The sural nerve, showing an accumulation of neurofilaments in axonal swelling and displacement of other organelles to the periphery, ×3000.

Orthostatic Hypotension (Shy–Drager Syndrome; Progressive Autonomic Decline; Idiopathic Orthostatic Hypotension; Multisystem Atrophy with Orthostatic Hypotension)

Orthostatic hypotension was described by Bradbury and Eggleston (1925), and the clinical syndrome was defined by Barker (1933) on the basis of his own case and a review of the literature. The first anatomopathological examination of a case was carried out by Shy and Drager (1960). Patients with autonomic impairment, clinically unassociated with other neurological abnormalities, are considered to have Bradbury–Eggleston syndrome (idiopathic orthostatic hypotension, or pure autonomic failure). Individuals

whose autonomic failure is accompanied by degeneration in other neurological systems are classified as having Shy–Drager syndrome (multiple system atrophy with autonomic failure) (Robertson *et al.*, 1993).

Both clinically and neuropathologically, two groups may be recognized: one with lesions typical of PD, the other belonging to the group of multisystem atrophies (Oppenheimer, 1983). In the latter, two subgroups may be distinguished: one associated with OPCA, the other with striatonigral degeneration. In all of these groups and subgroups, orthostatic hypotension is the most prominent symptom, the other manifestations remaining in the background or appearing in later stages of the disease. In view of the prominence of autonomic symptoms, it is justifiable to consider the syndrome among the degenerative disorders of the autonomic nervous system. In addition, combined forms have been recorded in which features of the different groups appear together (Sima *et al.*, 1987). The view that the two main groups represent different nosological entities cannot, therefore, be sustained.

Clinical Picture The disease may begin in adolescence, but in most cases the symptoms appear in the fifth or sixth decade, occasionally even in the eighth (Kakulas *et al.*, 1986). Orthostatic hypotension is usually the first symptom. Upon arising or standing, the blood pressure drops to abnormally low levels. This is associated with tachypnea and reduction of the CO_2 pressure in the blood. Other symptoms include disturbances of bladder and rectal functions, impotence, reduced sweating, atrophy of the iris, ophthalmoplegia, and amnesia. In 50% of the patients, there are abnormal sympathetic skin responses (Yokota *et al.*, 1993).

In the group of patients with neuropathological features of PD, overt parkinsonism is present only in one half of the cases. A neurogenic atrophy of the skeletal muscles has been observed in some cases. An association with the sleep apnea syndrome has also been reported.

In the group of patients with multisystem atrophy, ataxia, pyramidal signs, and intention tremor may be accompanied by parkinsonian symptoms due to striatonigral degeneration. In these patients the putaminal lesions can be confirmed by MRI (Maciel-Junior *et al.*, 1991). PET disclosed in two patients with longer disease duration a reduced (18F)6-fluoro-1-dopa uptake, suggesting impaired nigrostriatal dopaminergic function (Bhatt *et al.*, 1990).

Most cases are sporadic, but familial occurrence has been reported (Ilson *et al.*, 1982). Familial orthostatic hypotension may also be a manifestation of amyloid neuropathy type I (see p. 203). The duration of illness in the multisystem atrophy group is generally between 4 and 8 years.

Pathology Spherical eosinophilic inclusions have been seen in the adrenal medulla (Kimula *et al.*, 1983).

Neuropathology All cases show neuronal loss in the intermediolateral nucleus, as well as in the anterior horns of the thoracic and lumbar cords. Mannen *et al.* (1982) drew attention to the involvement of the sacral autonomic neurons, particularly the nucleus of Onufrowicz, in contrast with motor neuron diseases, in which this nucleus is almost invariably spared (see p. 637).

In the parkinsonian type there is neuronal loss and gliosis in the pars compacta of the substantia nigra. Lewy bodies are present in the pigmented cells of the substantia nigra and the locus coeruleus (Tomonaga, 1983) and also in the sympathetic ganglia. Dopamine receptors are diminished in the substantia nigra as in PD (see p. 548), as well as in the neurons of the caudate nucleus.

In the multisystem atrophy group degeneration of the cerebellar, corticobulbar, corticospinal, and extrapyramidal tracts (Fig. 316A,B) is accompanied by gliosis (Shy

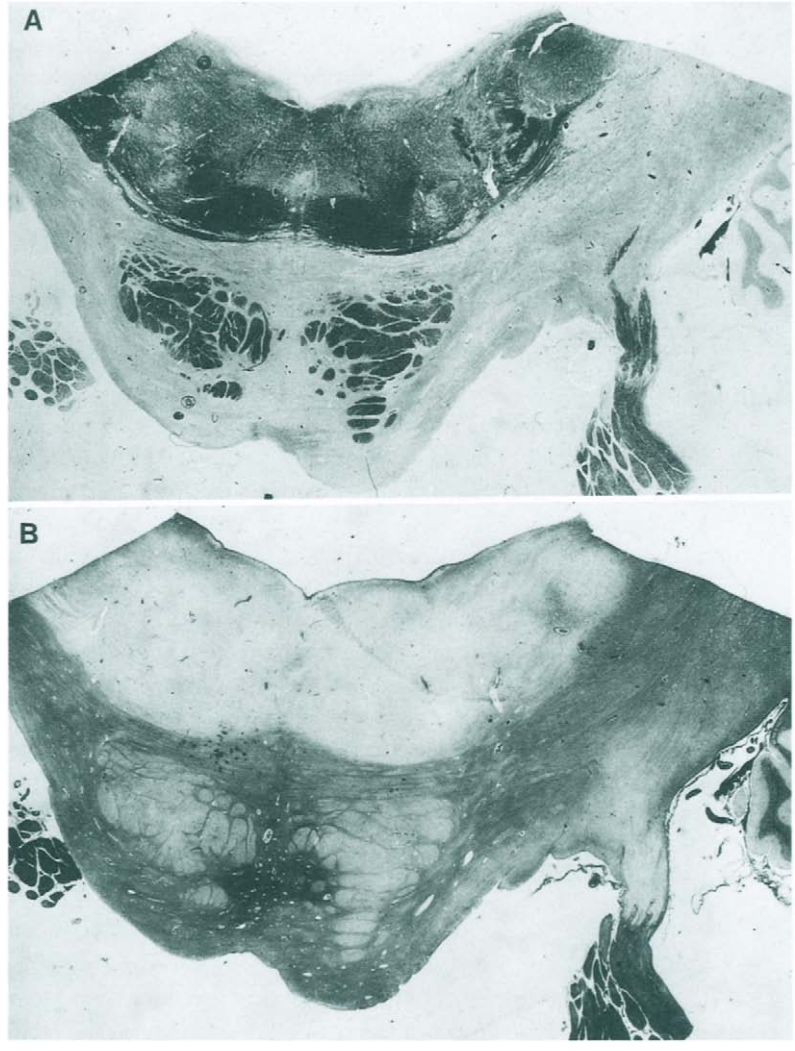


Fig. 316 (A) An extensive loss of myelin in the pontocerebellar tracts with (B) marked reactive gliosis. (A) Heidenhain–Wölcke stain; (B) Kanzler stain. (Courtesy of J. Escalona-Zapata, Madrid, Spain.)

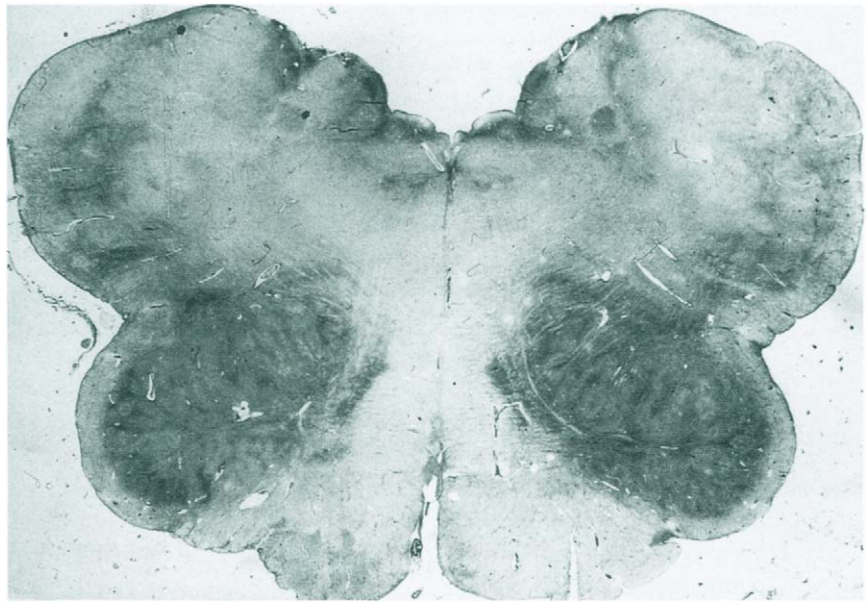


Fig. 317 Same case shown in Fig. 316. Severe gliosis of the olives. Kanzler stain.

and Drager, 1960; Kakulas *et al.*, 1986). Gliosis is also seen in the inferior olives (Fig. 317), the putamen, and the claustrum. Striatonigral degeneration without a cerebellar component has also been described (Linoli and Asioli, 1993). Inclusion bodies were demonstrated in the cytoplasm and the nucleus of both neuronal and oligodendroglial cells and in neuronal processes by means of silver staining, immunocytochemistry, and electron microscopy (Papp and Lantos, 1992).

Changes in sympathetic ganglia include a loss of neurons and diminution of dopamine β-hydroxylase and choline acetyltransferase (Petito and Black, 1978). There is a decrease in the number of cholinergic fibers in the bladder (Kirby *et al.*, 1986). A reduced adrenergic innervation of the blood vessels was found predominantly, and a hypersensitivity of adrenergic receptors (Polinsky, 1984) was seen exclusively in patients in whom orthostatic hypotension was the only abnormality.

On electron microscopy of a peripheral nerve, a selective loss was found of thin myelinated fibers and U-fibers, in addition to the presence of multilamellar Schwann cell processes (Tohgi *et al.*, 1982).

In a patient aged 54 years with a multiple dysautonomia, Bogousslavsky *et al.* (1983) found antibodies against acetylcholine receptors in the serum and the CSF. Neuropathological examination revealed diffuse neuronal loss and gliosis in the cerebral cortex without abnormalities in other parts of the CNS.

Pathogenesis A group of patients with orthostatic hypotension has been identified with a lack of activity of plasma bradykininase I (Johnson, 1982). Adrenergic denervation was postulated and an increase of α-adrenergic receptors was demonstrated (Kafka *et al.*,

1984) in patients with amyloid neuropathy (see p. 203). The tuberoinfundibular dopaminergic system may also be involved in Shy–Drager syndrome (Konagaya *et al.*, 1985). In the case reported by Bogousslavsky *et al.* (1983), the authors assumed a generalized cholinergic dysfunction. Orthostatic hypotension is commonly ascribed to a loss of neurons in the intermediolateral nucleus of the spinal cord.

On the other hand, Gray *et al.* (1988) found no correlation between neuronal loss in the intermediolateral nucleus and the severity of orthostatic hypotension. Similarly, no oligodendroglial cytoplasmic inclusions were found in the spinal cord, while a great abundance was seen in the reticular nuclei of the pons and the medulla (Papp *et al.*, 1989; Papp and Lantos, 1994). The authors suggest that the cause of the orthostatic hypotension lies in the lesions of the supraspinal, not the spinal, component of the sympathetic system.

Pure Autonomic Failure (Idiopathic Orthostatic Failure; Bradbury–Eggleston Syndrome)

The clinical picture includes severe orthostatic hypotension without pulse acceleration, leading to fainting, anhidrosis, impotence, and postprandial syncopal episodes. Autonomic failure gradually worsened over the years. No other neurological signs are present. In earlier published cases (Gibb, 1988) Lewy bodies in their pigmented brain stem nuclei, sometimes associated with neuronal loss, were described. In a case reported by Ingelghem *et al.* (1994) with postmortem examination, there was no evidence of multiple system atrophy. No cell loss, neuronal degeneration, or Lewy bodies in pigmented brain stem nuclei were found. The pathological alterations were limited to intermediolateral column cells and sympathetic ganglia. Intermediolateral column cells were appreciably depleted. In the sympathetic ganglia there was a pronounced loss of neurons and neuronal degeneration associated with Lewy bodies. This case indicates that pure autonomic failure can occur in the absence of presymptomatic PD. Furthermore, it supports the view that in pure autonomic failure the lesion is more distal than in autonomic failure associated with multiple system atrophy.

Congenital Disorders of Intestinal Innervation

Nervous control of gastrointestinal motility is extremely complex, regulated by the enteric system, the "brain of the gut," and modulated by extrinsic nerves. This system, with its multiplicity of transmitters and receptors, does not always allow a clear interpretation of experimental data, especially with compounds lacking specificity (Demol *et al.*, 1989).

Inborn errors of intestinal innervation can be classified in five different major forms:

1. Aganglionosis (including total aganglionosis of the colon, Hirschsprung's disease, ultrashort Hirschsprung's segment, and neurogenic sphincter achalasia)
2. Hypoganglionosis
3. Congenital malformation of sympathetic innervation of the colon [neuronal intestinal dysplasia type A (NID A)]

4. Congenital malformation of the submucous plexus (NID B)
5. Achalasia

Half of the biopsies cannot be introduced into the above classification due to moderate malformations of the intestinal innervation (Meier-Ruge, 1991).

Hirschsprung's Disease (Long-Segment Aganglionosis; Typical Form of Congenital Megacolon)

Hirschsprung's disease is characterized by the absence of enteric neurons from the distal colon and rectum. In this form the excess of extramural parasympathetic activity may cause permanent contraction of the ring musculature and a stenotic segment. Prestenotic dilatation of the colon (megacolon) is a secondary phenomenon.

Pathology Considerably more than half of the children with this condition show distinct to very severely pronounced fibrosis of the intestinal wall. Mostly the lamina muscularis mucosa is also widened and may be transformed, forming ring and longitudinal muscle fibers. Inflammatory infiltrates of the mucosa are frequent.

The ganglion cells of Auerbach's and Meissner's plexuses are completely missing in a distal large-bowel segment of varying length. The preponderance of parasympathetic innervation is recognizable by an increase in the acetylcholinesterase reaction (Figs. 318 and 319) in parasympathetic nerve fibers of the mucosa, which is of diagnostic importance. In addition to the standardized histological and enzymohistochemical methods, immunohistochemical examinations have provided valuable supplementary information in the diagnosis of Hirschsprung's disease and other related clinical pictures. Antibodies against neurofilaments, neuron-specific enolase, S-100 protein, and GFAP were used; furthermore, different transmitters, neuropeptides, and hormones were immunohistochemically proven (Kawana *et al.*, 1988). The involvement of intestinal endocrine cells in Hirschsprung's disease was also immunohistochemically examined (Nakagawa and Parentes, 1988). The diagnosis of Hirschsprung's disease was facilitated by these examinations.

In normal control gut GFAP, S-100, and GS were expressed strongly by the supporting cells of the myenteric and submucosal plexuses, interconnecting nerve fiber bundles of the plexuses, and fine nerve strands in the muscular layer. The nerve bundles of the subserosa merging into the muscular layer were also immunoreactive for GFAP and S-100, but negative or only faintly positive for GS. Aberrantly proliferated nerve bundles in the aganglionic segment of the Hirschsprung's disease colon were accompanied by supporting cells strongly positive for GFAP and S-100, but negative or faintly positive for GS. The supporting cells of the enteric neurons proper, enteric glia, express GFAP, S-100, and GS, whereas the supporting cells of the extrinsic components, which accompany peripheral nervous system axons, are negative or very weakly positive for GS. Therefore, GS immunocytochemistry may delineate intrinsic and extrinsic neural components in the enteric nervous system; and may provide an important clue for the differential diagnosis of Hirschsprung's disease (Kato *et al.*, 1990). In the narrow aganglionic segment very few synapses are seen in the muscle layers; proliferating nerve fibers and bundles are promi-

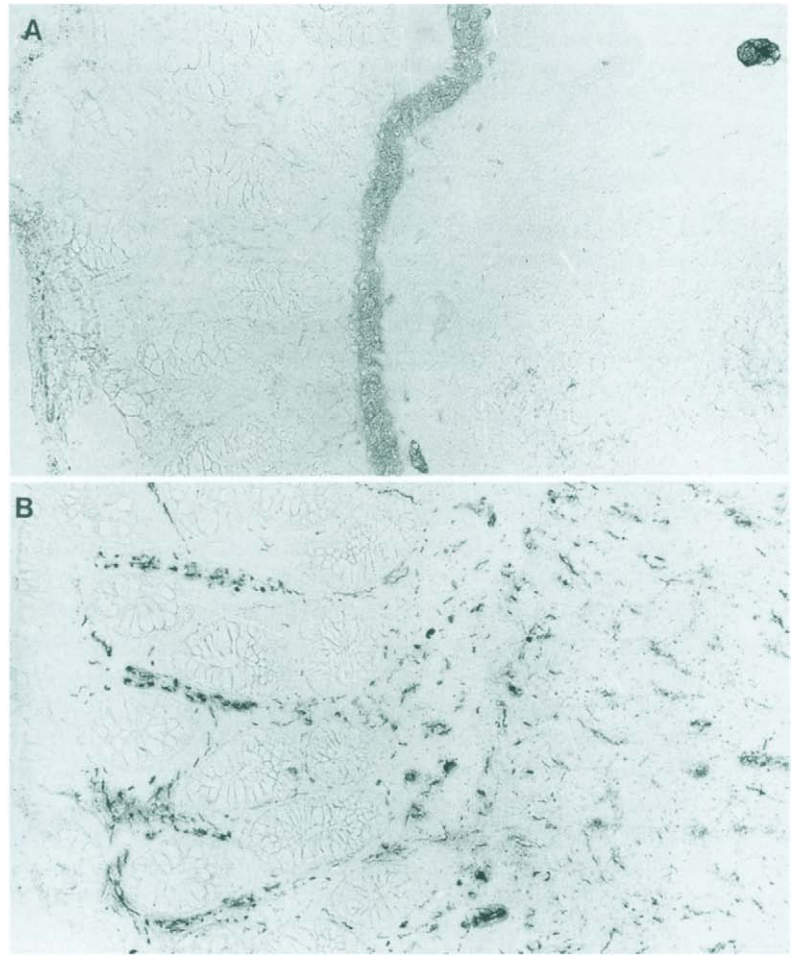


Fig. 318 Acetylcholinesterase (AChE) (A) in the normal bowel and (B) in Hirschsprung's disease. A massive AChE increase in the cholinergic fibers between the mucosal cavities. (A) The dark stripe corresponds to the physiological AChE reaction in the muscularis mucosae. On the right are two submucous ganglion cell plexuses, ×400.

nent (Yamataka *et al.*, 1992). In the transitional oligoganglionic segment many synapses are present in the myenteric plexus, but only a few appear in the muscle layers. The number of ganglion cells in the myenteric and submucous plexuses of the intestinal segment adjacent to aganglionic stretches can be strongly reduced (Blisard and Kleinmann, 1986). Immunocytochemistry using antisera against general markers of the enteric nervous system, detected at the proximal limit of resection, abnormalities of enteric innervation in eight of 10 studied specimens (Romanska *et al.*, 1993), suggesting that the widely practiced conventional histopathological assessment of the proximal limit of colonic neural

Fig. 319 Hirschsprung's disease. Markedly increased acetylcholinesterase reaction of the nerve fibers between the mucosal cavities, ×1000.

abnormalities may be inadequate. This could account for the 20% of children with Hirschsprung's disease who have an unsatisfactory postoperative result.

Zonal and Ultrashort-Segment Aganglionosis

Aganglionic colon segments independent of each other with intermittent normal bowel segments have been described in a few individual cases. However, the existence of this variant of Hirschsprung's disease was often questioned. Seldenrijk *et al.* (1986) confirmed its existence in many patients. The clinical presentation may be similar to that of classical Hirschsprung's disease.

The ultrashort segment is a rare special type of Hirschsprung's disease. This aganglionosis only affects very limited 1- to 3-cm segments of the distal rectum (Cervós-Navarro, 1991).

Total Intestinal Aganglionosis (Zülzer–Wilson Syndrome)

Total intestinal aganglionosis is a rare uniformly fatal condition first described by Zülzer and Wilson (1948) with an absence of ganglia from the duodenum to the rectum

(Caniano *et al.*, 1985). One third of the patients presented between 4 and 8 days of age, after passing meconium on the first day of life; complete obstipation at laparotomy, no intestinal distention, obstruction, or transition zone are evident. Hypertrophic nerve fibers seen in classical Hirschsprung's disease are absent in one quarter of the patients. A high incidence of the affected cases are siblings (Rudin *et al.*,1986).

Neuronal Colon Dysplasia (Neuronal Intestinal Dysplasia Type A)

Neuronal colon dysplasia occurs as an independent disease as well as in combination with Hirschsprung's disease. Fadda *et al.* (1983) distinguished between two clinically or morphologically different forms. The first form (type A), involving the sympathetic system and with clinical signs of intestinal spasticity with bloody diarrhea, histochemially shows aplasia or hypoplasia of the sympathetic system with intensified parasympathetic activity. This is recognizable by an increased acetylcholinesterase reaction in the lamina propria mucosae, mainly of the transverse and ascending colon (Figs. 320 and 321). The submucous plexus is generally formed normally, while the myenteric plexus is frequently hyperplastic.

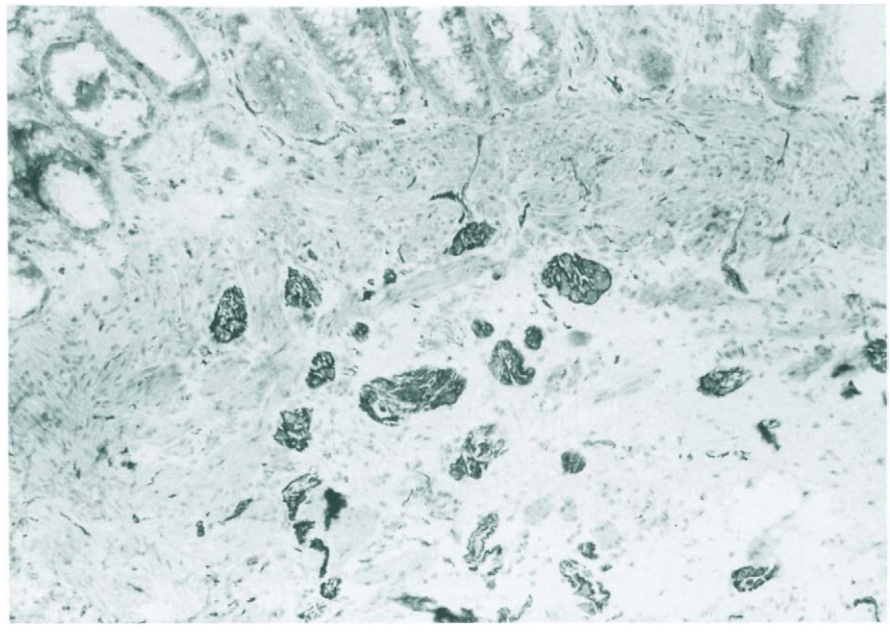


Fig. 320 Neuronal colon dysplasia. A strong positive histochemical reaction with an antineurofilament in the hyperplastic nerve cell plexus and nerve fibers of the submucosa. In addition, some ganglion cells have displaced up to the muscularis mucosae, ×400.

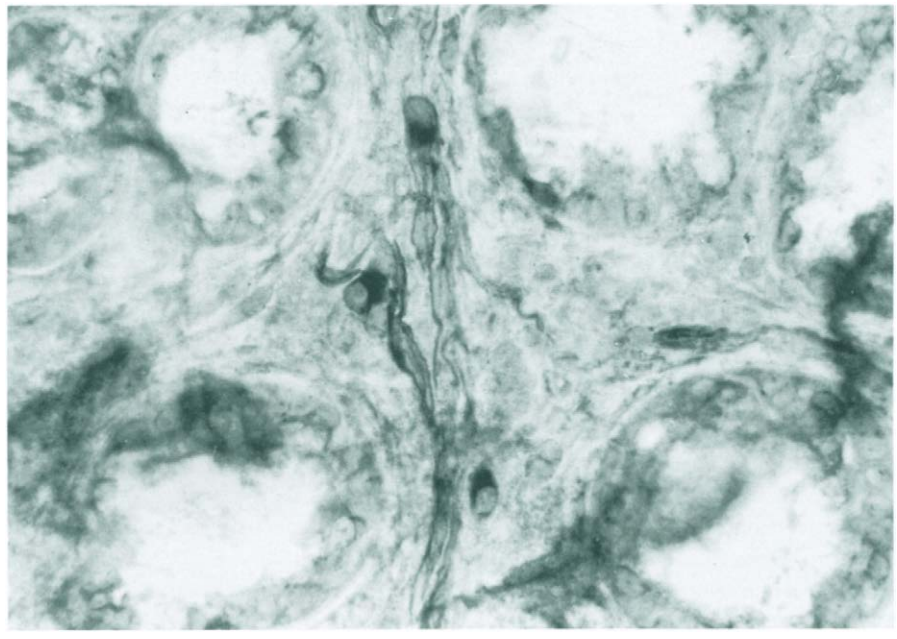


Fig. 321 Neuronal colon dysplasia. Three small ectopic antineurofilament-positive neurons between the cavities, ×1000.

Neuronal colon dysplasia has been diagnosed enzymohistochemically in adult patients with primary chronic constipation and diverticulosis of the sigmoid colon (Stoss and Meier-Ruge, 1991).

Neuronal Intestinal Dysplasia Type B (Hyperganglionosis)

NID type B is a disturbance of the innervation of the gut. A less common type involving the submucous plexus and the formation of a megacolon leads to adynamic behavior in these children. The first case of neuronal colon dysplasia, described by Meyer-Ruge in 1971, belonged to this second type. There are large groups of ganglion cells and Schwann cells in the submucosa that tend to sit on hypotrophic parasympathetic fibers. Occasionally, dystopic nerve cells and smooth muscle may appear in the propria of the mucosa, and the muscularis mucosae may become hypoplastic (Sacher *et al.*, 1982). The acetylcholinesterase activity is moderately elevated. Its symptoms resemble those seen in Hirschsprung's disease. Contrary to aganglionosis, however, there is hyperplasia of the ganglia (Briner *et al.*, 1986). Isolated hyperganglionosis is eight times rarer than aganglionosis. A combination of both diseases has been reported in 75% of the patients. It results in superposition of symptoms, thus rendering it impossible to differentiate between

NID type A with hypoplasia of sympathetic innervation and acute early onset and that with normal sympathetic innervation and chronic late onset on clinical grounds. Hyperganglionosis in this case was located proximal to the aganglionic segment and can reach the stomach.

Patients with hyperganglionosis have been reported in whom an initial diagnosis of Hirschsprung's disease was suspected. Inadequate suction rectal biopsy specimen can suggest Hirschsprung's disease on acetylcholinesterase staining (Athow *et al.*, 1991). Full-thickness bowel specimens are needed to confirm the diagnosis, and inadequate rectal suction biopsies must be interpreted with caution.

Hypoganglionosis (Dysganglionosis)

Hypoganglionosis differs from neuronal colon dysplasia. The clinical symptoms are similar to those of other forms of Hirschsprung-related disease; however, the course is usually less acute. While aganglionosis usually requires surgical therapy, in dysganglionosis a distinct differentiation is necessary between patients sufficiently treated by conservative methods and others requiring surgery. Frequently, a long bowel segment is involved, so that there is often a recurrence after resection.

Histologically, the clinical picture cannot be classified into one of the above-named groups. The intramural plexuses are structured normally and contain ganglion cells, which are, however, disturbed in their function and are usually already noticeable by their size and above all by their disturbed enzymohistochemical behavior. They have unusual forms and are much too small. In the NADH preparation they do not stain at all or only very weakly. Occasionally, there is a considerable discrepancy between the number of nerve cells visualized in the H&E preparation and those in NADH staining. Dysganglionosis may possibly be a dysmaturity or retarded maturation of the ganglion cell plexus in the intestinal wall.

Hypoganglionosis can occur as an independent clinical picture or as a consequence of inflammatory intestinal diseases, ischemic conditions, or chronic coprostasis.

Pathogenesis Jespers *et al.* (1993) described two siblings with Hirschsprung's disease and hypoplasia of the corpus callosum and/or cerebellar hypoplasia. Other cases with congenital muscular dystrophy and neurological abnormalities have been reported (Halal and Morel, 1990; Mandel *et al.*, 1993). An association with Hirschsprung's disease and multiple anterior pituitary hormone deficiencies was described (Radetti *et al.*, 1988). The different disorders leading to chronic constipation are partly conditionated by the fact that the human submucous plexus is made up of three interconnected ganglionated networks arranged along three different planes (Ibba-Manneschi *et al.*, 1995). Reduced peptide-containing nerves, fibers displaying neuropeptide Y immunoreactivity showed a marked increase in all aganglionic segments, particularly in the circular muscle, where few are found normally.

An autosomal-dominant gene causing the disease was mapped to chromosome 10q11.2 and subsequently localized to a 250-kb interval that contains the *RET* protooncogene. Four mutations (one frameshift and three missense) have been identified that totally dis-

rupt or partially change the structure of the tyrosine kinase domain of the RET protein (Romeo *et al.*, 1994). A targeted mutation in the tyrosine kinase domain of the same gene produced intestinal aganglionosis and kidney agenesis in homozygous transgenic mice.

Animal Models Piebald mice inherit a congenital megacolon associated with distal aganglionosis and with abnormalities in the peptidergic innervation of the proximal and distal colon (Kaufman *et al.*, 1985). The discovery that the murine piebald trait, a hereditary disorder with a high incidence of Hirschsprung's disease, is caused by mutations in a growth factor receptor highlights the importance of regulatory intercellular interactions between nonneuroblastic mesenchyme and neuroblasts during normal development of the enteric nervous system (Kapur, 1993). Congenital megacolon develops in transgenic mice that overexpress the homeobox-containing gene, *Hoxa-4* (Tennyson *et al.*, 1993). An extensive thickening and reduplication of the basal lamina surrounding the smooth muscle cells of the muscularis mucosa in these rats resembled that found in the *ls/ls* mice and are consistent with the hypothesis that the defects arise as a result of a defective interaction between the precursors of enteric neurons and smooth muscle.

Polyneuropathy, Ophthalmoplegia, Leukoencephalopathy, and Intestinal Pseudoobstruction (Familial Visceral Neuropathy)

Familial visceral neuropathy is a rare cause of chronic intestinal pseudoobstruction with dysmotility and associated early satiety, postprandial bloating, recurrent nausea and vomiting, abdominal distention, chronic diarrhea, weight loss, and malnutrition. Progressive neurological disorders are characterized by sensorimotor peripheral polyneuropathy and cranial neuropathies (external ophthalmoplegia and deafness) (Simon *et al.*, 1990). MRI shows widespread abnormality of the cerebral and the cerebellar white matter. Within 5 years of presentation, patients died from inanition and sepsis, despite aggressive nutritional support (Matulis *et al.*, 1994). Autopsy examination revealed widespread endoneurial fibrosis and demyelination in the peripheral nervous system, possibly secondary to axonal atrophy, and poorly defined changes in the cerebral white matter. The cranial nerves and the spinal roots were less severely involved.

Achalasia of the Cardia

The primary motor disturbance of the esophagus with incomplete relaxation of the lower sphincter was originally considered to be a simple ectasia. Mikulicz (1904) established cardiospasm as the essential etiological factor, and Hurst and Rake (1930) coined the term *achalasia*. According to Jänisch (1986), it should be distinguished from diffuse esophagospasm induced by contraction of the esophageal musculature during the act of swallowing. Both syndromes, however, were observed in siblings and interpreted as a single nosological entity. Transition from esophagospasm to achalasia occurs in about 5% of the cases.

The familial occurrence of the disease in twins and siblings (Ehrich *et al.*, 1987) points to genetic factors in its etiology. It has been recorded in association with neurofibromatosis (Foster *et al.*, 1987). Achalasia has also been observed together with microcephaly, Arnold–Chiari malformation, pulmonary sarcoidosis, and Chagas' disease (Pollack *et al.*, 1992). An association with PD is particularly common. Qualman *et al.* (1984) considered the parkinsonism–achalasia syndrome to be a distinct subgroup of the disease.

Neuropathology A loss of ganglion cells in the myenteric plexus, degeneration of the vagus nerve, and qualitative and quantitative changes in the nucleus dorsalis vagi have been described (Hurst and Rake, 1930). Changes in the dorsal nucleus of the vagus were also found in a case of diffuse esophagospasm in association with granular ependymitis (Lafay *et al.*, 1986). Csendes *et al.* (1985) found a total loss of ganglion cells in Auerbach's plexus in 17 cases of achalasia, and a severe reduction of these cells associated with an inflammatory infiltrate in one case. Aggestrup *et al.* (1983) found a loss of vasoactive intestinal polypeptide-positive nerve fibers in the esophagal muscle in achalasia by immunohistochemical methods. Adams *et al.* (1976) found an almost total loss of ganglion cells in the upper thickened segment. In the lower segment some nerve cells were still present, and in two cases normal numbers were found. Chromatolysis was found in nine cases, suggesting an active process. The preganglionic fibers were normal in number and appearance.

Electron microscopy. On electron microscopy Faussone-Pellegrini and Cortesini (1985) found changes in synaptic terminals and in the interstitial cells of Cajal with normal muscle cells in the lower esophageal sphincter.

A separate syndrome consists of defective production of glucocorticoids and adrenal androgens, absence of lachrymation, anisocoria, hyperkeratosis, sensory neuropathy, and achalasia (Grant *et al.*, 1993; Tsao *et al.*, 1994). In most of the cases, neurological abnormalities, including hyperreflexia, muscle weakness, dysarthria, and ataxia together with impaired intelligence, were present (Grant *et al.*, 1993).

Familial Dysautonomia (Riley–Day Syndrome; Hereditary Sensory and Autonomic Neuropathy Type III of Dyck and Ohta)

This disease was described by Riley *et al.* (1949) in Ashkenazi Jews. Its occurrence in non-Jewish patients was doubted by some authors but confirmed by others (Guzzetta *et al.*, 1986). Nevertheless, other hereditary sensory neuropathies should be excluded in these cases (Axelrod and Pearson, 1984).

Clinical Picture The disease manifests itself soon after birth and is slowly progressive with advancing age. The principal symptoms consist of lack of lachrymation (Moore, 1994), corneal hypesthesia, reduced sensitivity to pain, impairment of sense of taste, and defective temperature control and abnormal sweating (Montani *et al.*, 1992). Disturbances of coordination and dysesthesias may develop later. Optic atrophy occurs in longstanding cases (Rizzo *et al.*, 1986). Speech is often monotonous and dysarthric, and intel-

ligence is below average. Recurrent apnea during the daytime as well as during sleep can be present. Sera from familial dysautonomia patients are shown to contain high levels of antibodies to human serum albumin (Chapman *et al.*, 1993). Orodental self-mutilation has been reported in many patients (Mass and Gadoth, 1994). The course of the disease is extremely variable and ranges from a few months to 30 years. Psychiatric symptoms arise as a consequence of the autonomic nervous dysfunction and include emotional instabilities that are often regarded as hysterical overacting (Okada, 1990). Association of dysautonomia has been described with megaesophagus (Maayan *et al.*, 1990) and with megacolon (Azizi *et al.*, 1984).

Pathology Hypoplasia of the lingual papillae and a reduction in the number of taste buds are seen in most cases. Glomerosclerosis of the kidneys caused by sympathetic denervation has been observed in a few patients (Spohr *et al.*, 1981).

Neuropathology A loss of myelinated fibers has been seen in the reticular substance of the pons, in the medulla, and in the posterior columns of the spinal cord (Fogelson *et al.*, 1967). Dyck *et al.* (1978) found a reduction in the number of small motor neurons. Reduced numbers of Purkinje cells and neuronal loss in the spinal and autonomic ganglia have also been observed. Goto *et al.* (1990) found a significant depletion of synaptophysin-positive axon terminals in the substantia gelatinosa and in the dorsal nucleus of Clarke. The myenteric plexus of Auerbach is disorganized in the esophagus and the stomach (Ariel and Wells, 1985). Evidence of a progressive axonal degeneration with a loss of myelin in the peripheral nerves has been found occasionally and was confirmed morphometrically by a lack of the bimodal aspect in the histogram (Guzzetta *et al.*, 1986; Fontan, et al., 1990).

Pathogenesis The clinical symptoms are referable to the neuronal loss in the spinal and sympathetic ganglia, the cause of which is unknown. Anderson *et al.* (1973) assumed a deficiency of dopamine β-hydroxylase. An inhibition of the nerve growth factor in fetal life by a maternal antibody transmitted transplacentally was only partially supported by animal experiments and tissue cultures (Wrathall, 1986). No defect in the structure of β-nerve growth factor was detected. Previous reports of hypersensitivity to ionizing radiation were shown to be incorrect. Increased globotriaosylceramide in familial dysautonomia was reported by Strasberg *et al.* (1992), but without markedly decreased α-galactosidase activity, as in Fabry's disease, where patients also display decreased autonomic function (see p. 297).

Blumenfeld *et al.* (1993) localized the gene for familial dysautonomia on chromosome 9 and mapped it to 9q31–q33.

Familial Dysautonomia in Animals

A sensory neuropathy with neuropathological changes resembling those of human dysautonomia was found in English pointers (Cummings *et al.*, 1981) and in Sprague–Dawley rats (Jacobs *et al.*, 1980). A sporadic dysautonomia of unknown etiology was observed in cats (Pollin and Griffiths, 1987).

Fatal Familial Insomnia

Fatal familial insomnia is a genetically determined fatal prion disease characterized clinically by progressive insomnia, leading to total sleep deprivation, dysautonomia, hypertension, adrenal overactivity, and impaired motor functions.

PET showed in one case selective thalamic hypometabolism and in most cases with a more complex clinical picture, with multiple neurological deficits, both thalamic and widespread brain hypometabolisms involving the majority of the cortical structures, the basal ganglia, and the cerebellum (Perani *et al.*, 1993). Conspicuously, a loss of circadian rhythm for growth hormone and a less significant loss of melatonin, catecholamines, and gonadotrophins as well as cardiovascular dysautonomia have been reported (Cortelli *et al.*, 1991).

Neuropathologically, severe atrophy of the anterior ventral and mediodorsal thalamic nuclei as well as olivary atrophy were constant findings in the patients of many kindreds, but not in one kindred (Medori *et al.*, 1992a,b). Histological features are mainly constituted of neuronal vacuolation, neuronal death, and cerebral and cerebellar cortical gliosis with hyperastrocytosis. Spongiosis of the cerebral cortex was present in some cases (Medori *et al.*, 1992a,b). Neither inflammatory syndrome nor demyelination is detectable. The disease is autosomal dominant. The *PrP* gene located on chromosome 20 in humans (Dormont, 1994) shows several mutations linked at codon 178 of the gene. It causes the substitution of Asn for Asp (178Asn mutation) (Petersen *et al.*, 1992). The different genotypes are determined by this mutation and the Met–Va polymorphism at codon 129 of the PrP gene (Monari *et al.*, 1994).

Congenital Central Hypoventilation (Ondine Syndrome)

In 16% of the cases with ondine course, also known as congenital central hypoventilation syndrome, an association with Hirschsprung's disease has been reported (Weese-Mayer *et al.*, 1992; Shimotake and Iwai, 1994). The etiology of sleep apnea is not known. Mechanisms of central integration may be abnormal, but the association with neural crest maldevelopment implicates the peripheral nervous system. Diffuse CNS astrocytosis, and atrophy but no primary brain stem abnormality, were occasionally reported (Weese-Mayer *et al.*, 1992).

Muscular Dystrophies with Changes in the Central Nervous System

The original concept of muscular dystrophies as diseases affecting exclusively muscle has undergone revision in recent years. The emphasis has shifted onto generalized cell membrane defects that can manifest themselves in different cell types (Mollman *et al.*, 1980). Several muscular dystrophies and other myopathies are associated with congenital

mental retardation. Some muscle diseases with cerebral manifestations have recently been identified as mitochondrial encephalomyelopathies and classified with disorders of the respiratory chain (see p. 33). In this section we consider conditions in which neuropathological changes in the CNS have been demonstrated or have been presumed on the grounds of clinical symptomatology.

The classification of congenital muscular dystrophies based on perceived clinical and morphological similarities or differences is controversial. The syndromes with congenital muscular dystrophies with cerebral involvement are usually classified into at least three forms: The Fukuyama type of congenital muscular dystrophy, occurring almost exclusively in Japanese patients; congenital muscular dystrophy with hypomyelinization, sometimes also called the occidental type of cerebromuscular dystrophy; and Walker–Warburg syndrome. Muscle–eye–brain disease, described in a number of Finnish patients, may or may not belong in this last category. The appearance of two syndromes, Fukuyama-type congenital muscular dystrophy and Walker–Warburg syndrome, in members of the same family suggests that these syndromes could be allelic with variable phenotypes (Yoshioka *et al.*, 1992). On the basis of a large series, Laverda *et al.* (1993) emphasized the differences within both syndromes.

Fukuyama Syndrome (Congenital Muscular Dystrophy with Mental Retardation and Epilepsy)

Since Fukuyama *et al.* (1960) described this syndrome, several reports appeared in both the Japanese and English literature.

Clinical Picture Some children have respiratory difficulties from birth; most are hypotonic. Only a few patients eventually learn to walk. Sixty percent of the retarded children never acquire speech, while others do so with only a very limited vocabulary. About one half suffer from epileptic seizures. Ocular abnormalities have been noted in a proportion of the cases (Chijiiwa *et al.*, 1983). Encephalography revealed ventricular dilatation. CT showed hypodense areas in the subcortical white matter (Echenne *et al.*, 1986). The mode of inheritance is autosomal recessive (Fukuyama and Ohsawa, 1984).

Pathology The muscular lesions range from slight to severe dystrophic features (Kihira and Nonaka, 1985). 2C fibers are particularly abundant. Under electron microscopy immature fibers were seen, as well as vesicular nuclei and hypertrophic nucleoli (Terasawa, 1986).

Neuropathology *Gross appearances.* The main features were agyria (lissencephaly) and polymicrogyria in the cerebrum and the cerebellum. However, the general configuration of the CNS was well preserved (Takada, 1993). Adhesions between the two hemispheres (Koga *et al.*, 1984) and hypoplasia of the pyramidal tracts have been observed.

Light microscopy. The cytoarchitecture of the cortex is disturbed and heterotopias are common, some of them in the form of warty dysplasias. Dystopic myelinated axons have been repeatedly observed in the cerebellar leptomeninges (Kimura *et al.*, 1993). In patients who survived into the third or fourth decade neurofibrillary abnormalities have

been seen in the locus coeruleus and in the nucleus basalis (Takada *et al.*, 1986). Takada (1988) ascribed all lesions in the Fukuyama syndrome brains to disorders of migration. In Fukuyama syndrome connectin degradation begins much earlier than in other muscular dystrophies. It was presumed that connectin degradation would play an important role in the myofibrillar degeneration in the early stage of the disease (Matsumura *et al.*, 1990).

Occidental Type of Cerebromuscular Dystrophy

An intermediate form between the classical occidental type and Fukuyama congenital muscular dystrophy with early hypotonia, normal mental development, and leukodystrophic appearance on CT scan has been suggested and named *occidental-type cerebromuscular dystrophy*, because this form appears to be prevalent in the Western Hemisphere (Topaloglu *et al.*, 1991). This type also includes the three patients with congenital muscular dystrophy and extensive demyelination of the white matter reported by Egger *et al.* (1983). The patients invariably present with amyotrophy, multiple joint contractures, facial muscle involvement, normal or nearly normal intelligence, leukodystrophic appearances on CT scan, and dystrophic changes in muscle. The most striking change in the CNS is prominent white matter hyperlucency. Delayed myelination processing may be responsible. In the occidental type of CMD, the white matter hyperlucency persists after several years, differing from Fukuyama syndrome. In the latter it is usually seen at about 1 year of age, and when the child grows older, it is replaced by normalization.

Neuropathologically, cortical areas of polymicrogyria, cerebral neuronal loss, heterotopic nerve cells, degeneration of the myelin sheath, and cerebellar hypoplasia are present (Egger *et al.*, 1983).

Congenital Muscular Dystrophy with Cerebroocular Dysplasia (Muscle–Eye–Brain Syndrome)

The first case of this syndrome was reported by Kasubuchi *et al.* (1974). Further cases have been included in this group, in spite of considerable variation in the symptomatology and the clinical course (Miyake *et al.*, 1977). Some authors consider the condition to be a variant of Fukuyama syndrome (Dambska *et al.*, 1982), but separation of the two syndromes appears justified because of the ocular manifestations (Towfighi *et al.*, 1984). The differences between the muscle–eye–brain syndrome and Walker–Warburg syndrome were stressed by Santavuori *et al.* (1990). The wide variation in symptomatology is emphasized by the existence of a group of Finnish patients with an apparently milder form of the syndrome (Raitta *et al.*, 1978). Korinthenberg *et al.* (1984) reported a similar syndrome in German families.

Clinical Picture The patients are hypotonic from birth (Leyten *et al.*, 1991). The majority suffer from hydrocephalus, and all show severe psychomotor retardation and EEG abnormalities. Seizures may occur, and spasticity may develop in the later stages. The CT scan reveals a variable degree of hypodensity in the white matter. Clouding of the cornea, cataracts, and retinal abnormalities are the main ophthalmological features. The children

die before the age of 2 years. Longer survival occurs in the Santavuori (Finnish) variant of the muscle–eye–brain syndrome (Korinthenberg *et al.*, 1984).

Pathology The muscles show myopathic changes with basophilic and necrotic fibers and a wide variation in fiber diameters (Dambska *et al.*, 1982). Regenerating fibers and inflammatory infiltrates have also been observed (Towfighi *et al.*, 1984).

Neuropathology *Gross appearances.* Agyria and occasionally polymicrogyria are seen in the cerebral hemispheres. Polymicrogyria is always present in the cerebellum. Agenesis of the vermis, the olfactory bulbs, and occasionally the corpus callosum has been observed (Dambska *et al.*, 1982). Fusion of the frontal lobes may be present.

Light microscopy. Various forms of disorganization of the cerebral and the cerebellar cortex are found (Dambska *et al.*, 1983; Santavuori *et al.*, 1990). The cortex may be intersected by a band of gliomesodermal tissue extending from the leptomeninges (Towfighi *et al.*, 1984). A proliferation of astrocytes is seen, as a rule. Numerous neuronal heterotopias are scattered through the white matter. The pyramidal tracts are absent or rudimentary in the medulla oblongata and the spinal cord (Federico *et al.*, 1988). The optic nerves are hypoplastic (Heggie *et al.*, 1987).

Walker–Warburg Syndrome (Cerebroocular Dysplasia of the Walker Type; Hydrocephalus, Agyria, and Retinal Degeneration with or without Encephalocele)

This syndrome was described by Walker (1942) as lissencephaly (agyria). The separation of the syndrome from that of muscular dystrophy with cerebroocular dysplasia cannot be made with certainty, as the muscular pathology may be masked by the cerebral abnormalities and in some cases only the brain has been examined (Chan *et al.*, 1980). Neuroimaging of the agyria can be easily demonstrated with MRI (Schuierer *et al.*, 1993). Warburg (1978) identified a group of cases with hydrocephalus and congenital nonattachment of the retina, occurring particularly in girls. The mode of inheritance in Warburg syndrome is autosomal recessive (Whitley *et al.*, 1983).

Neuropathology *Gross appearances.* Both microcephaly (Yanoff *et al.*, 1978) and macrocephaly (Levine *et al.*, 1983) have been observed. Agyria of the cerebral hemispheres, polymicrogyria, hypoplasia of the cerebellum, and hydrocephalus are constant features (Miller *et al.*, 1991). Occipital encephalocele is present in some cases. Occasionally, atretic cephalocele is the main diagnostic clue to the syndrome (Martinez-Lage *et al.*, 1992). The cerebellar cortex can be diffusely changed with fused and irregularly distorted folia (Lyon *et al.*, 1993).

Light microscopy. The appearances are identical to those seen in muscular dystrophy with cerebroocular dysplasia (Towfighi *et al.*, 1984). Both the cerebral and cerebellar cortices are grossly disorganized, with glial and neuronal displacement into the meninges (Miller *et al.*, 1991). A double cortical layer was reported in one case (Yamaguchi *et al.*, 1993). Peripheral neuropathy was found by Kimura *et al.* (1992). The retina can present

various grades of differentiation with rosettes and atypical sequences of cells (Gerding *et al.*, 1993).

Myotonic Muscular Dystrophy (Dystrophia Myotonica; Myotonia Atrophica; Curschmann–Steinert Disease)

Clinical Picture Myotonic dystrophy is a dominantly inherited disorder that may be accompanied by the involvement of multiple organ systems (Steinert, 1909). The condition is considered to be a genetic progeric disease. Aside from the skeletal muscles, the disease affects a variety of organs, cardiac and smooth muscle, endocrine glands (testicular atrophy and diabetes), eyes (cataracts), skin (alopecia), and, in a proportion of the cases, the CNS. Some degree of cognitive impairment is present in most cases and is usually more pronounced in patients with maternal rather than paternal inheritance. This is particularly striking in the infantile form of the disease inherited exclusively from mothers. In some adults the intellectual impairment may be progressive. The EEG is frequently abnormal. Pneumoencephalography revealed dilatation of the lateral ventricles, which was found to have increased on repeated examination in five cases out of 10.

Neuropathology In the CNS intracytoplasmatic inclusion bodies and disorganization of the neuronal architecture in the cerebral cortex have been reported (Ono *et al.*, 1989). Usually single, sharply defined, peripherally located inclusions were found in the cerebral cortex, thalamus, caudate nucleus, and putamen. In the substantia nigra multiple irregular bodies were scattered among the neuromelanin granules. Ultrastructurally, all of these inclusions consisted of stacks of alternating parallel light and dark rectilinear profiles. Ono *et al.* (1987) also noted the presence of a large number of Marinesco bodies in the substantia nigra. While all of these lesions are nonspecific, morphometric studies revealed a significantly higher number of inclusions and Marinesco bodies in myotonic dystrophy than in controls (Ono *et al.*, 1989). Kiuchi *et al.* (1991) described the presence of abundant Alzheimer's NFTs without SPs in seven patients with myotonic dystrophy aged 35–56 years. The tangles were localized predominantly in the parahippocampal gyrus, increasing in number with age, and involving the hippocampus in older patients. In the caudatum rodlike inclusions were observed in the cytoplasm near the nucleus (Oyanagi *et al.*, 1994). They showed eosinophilic staining with H&E and stained blue with phosphotungstic acid–hematoxylin, red with Masson's trichrome, and blue with toluidine blue. In an unpublished personal series of four cases with adult onset (by H.U.) ventricular dilatation was found in all cases, but aside from gliosis of variable distribution, no significant abnormalities were seen on routine histological examination. Reduction of the spinal anterior horn cells (Walton *et al.*, 1977) has been reported. Cros *et al.* (1988) found degeneration of the peripheral nerves.

A progressive neuromuscular disorder in young horses, which resembles myotonic dystrophy, has been identified (Hegreberg and Reed, 1990).

Pathogenesis Dystrophia myotonica is an autosomal-dominant genetic disorder with its gene located on the long arm of chromosome 19 (Shaw and Harper, 1989). The abnormality consists of repeats of the AGC nucleotide triplet in the gene that normally codes

for the enzyme myotonin protein kinase (Pizzuti *et al.*, 1993). An unusual combination of dystrophia myotonica with syringomyelia was described by Weingarten and Gerstenbrand (1958) in four siblings of an Austrian family. Other families have been reported by many authors.

Miscellaneous

Polymicrogyria and Dermatomyositis with Paracrystalline Inclusions

The combination of a dermatomyositis with paracrystalline inclusions on electron microscopy and cerebral and cerebellar polymicrogyria in an apparently autosomal-recessive syndrome has been described by DeBleecker *et al.* (1990). A genetically determined immunological disorder causing prenatal CNS vasculitis resulting in cortical laminar necrosis and a postnatal autoimmune reaction against the intramuscular blood vessels are a possible hypothesis for its pathogenesis.

Myopathies with Tremor and Dementia

Torvik *et al.* (1974) described a woman, aged 78 years, who, like her brother, developed a painless atrophy and weakness of her extremities after the age of 60 years, followed later by dementia and tremor. Similar cases without CNS involvement were reported by Coquet *et al.* (1981).

Pathology *Light microscopy.* An accumulation of PAS- and Alcian green- and blue-positive material was found on muscle biopsies.

Electron microscopy. Granular and fibrillary material, surrounded by glycogen granules, was seen in muscle cells. Similar changes were found in the myocardium. No biochemical studies were carried out, but morphologically, the material resembled the amylopectin of glycogenosis type IV (see p. 632).

Neuropathology A marked proliferation of astrocytes was found in the outer layers of the cerebral cortex in the case documented by Torvik *et al.* (1974).

Miscellaneous Conditions

Neurocutaneous and Oculocerebral Syndromes

Van Der Hoeve (1923) introduced the concept of *phakomatosis*, derived from the retinal lesions of tuberous sclerosis, to denote syndromes in which lesions occur in different tissues derived from the same germinal layer. As all pigment cells, with the exception of those of the retina, are derived from the neural crest, the involvement of the nervous system and the skin is common in genetic syndromes. Some of the neurocutaneous syndromes have since been ascribed to disorders of DNA repair. In most of the neurocutaneous syndromes, the pathogenesis has not been elucidated. Sturge–Weber syndrome, von Hippel–Lindau disease, and tuberous sclerosis have a clear-cut tumoral manifestation and are not within the scope of this book. Here we describe briefly a number of conditions with a more degenerative character, affecting, as a rule, only a few patients, or sometimes only a single family.

Arthrogryposis Multiplex Congenita (Pena–Shokeir Syndrome Type I; Focal Sequelae of Akinesia; Multiple Ankyloses with Facial Anomalies and Pulmonary Hypoplasia)

Pena and Shokeir (1974a) described a syndrome in two siblings which is known as Pena–Shokeir syndrome type I, to distinguish it from the cerebrooculofacial syndrome, known as Pena–Shokeir syndrome type II (see p. 501). Its differentiation from the congenital form of spinal muscular atrophy with contractures is barely possible.

Clinical Picture Some of the affected infants are stillborn (Herva *et al.*, 1985). The arthrogryposis with fixed contractures of the fingers and immobility of the elbows, knees, and hips is apparent at birth. The feet show a prominent equinovarus deformity. Facial abnormalities include prominent bulging eyes, hypertelorism, telecathus, and epicanthic folds. Ciofu *et al.* (1993) reported arthrogryposis in three male siblings, and a dominant

hereditary variation of the syndrome has also been described (Vlaanderen *et al.*, 1991). A nonfamilial form, confined to the upper limbs, was described by Hageman *et al.* (1993).

Pathology Pulmonary hypoplasia is present in most cases. Neurogenic atrophy is seen in the skeletal muscles.

Neuropathology *Gross appearances.* Some cases show polymicrogyria with cortical atrophy, dilated ventricles, blurring of demarcation between the gray and the white matter, and multiple foci of softening (Horoupian and Yoon, 1988). Subependymal hemorrhages have been described in several cases (Shokeir, 1982). In other cases no macroscopic abnormalities were found in the brain (Williams and Holmes, 1980). Thinning of the anterior roots may be observed in the spinal cord.

Light microscopy. Disorders of neuronal migration were seen in the case reported by Choi *et al.* (1986). A loss of neurons and gliosis, diffuse or focal, are found in the cerebral cortex. Abnormally long and tortuous dendritic spines are seen in Golgi impregnations in some neurons. Neuronal loss also occurs in the thalamus (Horoupian and Yoon, 1988). In the hippocampus neuronal loss and gliosis affect predominantly the pyramidal cell layer. The main lesions are observed in the brain stem, particularly in the cranial nerve nuclei and the reticular substance, where the loss of neurons and reactive gliosis are severe (Schliwinsky *et al.*, 1984). In the cerebellum there is an obvious depletion of the external and internal granular layers and some reduction in the number of Purkinje cells. A loss of anterior horn cells, with or without gliosis, is found in the spinal cord (Williams and Holmes, 1980). A child with the typical syndrome, but without cell loss in the anterior horns, and bilateral posterior column degeneration was described by Folkerth *et al.* (1993).

Pathogenesis It has been demonstrated, both clinically and experimentally, that arthrogryposis is the result of impaired movements of the extremities during the development of joints *in utero*. It is assumed that the neuromuscular changes due to lesions in the brain stem and the thoracic spinal cord are the cause of the pulmonary hypoplasia and the facial deformity. The loss of motor neurons is the primary lesion, caused either by a metabolic disorder or by ischemia (Horoupian and Yoon, 1988).

Aicardi's Syndrome (Agenesis of the Corpus Callosum; Infantile Spasms and Ocular Anomalies)

This syndrome was defined by Aicardi *et al.* (1965) as a nosological entity, consisting of a triad of absent corpus callosum, lacunar chorioretinopathy, and hypsarrhythmia.

Clinical Picture The patients suffer from seizures or flexion spasms within a few months after birth. Most patients show mental retardation, hypotonia, and a hypsarrhythmic EEG pattern (Fariello *et al.*, 1977). Aside from infantile spasms, other epileptic manifestations can occur, such as bilateral independent bursts or synchronous spike–wave EEG patterns (Ohtsuka *et al.*, 1993). Cases without hypsarrhythmia can be accepted as belonging to this syndrome, provided that the corpus callosum is absent and lacunar chorioretini-

tis is present (Yamagata *et al.*, 1990a). Other combinations of abnormalities must be considered atypical. The lacunar chorioretinopathy is characteristic and may be associated with microphthalmia and other ocular anomalies. A total absence of the corpus callosum is seen on CT scans, often in association with cortical atrophy, asymmetry of the lateral ventricles, and cerebellar abnormalities. Almost all cases show more or less prominent skeletal anomalies. A cleft lip and palate have been reported in one case (Umansky *et al.*, 1994). The syndrome appears only in girls, with the exception of boys with trisomy XXY. It does not show a definite familial clustering (Chevrie and Aicardi, 1984).

Neuropathology *Gross appearances.* Both the skull and the cerebellum are asymmetrical in most cases. The convolutional pattern of the cerebral cortex is abnormal; both agyria and polymicrogyria may be present (Tanaka *et al.*, 1985), as well as porencephalia. Aside from asymmetry, the cerebellum shows a variety of malformations. Absence of the pineal body appears to be a constant feature (Gardner, 1982). The agenesis of the corpus callosum is total. Occasional plexus papillomas have been reported (Robinow *et al.*, 1984; Font *et al.*, 1991). Multiple cerebral tumors were observed in one case (Hamano *et al.*, 1991). Aside from lacunar chorioretinitis, ocular abnormalities include microphthalmia, hypoplasia of the optic nerves, colobomas, retinal detachment, and atrophy of the pigment epithelium (Font *et al.*, 1991). Posterior scleral ectasia, anomalous retinal vessels, and a peripheral fibrous ridge have also been described (Carney *et al.*, 1993).

Light microscopy. The lamination of the cortex is disturbed and may be unrecognizable in some areas. The individual neurons, however, appear normal. An increase in the number of astrocytes may appear locally. Ectopic neurons are particularly numerous in the occipital lobes. The number of Purkinje cells is considerably reduced. A spongiosis of the white matter was noted in two siblings (Pineda *et al.*, 1984).

Intracytoplasmic brightly eosinophilic inclusions within protoplasmic astrocytes in the cerebral cortex were found by Abe *et al.* (1992). They were numerous in the cerebral cortex, especially in part of the microgyri, and absent in the deep cerebral white matter, subcortical nuclei, brain stem, and cerebellum. Ultrastructurally, the inclusions were composed of electron-dense granules and amorphous substances and were not surrounded by a limiting membrane.

Pathogenesis The cause of Aicardi's syndrome is unknown. The lesions point to a disturbance of embryogenesis between the first and third months of fetal life. The fact that the disease affects exclusively girls (or boys with the XXY trisomy) has led to the hypothesis that the condition may be due to a dominant gene on the X chromosome (Wieacker *et al.*, 1985; Neidich *et al.*, 1990), lethal in a male hemizygote and manifesting itself in a female heterozygote. It has been suggested that the absence of the pineal body, indispensable for the survival of boys, was responsible for the lethal outcome. A binovular male twin of an affected girl was normal (Constad *et al.*, 1985). A search for abnormalities on the X chromosome has proved inconclusive. A deletion of Xp22.2–pter was found in an atypical case (Donnenfeld *et al.*, 1990), but no deletions have ever been found in typical cases. Other chromosomal abnormalities have been discussed (Rosenfeld *et al.*, 1985). These include an Xp22–autosome translocation (Neidich *et al.*, 1990), and a t(12–21) translocation (Ohtahara *et al.*, 1993).

Livedo Reticularis (Sneddon's Syndrome)

Sneddon (1965) described the occurrence of cerebrovascular lesions in idiopathic livedo reticularis. Immunological disturbances (McHugh *et al.*, 1988) and the possible relationship with systemic lupus erythematosus (Burton, 1988) have been considered. Ellie *et al.* (1987) could not detect any significant clinical differences between this syndrome and the cortico-meningeal angiomatosis of Divry and van Bogaert (1946).

Clinical Picture The disease affects mainly young adults, livedo reticularis being the first symptom, with the cerebral manifestations following years later. The obliterative angiopathy of the deeper layers of the dermis manifests itself in a garlandlike cutaneous pattern. Ischemic strokes, often recurrent, occur in all cases (Deffer *et al.*, 1987). Transient ischemic attacks have also been observed. CT and MRI reveal multiple cerebral infarcts (Laufer *et al.*, 1993). Abnormal high-intensity spots on T_2-weighted images were found in patients who were neuropsychiatrically asymptomatic (Ishikawa *et al.*, 1994). Epileptic seizures are common in advanced stages of the disease, and may rarely represent the only neurological symptom. Occasionally, dementia sets in before the age of 40 years (Jura *et al.*, 1994). The generalized angiopathy may also cause cardiac and renal symptoms. In isolated cases livedo reticularis was found associated with myasthenia or moyamoya disease (Lauret *et al.*, 1985). Nicolle and McLachlan (1991) reported a rare syndrome of acute encephalopathy followed by deafness and retinopathy. System symptoms included polyarthralgia–arthritis and livedo reticularis. Immunological investigations were repeatedly normal. In more than one half of the patients, the disease was familial, with autosomal-dominant inheritance.

Pathology Skin biopsies reveal narrowing of the lumen of cutaneous arteries and arterioles, dilatation of the capillaries and venules, endothelial proliferation, and occasional lymphocytic infiltrates. An increase in coagulation factor VII activity and a deficiency in free protein S were documented in one case (Martini *et al.*, 1992).

Neuropathology In the few cases examined at autopsy a cerebral angiitis was present (Stamm *et al.*, 1982). The medium-sized arteries showed a subintimal musculoelastic hyperplasia.

Pathogenesis The relationship between the cerebral and cutaneous vascular changes and the presence of lupus anticoagulant is supported by a common noninflammatory vascular thrombosis histologically in the patients with livedo reticularis and by the presence of similar pathological and clinical findings in patients with lupus anticoagulant syndrome (Alegre *et al.*, 1990). In familial cases an inherited predisposition to antiphospholipid antibody production may be involved in the disease pathogenesis (Pettee *et al.*, 1994).

Multiple Neuroretinal Angiomatosis (Bonnet–Dechaume–Blanc Syndrome)

This refers to a congenital vascular dysplasia affecting the eye and the CNS. The arteriovenous angiomas of the retina may lead to unilateral blindness. Skin lesions are gener-

ally localized in the trigeminal territory and consist of nevi, angiomas, and telangiectasias. The neurological symptoms depend on the localization of the intracranial angiomas. Seizures with or without mental retardation and headaches occur in most cases.

The intracranial angiomas are formed by arteriovenous aneurysms and may be localized in the thalamus, midbrain, or pons. They are drained through the great vein of Galen (Sedgwick, 1982).

Systemic Angiomatosis (Ullman's Syndrome; Cerebrovisceral Angiomatosis)

van Bogaert (1950) understood this term to include cases of cavernous angiomas or telangiectases of the CNS with similar involvement of the viscera. Kissel and Dureux (1972) cast doubt on the independent identity of the syndrome, as they found difficulty in separating it from retinocerebellar and encephalotrigeminal angiomatoses, on the one hand, and from hereditary hemorrhagic telangiectasia with visceral involvement, on the other.

Multiple Nevoid Basal Cell Carcinomas (Järisch's Syndrome)

The head appears enlarged in this disorder because of bulging masses in the frontal and temporoparietal areas. In 40% of the cases, hypertelorism and a slight prognathism are present. Multiple nevoid basal cell carcinomas appear already in childhood.

In the CNS the findings include calcification of the falx, hydrocephalus, cysts of the choroid plexus, glial nodules in the ependyma, and frequently also neuroblastomas (Lacombe *et al.*, 1990). In one case MRI revealed a colloid cyst of the third ventricle and mild dilatation of the lateral ventricle (Nishino *et al.*, 1991).

The gene has been mapped to 9q23.1–q31. Evaluation of recombinants suggested that the nevoid basal cell carcinoma syndrome locus lies in the interval defined distally by *D9S127* (Compton *et al.*, 1994). A loss of heterozygosity for genetic markers in this region has been detected in sporadic cases, indicating that the nevoid basal cell carcinoma gene is probably a tumor suppressor gene (Chenevix-Trench *et al.*, 1993).

Neurocutaneous Melanosis

This disease is characterized by cutaneous melanotic nevi. Most patients with neurocutaneous melanosis presented in the first 2 years of life with neurological manifestations of increased intracranial pressure, mass lesions, or spinal cord compression. The patients are hydrocephalic and may suffer occasionally from subarachnoid hemorrhages or seizures.

The CNS is affected in practically all of the cases. Leptomeningeal melanoma was present in 62% of the cases (Kadonaga and Frieden, 1991). Primary melanosis of the leptomeninges is associated with meningeal thickening. Meningeal malignant melanomas are predominantly located at the base of the brain and the benign meningeal melanosis over the cerebral cortex (Yoshioka *et al.*, 1994). Intracerebral and intracerebellar pigmentation may also be found (Chalhub, 1982). Neurocutaneous melanosis associated with partial agenesis of the right parietal lobe (Garcia-Penas *et al.*, 1992) and with inferior vermian hypoplasia (Ko *et al.*, 1993) has been reported. The syndrome is thought to represent an error in morphogenesis.

Bloch–Sulzberger Syndrome (Incontinentia Pigmenti)

This is an X-linked dominant condition first described by Bloch (1926), predominantly affecting female neonates and usually fatal in males. Ophthalmic problems develop in approximately one third of the patients and neurological symptoms are present in about one half of the cases. The rare cases examined neuropathologically (Shuper *et al.*, 1990) revealed polymicrogyria, ulegyria, cystic changes in the white matter, and neuronal loss with gliosis in the cerebellum. Goldberg and Custis (1993) reported on a child with a normal brain shown on CT scan at 3 days old, which evolved to devastating cerebral ischemia, edema, and cortical blindness beginning at 6 days old. Changes in the retinal pigment are predominant (Heathcote *et al.*, 1991).

An unusual sensitivity to anoxia or spread of an inflammatory process from the skin to the CNS, among other organs, has been postulated as the cause of the cerebral lesions.

Oculocutaneous Albinism

In various forms of oculocutaneous albinism, an abnormal course of retinofugal fibers has been observed (Witkopp, 1982). In several members of one family, a peculiar oculocerebrocutaneous syndrome was observed, consisting of mental subnormality, athetosis, hypopigmentation, and microphthalmia.

Oculocutaneous Melanocytosis (Nevus of Ota)

This rare dermatological abnormality is found predominantly in Japan and may be associated with sensorineural deafness, spinocerebellar degeneration (Whyte and Dekaban, 1976), Sturge–Weber syndrome, or intracranial arteriovenous malformation as well as seizures and mental retardation (Mata Moreno *et al.*, 1992). Neuropathologically, Schnabel *et al.* (1992) found dysgyria and microdysgenesia of the cortex in a multifocal pattern. The boundary between cortical and white substance was poorly defined, with many dystopic neurons in the gyral medulla. Leptomeningeal melanocytic lesions have been found in many cases (Balmaceda *et al.*, 1993).

Oculorenocerebellar Syndrome

Hunter *et al.* (1982) described several members of a family with mental retardation, choreoathetosis, spastic diplegia, tapetoretinal degeneration, glomerulopathy, and absence of the cerebellar granular layer. Death occurred toward the end of the first decade or, rarely, during the second.

Congenital Cerebral Abnormalities with Skeletal Malformations

Many of the congenital bone dysplasias and many of the over 150 syndromes of dwarfism (François, 1981) are associated with changes in the skull bones and mental deficiency. It is not always possible to establish a causal relationship between the various manifestations of the syndrome, which may, in some cases, be derived from a common primary cause. Some of the bony dysplasias with severe cerebral malformations lead to death immediately after birth (thanatophoric dysplasias; Ho *et al.*, 1984). These are not considered here.

Osteopetrosis (Osteosclerosis; Albers–Schönberg Disease; Marble Bone Disease)

Osteopetrosis, a rare condition characterized by the thickening and increased density of bones, appears in two forms: a benign adult form, inherited as an autosomal-dominant trait, and a malignant infantile form, inherited as an autosomal-recessive trait. Neurological complications are confined to the latter.

Clinical Picture The abnormality in the infantile form is present since birth, and neurological manifestations may appear in early infancy. The most common disturbances are optic atrophy, deafness, nystagmus, and facial palsy. Psychomotor development may be normal, but mental retardation has been reported in several cases (Funderbunck, 1975). A rapidly progressive form with severe neurological deficit, leading to death in infancy, has been reported (Jagadha *et al.*, 1988; Alroy *et al.*, 1994).

Pathology The bones consist almost entirely of compact tissue with obliteration of the marrow spaces (Takahashi *et al.*, 1990). Hepatosplenomegaly with extramedullary hemopoiesis is a common feature.

Neuropathology *Gross appearances.* In some cases no obvious lesions have been found. Hydrocephalus has been seen in several children. Atrophy of the cerebral cortex was observed in the severe cases (Jagadha *et al.*, 1988; Takahashi, 1990; Alroy *et al.*, 1994).

Light microscopy. The most severe lesions were seen in the cases of Ambler *et al.* (1983), Jagadha *et al.* (1988), and Alroy *et al.* (1994). These consisted of widespread swelling of the neuronal perikarya and proximal axons (meganeurites) containing storage material, which stained with PAS, luxol fast blue, and Sudan black and was autofluorescent, thus exhibiting the features of neuronal ceroid lipofuscinosis. The reaction for acid phosphatase was strongly positive. This accumulation was extensive and widespread, involving the spinal anterior horn cells, all neuronal elements in the brain stem, the cerebellar Purkinje cells, the cerebellar deep nuclei, the cerebral cortex, and the subcortical nuclei. Axonal swellings, apparently independent of neuronal storage, were present in the CNS and the peripheral nervous system. Retinal atrophy with a loss of rods and cones as well as of ganglion cells is present in the recently reported cases. Lectin histochemistry demonstrated an accumulation of fucosylated *N*-glycosidically linked oligosaccharides containing β- and α-galactosyl residues and compounds containing *N*-acetyllactosamine (Alroy *et al.*, 1994).

Electron microscopy. The stored material was membrane bound and consisted of electron-dense granular material, occasionally exhibiting a laminar structure (Takahashi *et al.*, 1990), closely resembling the appearances of the infantile type of ceroid lipofuscinosis (see p. 391).

Pathogenesis The bone lesions are due to an imbalance between normal osteoblastic bone formation and defective osteoclastic bone absorption. The abnormality of the osteoclasts is thought to be due to a deficiency of an unidentified lysosomal enzyme. The lysosomal storage in neurons is also caused by an enzyme deficiency. Whether both abnormalities are due to a lack of the same enzyme, or closely related ones, requires further elucidation, including identification of the responsible gene.

Some of the more common manifestations, such as cranial nerve palsies and possibly hydrocephalus, may be related directly to the skeletal abnormalities. However, neurological symptoms cannot always be attributed to the primary bone disease of the skull. It must be primary parenchymal disease of the brain with neuronal cytoplasmic storage.

Galloway Syndrome

This rare autosomal-recessive syndrome was first described by Galloway and Mowath (1968). Additional cases have been reported (Kozlowski *et al.*, 1989; Cooperstone *et al.*, 1993; Morys, 1993).

Clinical Picture The syndrome consists of microcephaly associated with congenital nephrosis. A hiatal hernia may also be present. Epileptic seizures may occur. The prognosis is extremely poor; every patient but one has died before the age of $5\frac{1}{2}$ years, usually of apnea and bradycardia (Cooperstone *et al.*, 1993).

Pathology The renal lesions are heterogeneous. A nephrosis of the microcystic type, changes in the glomeruli and the proximal tubules, and diffuse mesangial sclerosis have all been described.

Neuropathology *Gross appearances.* The brain weight is considerably reduced. The surface of the brain is agyric and macrogyric (Morys *et al.*, 1994). The cerebellum is hypoplastic. The white matter is soft and gray; only the internal capsule has an approximately normal appearance. The ventricular system is dilated.

Light microscopy. Kozlowski *et al.* (1989) found numerous glioneuronal heterotopias in the leptomeninges, and fusion of the leptomeninges with the molecular layer was seen in several places. The cytoarchitecture of the cortex is irregular. The number of cortical neurons is reduced and some are calcified. The most severe neuronal loss was found in the insula, which was almost completely replaced by gliosis. Neuronal loss and gliosis are also present in the basal ganglia. Abnormalities in the claustrum were described by Morys *et al.* (1993). The dentate fascia in the hippocampus was absent. Gliosis was prominent in the hippocampus and the parahippocampal gyrus. The internal granular layer is absent in the cerebellum.

Seckel's Dwarfism (Bird-Headed Dwarfism; Nanocephalic Dwarfism)

Virchow (1862) attempted to define nanocephalic dwarfism, but the syndrome was only definitely characterized by Seckel (1960) on the basis of 15 cases. Numerous cases, most of which fulfill Seckel's criteria, have since been described (Majewski *et al.*, 1982).

These patients are well-proportioned dwarfs with pronounced microcephaly, mental retardation, a characteristic birdlike facies, and various skeleton abnormalities (Mitzkat and Dietz, 1980). A spastic quadriparesis was recorded in one case (Fehlow, 1985).

Gross appearances. The brain is small, with a paucity of convolutions, occasional aplasia (Bixler, 1982), or hypoplasia (Rodriguez *et al.*, 1980) of the frontal lobes.

Light microscopy. Glial nests have been seen in the leptomeninges, as well as polymicrogyria and ectopic neurons in the white matter (Rodriguez *et al.*, 1980).

Dwarfism with Short Legs and Microcephaly

This syndrome was described in only one family (Juberg and Van Ness, 1975). The affected siblings were dwarfs with exceptionally short legs, craniofacial disproportion, and short ribs. One of the patients died at the age of 3 months with a respiratory infection; another, at 5 months with epileptic seizures. In both cases a small hydrocephalic brain was found; in one of them, with an absent corpus callosum. Kozlowski *et al.* (1993) reported agyria, aplasia of the corpus callosum, and histological abnormalities.

Autosomal-recessive (Meinecke and Passarge, 1991) as well as autosomal-dominant inheritance of the disease has been suggested (Sugio *et al.*, 1993).

Taybi–Linder Syndrome (Dwarfism; Skeletal Dysplasia and Cerebral Malformations)

This syndrome was first described by Taybi and Linder (1967) in two siblings of Italian origin, and later by Thomas and Nevin (1976) in two brothers of Irish extraction. The children had a pronounced microcephaly, bulging eyes, and spatulate hands. Other skeletal abnormalities were present in the ribs, vertebrae, and limbs. Majewski and Goecke (1982) classified the syndrome as dwarfism with microcephaly type I.

Gross appearances. An absent corpus callosum with a single ventricle was found in the cases of Taybi and Linder. Those of Thomas and Nevin showed a hypoplastic brain (200 g), but no agenesis of the corpus callosum.

Light microscopy. The cerebral cortex showed a lack of lamination and abnormal orientation of individual neurons. Numerous heterotopias were present in the subcortical white matter (Kaufman, 1982).

Maroteaux and Badoual (1990) postulated that Taybi–Linder syndrome and primordial dwarfism types I and III of Majewski are a single autosomal-recessive entity. Because of the skeletal lesions, lacking in the Seckel syndrome, they proposed the name *sublethal microcephalic chondrodysplasia* for this disease.

Rubinstein–Taybi Syndrome (Dysmorphic Dwarfism)

This syndrome was described by Rubinstein and Taybi (1963). Dwarfism is accompanied by mental retardation and defective speech. Other neurological symptoms include epileptic seizures, muscular hypotonia, and disturbances of gait. The eyes have an "antimongoloid" slant and the face is triangular. Microcephaly is an almost constant feature (Hennekam *et al.*, 1991). Neurogenic atrophy was seen on muscle biopsy, as well as changes in the sarcoplasmic reticulum and the myofilaments.

The prognosis is favorable. The syndrome is familial, with variable phenotypic expression within the same family and different modes of inheritance in different families (Gillies and Roussounis, 1985). A small deletion at chromosome 16p13.3 may be found in some patients (Hennekam *et al.*, 1993). The clinical features were essentially the same in patients with and without visible deletion, with the possible exception of the incidence of microcephaly. No autopsy findings have been reported to date.

Oculodentodigital Dysplasia

This syndrome was described by Gorlin *et al.* (1963). The patients show a characteristic facies with a thin nose and hypoplastic alae nasi, microcornea, and syndactyly of the fourth and fifth fingers. Some patients are slightly retarded; blindness due to glaucoma may also occur (Traboulsi and Parks, 1990). Calcifications were demonstrated in the brain in a few cases (Christian, 1982). No autopsy findings are available.

Epilepsy in Neurodegenerative Disorders

Seizure disorders are among the most common neurological diseases. Approximately 1% of the population suffers from them, and probably 5% will have a seizure once in their lifetime. As a result of the increasing refinement of imaging and EEG techniques, the epilepsies are being continuously reclassified and elaborated on. Nevertheless, the old division into idiopathic and symptomatic, generalized and focal forms retains limited validity. If we understand *idiopathic epilepsies* to include those not associated with any underlying disease and therefore not associated with structural changes, either gross or visible under conventional light microscopy, this does not rule out structural lesions at the submicroscopic level. Honer *et al.* (1994) have drawn attention to abnormalities at the synaptic level that may underlie some seizure disorders. In the symptomatic group seizures may occur in malformations, perinatal brain damage, infections, vascular lesions, trauma, and neoplasms, conditions outside the scope of this book. They are also a common feature of metabolic and degenerative diseases and are discussed in the appropriate chapters. Imaging techniques, particularly MRI, have visualized the underlying lesions during the patient's life and PET scanning can detect more subtle abnormalities that may remain undetected by MRI (Sperling, 1990; Kotagal and Lüders, 1994). All of these techniques, as well as neuropathological studies, have helped to define certain specific syndromes that are the subject of this chapter.

General Pathogenetic Mechanisms

The clinical epileptic syndrome is determined by the anatomical localization and extent of the cerebral lesions, even with the same pathogenetic basis. In the absence of exogenous cerebral damage or in the presence of a diffuse cerebral lesion, a primary general-

ized epilepsy is likely to develop as an expression of genetic factors. If a circumscribed brain lesion is present, similar genetic factors may result in focal epilepsy.

Four factors must be present to produce an epileptogenic potential.

1. There must be neurons capable of firing a rapid sequence of action potentials ("intrinsic burst generation"). Such neurons have been identified in sectors CA2 and CA3 of the hippocampus and in laminae IV and V of the neocortex.
2. Postsynaptic inhibitory control mechanisms must be disturbed.
3. A sufficient excitatory synaptic network must be available in the neuronal population.
4. The modulation of ionic and transmitter concentrations must be disturbed (Prince, 1985).

Some mechanisms influencing these four factors are known. Inhibitory interneurons are selectively vulnerable (Ribak *et al.*, 1982). The development of new excitatory contacts in cerebral lesions has been demonstrated (Tsukahara, 1981). Focal reactive gliosis can interfere with the clearance of potassium ions (Somjen, 1984). Changes in membrane characteristics are genetically determined (Wu *et al.*, 1983). Disturbances of the calcium-regulated control of membrane excitability and disorders of transmitter metabolism may be caused by either genetic or exogenous factors (Moody, 1984).

It is becoming increasingly apparent that many epileptic syndromes, both idiopathic and symptomatic, have a genetic background (Leppert *et al.*, 1993; Delgado-Escueta *et al.*, 1994). Among the idiopathic forms gene loci have been identified for juvenile myoclonus epilepsy and for benign familial neonatal convulsions. Juvenile myoclonus epilepsy is one of the more common forms of epilepsy, usually beginning in adolescence. It is inherited as an autosomal-dominant trait, with variable expressivity. It is genetically heterogeneous, with one group having its gene located on chromosome 6p21.3 (Greenberg *et al.*, 1988); the gene for the remaining group is unidentified, but it is not located on chromosome 6p. Benign familial neonatal convulsions are a self-limiting condition, inherited as an autosomal-dominant trait, and are also genetically heterogeneous, with the gene located on chromosome 20q in some families and on chromosome 8q in others (Leppert *et al.*, 1989; Lewis *et al.*, 1993).

In the symptomatic forms the main group consists of the various diseases associated with progressive myoclonus epilepsy. This includes Unverricht–Lundborg's disease, Lafora's disease, the ceroid lipofuscinoses (except the infantile form), juvenile Gaucher's disease, sialidosis type I, and MERRF (Berkovic *et al.*, 1986). The gene for Unverricht–Lundborg's disease has been located on chromosome 21q22.3 in both Baltic (Lehesjoki *et al.*, 1991) and Mediterranean families (Malafosse *et al.*, 1982). The Lafora's disease gene has not been identified, but it is not on chromosome 21q. Of the ceroid lipofuscinoses with progressive myoclonus epilepsy, only the gene for the juvenile form has been located on chromosome 16p (see p. 390).

The gene coding for β-glucocerebrosidase in Gaucher's disease has been located on chromosome 1q21–q31 (Barneveld *et al.*, 1983); that for sialidosis type I, in the band 10pter–23 (Mueller *et al.*, 1986). MERRF is a mitochondrial disease caused by a mutation on mitochondrial tRNA Lys (Shoffner *et al.*, 1990). All of these diseases are discussed in greater detail in the appropriate chapters.

West Syndrome (Propulsive Petit Mal; Lightning Salaam Seizures; Infantile Spasms)

Infantile spasms were first observed by English physician E. J. West (1841). They have subsequently become known as lightning, flexor, or salaam spasms.

Clinical Picture West syndrome is responsible for over 40% of the epileptic seizures in infants, while it represents only 2–5% of the total epileptic disorders in all age groups. Three quarters of the cases occur during the first year, with a peak incidence at the age of 5–6 months. The essential feature of the attacks is a rapid forward movement of the body, hence the term *propulsive petit mal.* According to the course of the attacks, one can distinguish lightning, flexion, or salaam spasms. The EEG shows the pattern of hypsarrhythmia.

Neuropathology Macroscopically, the brain weight is reduced in about one half of the cases, and in one fifth it may be below 50% of the normal values. Hydrocephalus is present in three quarters of the cases. Agyria (lissencephaly), macrogyria and polymicrogyria (Figs. 322 and 323), encephaloceles, macrencephaly, cortical dysplasias, schizencephaly, or tuberous sclerosis may be found in individual cases. Porencephalias, ulegyrias, lobar sclerosis, and chronic subdural hematomas may be the result of circulatory disturbances.

Under light microscopy selective neuronal necrosis is prominent, particularly in the neocortex and the hippocampus. In the latter neuronal loss (Fig. 324) affects with equal frequency the end plate (CA4) and Sommer's sector (CA1). On the other hand, CA2 is relatively resistant and rarely affected. This sclerosis of Ammon's horn is usually bilateral and is associated with hypoxic–ischemic lesions in other parts of the brain, particularly in the cerebellum and the diencephalic nuclei. Diffuse gliosis is often present in the white matter.

Microdysgenetic changes with protrusions of the cortex under the pia and disorganized cytoarchitecture of the deeper layers of the cortex are common (Fig. 325). The reduced brain weight implies a global reduction in the number of neurons. In normal controls minor disorders of the cytoarchitecture are present in only 3% of the cases.

Pathogenesis An analysis of the time of formation of the heterogeneous lesions shows that in two thirds of the cases they are of prenatal origin. These cases can be classified as fetal epilepsy. Metabolic and degenerative disorders may also cause West syndrome. The sequelae of meningitis and encephalitis may also be responsible. It is significant that the clinical onset of symptoms is earlier in prenatal malformations than in perinatal or postnatal lesions (Meencke and Gerhard, 1985). There is no correlation between the frequency and extent of the selective parenchymal necrosis and the occurrence of grand mal or the duration of hypsarrhythmia.

Juvenile Myoclonus Epilepsy (Janz Syndrome; Impulsive Petit Mal)

Herpin (1867) was the first to describe attacks accompanied by violent jerks involving the whole body. The clinical characterization of these seizures is due to the work of Janz and Christian (1957), who defined the syndrome.

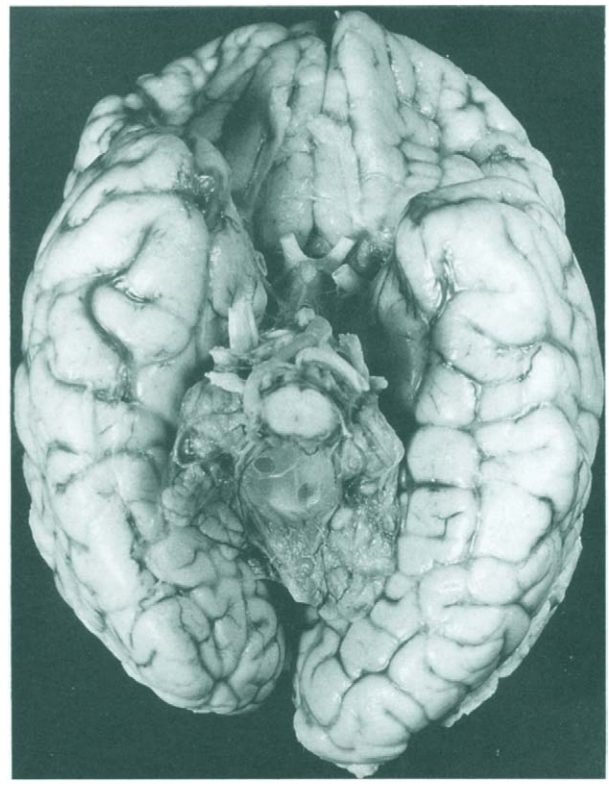


Fig. 322 West syndrome. Macrogyria in the temporal lobe and polymicrogyria in the frontal lobe.

Clinical Picture Impulsive petit mal accounts for about 5% of all epilepsies. Two thirds of the patients develop the disease between the ages of 14 and 18 years. The characteristic features of the movements are suddenness, short duration, and lack of direction. Bilateral synchronous poly-spike–wave complexes are seen on the EEG.

Neuropathology Neuropathological observations are still scanty and include only 16 fully examined cases. Macroscopically, the brains are unremarkable. A small arachnoid cyst, a cavum septi pellucidi, and a discrete hamartoma in the brain stem were seen in one case each.

On light microscopy no postictal changes were found in any of the hitherto examined cases. Selective neuronal necroses were present in only four cases and could be ascribed to cardiac arrest with resuscitation or severe atherosclerosis. Minor dysgenetic changes were found with great regularity. These consisted of a diffuse increase in the number of nonpyramidal neurons in the molecular layer and the subcortical white matter. Morphometrically, their number significantly exceeded that found in age-matched controls or in patients with Lennox syndrome (Meencke, 1985).

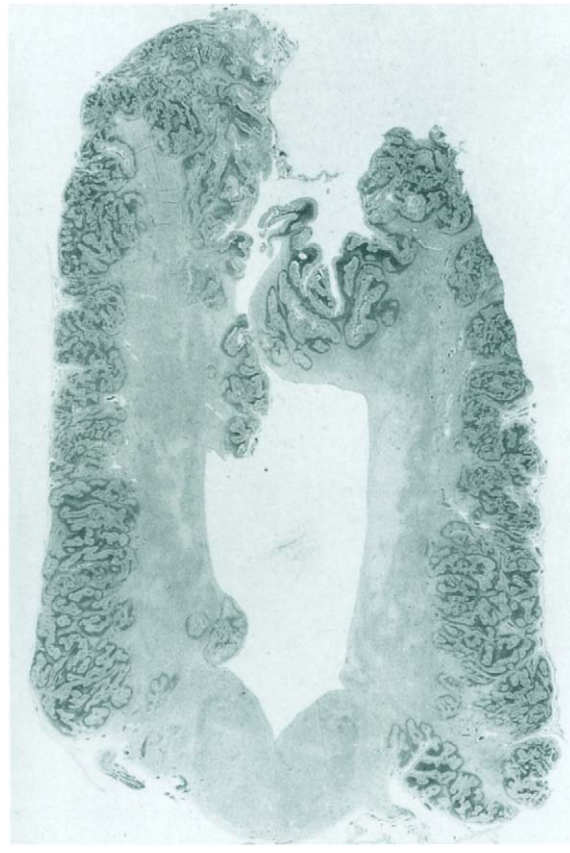


Fig. 323 West syndrome. Polymicrogyria.

Pathogenesis The subtle malformations with ectopic nonpyramidal cells are the significant feature. What is not clear is whether they are genetically conditioned or caused by exogenous factors operating *in utero*. Developmental abnormalities are present in all generalized epilepsies of childhood and adolescence (West, Lennox, Friedmann, and Janz syndromes), although they differ in the extent and time of their development, thus defining the nosological entities and clinical classification of the generalized epilepsies.

Heterotopias ("Double-Cortex" Syndrome)

The MRI appearances of this condition were first described by Barkovich *et al.* (1989). They consist of an apparently normal cortex with a subjacent thin layer of white matter, followed by another band of tissue of the same density as the cortex. Subsequent MRI

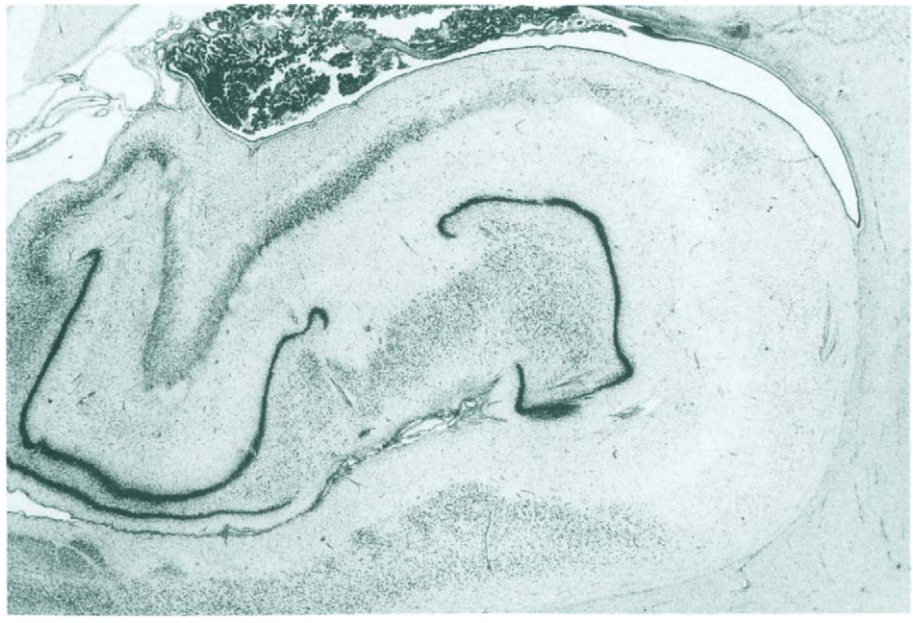


Fig. 324 West syndrome. Neuronal loss in the hippocampus affecting sectors CA4 and CA1. Nissl stain, ×12.

studies of epileptics have revealed several cases with this pattern (Palmini *et al.*, 1991; Ricci *et al.*, 1992; Granata *et al.*, 1994). All patients are mentally retarded and severe epileptics. In a significant proportion of the cases, the seizure pattern is that of Lennox–Gastaut syndrome. The cerebral cortex may appear normal or near-normal and slightly or grossly macrogyric. The severity of the condition is roughly proportional to the degree of cortical abnormality.

As patients with a normal or near-normal cortical pattern tend to have a normal life span, neuropathological observations are scanty. The repeatedly quoted autopsy case is that of Jakob (1936). A cortical biopsy in one of the cases of Palmini *et al.* (1991) showed normal lamination in layers I–IV of the cortex, with blurring of the pattern in layers V and VI. The underlying thin layer of white matter corresponded to the normal U-fibers. The heterotopic band consisted of cortical-type neurons without any attempt at lamination. It is apparent that this represents one end of the spectrum of migration disorders, the more severe, and better known, forms being found in macrogyria and agyria (Barth, 1987).

Lennox–Gastaut Syndrome (Myoclonic–Astatic Petit Mal; Akinetic Petit Mal)

The first patient with this syndrome was reported by Hughlings Jackson (1871). Lennox (1945) defined the disease as an independent syndrome.

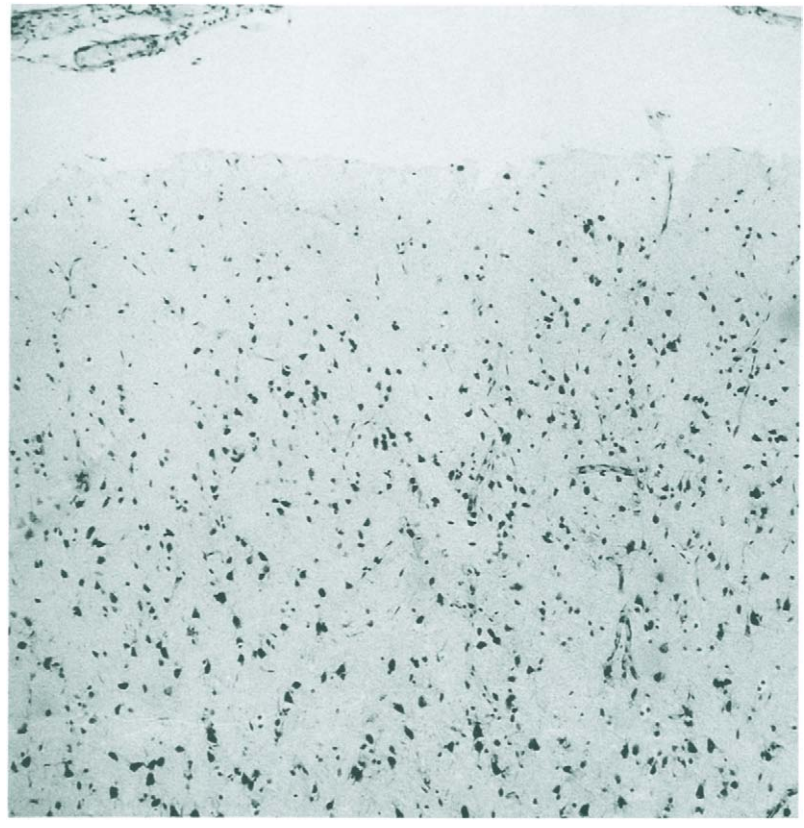


Fig. 325 West syndrome. Microdysgenetic changes in the molecular layer and disorganized cytoarchitecture in the deeper cortex. Nissl stain, ×80.

Clinical Picture About 5% of childhood epilepsies present as myoclonic–astatic petit mal. The peak of incidence lies between the ages of 2 and 3 years. The disorder consists of fall attacks, with or without myoclonus, and with short absences. The attacks are often pyknoleptic, and occur predominantly in the morning. The EEG shows a slow variant of the spike–wave pattern. The propulsive petit mal not infrequently evolves into the akinetic petit mal.

Neuropathology Macroscopically, reduced brain weight has been observed in some cases, with weights under 1000 g in the third decade. In a review of all autopsied cases reported to date, Roger and Gambarelli-Dubois (1988) found that most cases showed dysplastic lesions of various types and severity, the remainder showing only nonspecific lesions. Anoxic–ischemic lesions predominate in the cerebellum. A loss of Purkinje cells is the most common lesion, but lobular sclerosis also occurs. Minor dysgenetic changes are found in the cerebral cortex, mainly in the form of protrusion of neurons into the molecu-

lar layer and disordered architecture of the deeper layers. Morphometric analysis revealed a significant increase in the number of nonpyramidal neurons in the molecular layer (Meencke, 1986).

Pathogenesis In this syndrome there are pointers to early disturbances of development and maturation. Whether the ischemic cerebellar lesions, which show no correlation with the occurrence of major seizures, contribute to the causation of epilepsy is still debatable (Meencke and Veith, 1985).

Epilepsy with Dense Microsphere Accumulation

George and Munoz (1991) reported a case of a mutually retarded epileptic in whom the only abnormality found at autopsy was an excessive accumulation of dense microspheres in the cerebral neocortex, hippocampus, amygdala, and striatum and, to a lesser extent, in the thalamus and the molecular layer of the cerebellar cortex. Dense microspheres are found in small numbers in normal brains (Averback, 1983). These are small, round, and strongly eosinophilic in the neuropil, and are easily mistaken for dislodged red blood cells. Ultrastructurally, they are uniformly dense, spherical, membrane-bound bodies lying within neuronal processes, mainly dendrites.

Friedmann's Syndrome (Pyknoleptic Absences)

The concept of pyknolepsy originally covered apparently nonepileptic clustered absences in childhood (Friedmann, 1906), thought by some authors to be hysterical. The introduction of EEG and the investigations of Jung (1939) and Lennox (1945) revealed the occurrence of three-per-second spike–wave potentials, thus placing the syndrome in the group of petit mal epilepsies.

Clinical Picture Pyknolepsies account for about 8% of all epilepsies. The onset of the disease falls between the ages of 4 and 14 years, with a peak at the ages of 7 and 8 years. The principal symptom is a loss of consciousness, which does not exceed 30 seconds in duration. This may be accompanied by physical manifestations, such as changes in head posture and movements of the eyelids or arms and hands that constitute myoclonic absences. An EEG taken during an attack reveals bilateral synchronous three-per-second spike–wave complexes.

Epilepsies with Psychomotor Seizures

Jackson and Beevor (1889) described these seizures as separate epileptic phenomena and discussed their connection with lesions in the temporal lobes.

Clinical Picture About one third of all epilepsies are accompanied by psychomotor seizures. They occur in all age groups. The clinical course of the seizures can be divided into three phases: the aura (self-awareness), the central seizure (automatisms), and the postictal semiconscious state. The attacks do not start or end abruptly. Both the aura and

the central seizures vary depending on the anatomical substrate, whether temporolateral or rhinencephalic. About 50% of the affected patients are resistant to drug treatment.

Neuropathology Almost all pathological processes in the temporal lobe may lead to psychomotor seizures. Aside from intrinsic tumors involving the temporal lobe, 30% of the resected temporal lobes show sclerosis of Ammon's horn, 12% scars and old infarcts (ulegyrias), and 10% hamartomas and the remainder exhibit nonspecific gliosis or no appreciable lesions. Vital *et al.* (1994) found 10 glial hamartomas and 11 neuronoglial cortical dysplasias in a series of 116 resected temporal lobes. Honer *et al.* (1994) found a reduction in synaptic terminals in sector CA4 and increased synaptic immunostaining in the inner molecular layer of the dentate gyrus of the hippocampus. MacKenzie and Miller (1994) described SPs in 10 of 101 resected temporal lobes from middle-aged epileptics. Aside from the classical form of Ammon's horn sclerosis involving sectors CA1 and CA4 and the dentate fascia, an isolated sclerosis of the end plate (CA4) can be observed, particularly in cases of late onset. If the amygdaloid nucleus, fusiform gyrus, uncus, and lateral neocortical areas are also involved, the lesion is called "mesial temporal sclerosis" and a perinatal temporal lobe herniation is suspected. In undertaking surgical treatment, it must be taken into account that in 50–60% of the cases Ammon's horn sclerosis is bilateral and that in 80% lesions may be found outside the temporal lobes, where they may also act as epileptogenic foci. Furthermore, the morphological abnormality may not always represent the relevant epileptogenic lesion.

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