Bones and Joints in Diabetes Mellitus

G. Flegg et al. (eds.), *Nicolas Chuquet, Renaissance Mathematician*

Series in Radiology

Volume 4

Bones and Joints in Diabetes Mellitus

by

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Budapest

1982

Martinus Nijhoff Publishers

The Hague / Boston / London

Distributors:

for the United States and Canada

Kluwer Boston, Inc.
160 Old Derby Street
Hingham, MA 02043
USA

for all other countries

Kluwer Academic Publishers Group
Distribution Center
P.O. Box 322
3300 AH Dordrecht
The Netherlands

for Hungary, Albania, Bulgaria, China, Cuba, Czechoslovakia, German Democratic Republic, Democratic People's Republic of Korea, Mongolia, Poland, Roumania, Soviet Union, Vietnam, and Yugoslavia

KULTURA
Hungarian Foreign
Trading Company
H-1389 Budapest
P.O.B. 149

Library of Congress Cataloging in Publication Data

Forgács, S.
Bones and joints in diabetes mellitus.

(Series in radiology; v. 4)
Based on the author's thesis.
Includes bibliographies and index.
1. Bones — Diseases. 2. Joints — Diseases.
3. Diabetes — Complications and sequelae. I. Title.
II. Series. (DNLM: 1. Bone and bones—Radiography.
2. Joints—Radiography. 3. Bone diseases—Etiology.
4. Joint diseases—Etiology. 5. Diabetes
mellitus—Complications. WK835 F721b)
RC930.F57 1980 616 7 80-18430

ISBN-13: 978-94-009-7429-6 e-ISBN-13: 978-94-009-7427-2
DOI: 10.1007/978-94-009-7427-2

Joint edition published by

MARTINUS NIJHOFF PUBLISHERS
P.O.B. 566, 2501 CN The Hague, The Netherlands
and
AKADÉMIAI KIADÓ
P.O.B. 24, H-1363, Budapest, Hungary

To Katalin

Contents

Introduction

Complex disorders of the carbohydrate metabolism and associated complications cause many abnormalities detectable by radiography in the bones and joints.

Mild clinical symptoms associated with very severe radiological changes were first recognized in relation to the gastroenterologic complications of diabetes. This phenomenon is more frequent in the skeletal system. For example, mild and painless swelling of the foot joints may often mask extremely severe bone destruction. Several other bone changes associated with diabetes are only detectable by radiography. Thus, the radiologist plays an important role in confirming these diabetic complications, furthermore he is involved in the therapeutic management of the patient.

Although many details on this subject have been published, however no summarizing monograph has yet appeared. Manuals discussing diabetes include only short reviews on complications of the osseous system. The fact that the incidence of diabetes is very high, at present 1%–2% of the population is affected and their number is gradually increasing – displays the timeliness of this subject. Fifty years of experience with insulin therapy indicates that several important problems still remain to be solved. Insulin and modern oral antidiabetic drugs proved extremely efficient in the management of hyperglycemia and ketosis, but the incidence of other complications has not decreased. Moreover, as the number of diabetics and their life expectancy increase, late complications become likewise more frequent. Diabetic osteoarthropathy is one of these complications.

Bone changes associated with diabetes may affect the whole skeletal system or may cause localized defects. Osteoporosis and hyperostosis belong to the former group, diabetic osteoarthropathy to the latter, and these will be discussed in detail in this volume. Besides the aforementioned changes, all other bone defects related to diabetes, according to the literature and to our observations, will also be included.

This monograph is based on the examination of a large number of patients. Most of them were treated at János Hospital, Budapest (approximately 2000 beds), and at the Diabetic Outpatients Centre, which regularly follows up over 1000 diabetics. All the roentgenological examinations and diabetic control of these patients have been carried out by the author. The studies were completed at the Semmelweis University Medical School.

The help of all those who have contributed to this monograph is gratefully acknowledged. The remarks and advice of Professor I. Magyar and Professor F. Horváth, who revised my manuscript with great care and attention, were particularly useful.

Dr. Zsuzsa Csató and Professor J. Forrai made valuable remarks and suggestions about my Ph.D. Thesis, which served as a basis for this volume.

Dr. J. Juhász (János Hospital, Department of Orthopedics) was kind enough to undertake the histological examinations and to allow the use of the documentation on several patients, while Dr. Antonia Rosinger helped in the assay of osteoporosis.

The majority of patients examined were outpatients at the Diabetic Clinic, led by Dr. T. Halmos, head physician, to whom I am also indebted.

Dr. Katalin László (Semmelweis University Medical School, Institute of Physiology) has written the chapter "Pathophysiology of the diabetic bone."

The photographic work was done by F. Ruzs-Molnár.

Finally, I should like to express my gratitude to the team of Akadémiai Kiadó for their conscientious work.

Chapter 1

Pathophysiology of the diabetic bone

(by Dr. Katalin László)

Bone formation and resorption are balanced, uninterrupted processes in the adult organism, the bone mass remains constant. This equilibrium is ensured by the coordinated function of the osteoblasts and osteoclasts.

Osteoblasts are involved in bone formation. The activity of these cells is detectable in all living bones, thus new bone substance is continuously formed. The osteoclasts are responsible for bone resorption, although finally enzymes and organic acids decompose the organic matrix and dissolve the bone salts. Generally, the osteoclasts form masses and chew the bone to pieces, hollowing out a tunnel sometimes even 1 mm in diameter.

Osteoblasts and osteoclasts develop from the mutual progenic cell, the osteoprogenitor, and they may transform into each other. The resting osteocyte transforms into an osteolytic osteocyte, and this develops into a real osteoclast. Osteoblasts with one nucleus are formed directly from osteoclasts, these are surrounded by collagen and produce thus an osteoid osteocyte.

Besides developing from osteocytes, osteoclasts may develop from osteoblasts or from the fibroblasts of the bone marrow. Thus, the osteoblasts are generated by mesenchymal cells. After the tunnel is formed, the osteoclasts transform into osteoblasts, thereafter, the formation of the new bone begins. The new osteoid matrix is deposited in successive layers onto the inner wall of the cavity, until this is again entirely refilled. The remaining central canal is called the haversian canal and the whole area formed in this way is termed osteon.

Parathormone in synergism with vitamin D promotes the differentiation into osteoclasts, calcitonin (which in human is supposed to be synthetized only above a critical serum calcium level) inhibits this process. Parathormone through adenylcyclase stimulation, increases the cyclic AMP concentration in bone tissues, in the kidneys and increases urinary cAMP excretion.

Experiments in rats suggest that adenylcyclase is magnesium dependent, because after the depletion of magnesium, parathormone becomes ineffective. The detailed studies of Bell et al. (1973) have shown that glucagon has a similar effect on parathormone, namely it causes a 30-fold increase in cAMP excretion.

Recently considerable interest has been focused on bone resorption and formation. The extent of the area of bone formation has been studied with labeled tetracycline techniques, while microradiography has been used for determining the size of the resorptive area. It has been shown that first the resorptive phase takes place "in situ"; thereafter, the new matrix is formed, and this is followed by the mineralization of the matrix. The exact time of these periods can be determined. Osteoid mineralization lasts 5–8 days, a prolongation of this period indicates vitamin D deficiency. Bordier and Chot (1973) pointed out that the active resorptive surface does not change substantially with age, although in subjects over 50

years of age, they observed a slightly enlarged total resorptive area and a slightly reduced mineralization.

In the majority of metabolic bone diseases abnormal cell population dynamics occur without any detectable abnormal chemical material, or abnormal enzymes, and no deficit of normal enzymes can be detected.

After this short review of physiological cell population, the dynamics of bone development and the pathophysiology of the diabetic bone will be more easy to understand. Pathophysiology of the diabetic bone will be discussed according to the following aspects:

1. Disorders of cell population dynamics.
2. Role of inorganic ions and hormones.

Disorders of cell population dynamics

Our knowledge about these disorders is based on the studies performed in the Henry Ford Hospital by Frost and co-workers. According to these authors, the amount of bone resorbed or formed in a given amount of bone depends on three factors: 1. number of foci in which these activities occur; 2. mean size of the foci, and 3. mean rate of formation.

The number of remodeling foci is determined by the activity of mesenchymal (i.e., progenitor) cells. The size of the remodeling foci and the individual rate of bone formation are regulated by osteoblastic and osteoclastic activity.

According to the measurements of Frost (1963, 1964), it is possible to study separately the regulation of the mesenchymal cell activation and the regulation of target cell metabolic activity.

Studies were made on diabetics who had long-standing disease, all patients under good diabetic control. Samples of ribs for examination were obtained during surgery or at autopsy. A complete cross-section of the ribs was made, cut from a standard site (12 cm from the sternal junction). According to the studies of Klein et al. (1964), the size of the osteoid seams, which should be considered an index of the osteoblastic metabolism, was significantly larger in diabetics as compared to healthy controls. At the same time they observed that the number of osteoid forming foci was 43% lower in diabetics, indicating that less new bone matrix was being formed. This indicates a depression of mesenchymal cell activity in diabetes.

The radial rate of osteon closure was measured by tetracycline labeling by Landeros et al. (1964) who found that the rate of actively forming osteons in diabetes was decreased to 36% of normal. Their further investigations, however, showed that the ratio of resorbed and formed bone was identical in both diabetics and healthy subjects. This suggests that there is a separate functional mechanism in the local cell system, which determines the participation of bone in the average osteon. To a certain degree, this mechanism seems to be functionally independent of the mechanism which determines the time necessary for the production of bone. If the average size of the diabetic osteon is normal, this means the decrease of the rate of closure in diabetics that it takes 2.8 times longer (i.e., $100 : 36 = 2.8$) to make a diabetic osteon than it takes to make a normal one. This results in a considerable prolongation of osteon formation time in diabetics, i.e., the rate of bone formation is depressed in this disease. This decrease has been demonstrated by Wu et al. (1970) with other techniques, too. However, this does not mean that diabetes leads to osteoporosis. Thinning of the cortical area, a characteristic feature of osteoporosis was

not observed. Moreover, postmortem Klein and Frost (1964) found significantly thicker cortical areas in the ribs of diabetics as compared to the normal situation. The following chapter will discuss similar in vivo findings.

Takahasi and Frost (1964), when comparing the kinetics of normal and diabetic bone formation found that the average time of the complete resorption process was three times longer in diabetics than in age-matched normal subjects. No abnormality was found in the chemical or mineralization properties of the bone matrix of the diabetic bone. The authors concluded the abnormalities to be purely of a kinetic nature, as the shape of the curves did not differ.

Only few data are available confirming whether morphological changes accompany the kinetic disorders. Jaffe (1972) mentioned a special discoloration of the bones. The calvarium in these cases showed frequently a golden or brownish yellow discoloration. This was also noted in the compacta of the long tubular bones, but it was never so intense as in the calvarium. The substance responsible for the yellow color has not been identified. It might be in connection with hypercholesterolemia so common in advanced cases of diabetes mellitus.

Bartl et al. (1978) performed iliac crest biopsies in 118 patients with manifest diabetes. Bone changes in the form of atrophic osteopathy without essentially increased bone remodeling were found more frequently in diabetes mellitus than in the controls of similar age. Histological examination of the biopsy specimens showed that diabetic microangiopathy is also manifest in the vascular system of the bone marrow.

Silberberg et al. (1976) found changes in the chondrocytes of the femoral head of diabetic animals. Histomorphologic changes of the synovial membrane were established by Huth et al. (1977). Generally, acidosis is assumed to result in increased osteoclastic activity. Hernberg's (1952) histological studies, however, did not support this concept, as he found a reduced osteoblastic activity due to acidosis. The haversian canals were widened in the compact substance, and the spongy substance became excentric.

The role of inorganic ions and hormones

In normal experimental animals and healthy humans, the exogenous insulin influences the calcium, phosphorous, and magnesium metabolism. In nontreated alloxan diabetic animals, the calcium and phosphorous resorption of the bones were decreased. However, very little is known about the effect of long-term insulin treatment on the mineral composition of the bones of diabetics. De Leeuw et al. (1976*a*, *b*), who studied this problem in various types of diabetes, found that the calcium content of diabetic bones was identical to that of the controls, and no significant change in the phosphorous content was observed. The magnesium content, however, was significantly lower in patients treated with insulin. In patients managed by diet or taking oral antidiabetic drugs no change in the magnesium content was found. Thus, the low magnesium content appears to be due to insulin therapy.

The latter observation throws new light on the problem, considering – as already discussed above – that adenylcyclase is magnesium dependent.

The question arises, however, whether the bone changes of diabetics could be connected to any disorder in calcium metabolism.

Calcium plays an important role in carbohydrate metabolism. Schneider and Schedl (1972) found insulin to stimulate intestinal calcium absorption in rats. Calcium is essential

for insulin secretion and excretion (Grodsky and Bennett 1966, Gerő et al. 1976, 1977, Malaisse 1973) and potentiates the effect of several insulinotropic substances. Presumably, calcium ions are also necessary for the action of insulin acting as intracellular mediators (Gerő et al. 1976, 1977, Hope-Gill 1974, Kissebach et al. 1975). Recently, Sargent et al. (1976) demonstrated that insulin-dependent patients have a decreased whole body retention of ^{47}Ca. This is additional evidence for defective mineralization of the slowly formed new osteons. At the same time, no *per se* disorder of the calcium metabolism was detected, which might have been responsible for the carbohydrate metabolic disorders. These data are in accordance with clinical laboratory findings in diabetic osteopathy, which do not indicate changes in serum calcium level.

Since calcium reabsorption from the gut depends upon vitamin D – particularly 1,25-dihydroxycholecalciferol and its conversion from 25-hydroxycholecalciferol in the kidney – it is possible that a decrease in bone mass in diabetics may be the result of an acquired anomaly in vitamin D metabolism. In alloxan diabetic rats disorder in vitamin D metabolism was observed, which resulted in histologically detectable reduced mineralization of the bones. De Leeuw et al. (1976*a*, *b*), studying human biopsy specimens of iliac crest, found no evidence in support of vitamin D deficiency that could be involved in the mineralization disorders of the bone.

Villanueva et al. (1964) studied the iron content of diabetic bones. Homogeneously distributed iron was detected in the nonmineralized osteoid. This was assumed to be the symptom of disturbed cellular iron metabolism. According to Thomas (1965), iron is detectable also in the normal bone, the only difference being that, in the diabetic bone, iron occurs in some other form. There may be a change in the balance between the influx of the iron-containing substance and its subsequent efflux.

It has been repeatedly suggested that insulin may be a growth-promoting hormone. This is in connection with the problem of bone development and growth of diabetic children (see Chapter 7). Heinze et al. (1979) suggest a possible significance of glibenclamide as a growth-stimulating substance. The explanation is that glibenclamide increases insulin secretion, or there is a direct effect on somatomedin release.

Of the numerous and extensive hormonal effects only the action of insulin on collagen synthesis will be discussed. Bone collagen synthesis has been shown to be stimulated by insulin in vitro and, according to Canalis (1977), the continuous presence of insulin appears necessary for this anabolic effect. A decreased proliferative capacity of the diabetic fibroblast in tissue culture was observed. Schwartz et al. (1970) studied the effect of insulin on proline and hydroxyproline incorporation in bone tissue cultures. They observed a delayed onset of insulin activity in contrast to the rapid effect on skin collagen synthesis. Obviously, the bone tissues are sensitized to insulin only after a long exposure time. Because of the extremely prolonged onset of insulin effect, there is a possibility that insulin acts as a stabilizer, preventing the breakdown of protein rather than stimulating protein synthesis. The experiments of Hahn et al. (1971) also support the concept, pointed out by Wettenhall et al. (1969), that in bone organ culture chondroitin sulphate synthesis was influenced by insulin.

The relation between insulin and polysaccharide metabolism deserves attention. It is well known that mucopolysaccharide synthesis in the skin of diabetic rats is reduced. Impaired glucose utilization would lead to diminished formation of polysaccharides, which may be in accord with the biochemical abnormalities of osteoarthritis (Lee et al. 1974). Gray and Gottlieb (1976) demonstrated that the reduction of mucopolysaccharides in the

cartilaginous part of the end-plate of the vertebral body results in a relative condensation of the collagens. Thus, the disposition to calcification and, in consequence, to ossification is highly increased. This mechanism is assumed to be involved in the development of hyperostosis.

Silberberg et al. (1976) examined the articular cartilage of rats for the activities of enzymes engaged in the synthesis and degradation of the mucopolysaccharides. In the diabetic animals all enzyme activities were increased, those of the degrading enzymes more than those of the others. Implantation of pancreatic islets reversed the changes produced by diabetes.

The relation of diabetes and anterior pituitary hormones, growth hormone in the first place, is already well known. Experimentally induced diabetes in rats was associated with a significant decrease in serum somatomedin (the effective growth-responsible hormone) and a decrease in cartilage growth activity. These changes are not affected by growth hormone administration. On the other hand, insulin therapy could prevent and reverse this fall of somatomedin and cartilage growth activity in rats (Philips and Young 1976). At the same time glucose intolerance or diabetes develops in only a few patients with acromegaly who produce large amounts of somatotrophic hormones.

Luft and Guillemin's (1974) studies suggest that human growth hormone is diabetogenic only in the pancreatic beta cells which, most likely due to an inherited defect, are unable to respond to the growth hormone, i.e. they do not produce the amount of insulin necessary. These patients are designated "low insulin responders" and are assumably susceptible to diabetes, i.e., they are prediabetics.

The growth hormone overproduction results in well detectable pathological and radiological bone changes. These are most striking in acromegaly. Several similar bone changes occur in diabetes (for details see Chapter 3). Initially, experiments studying the relationship between spondylosis, growth hormone, and diabetes have been performed.

The development of spondylosis is generally attributed to local mechanical causes. The degeneration of the intervertebral discs, followed by the prolapse of the nucleus pulposus and the change of stability of the spine is a mechanical stress on the cartilage and on the bone-forming sites at the edges of the vertebrae. A cartilaginous proliferation starts, and cartilaginous-bony growths are formed. These potential cartilage- and bone-forming foci, however, are not only capable of responding to mechanical stimuli but also to systemic effects. Growth hormone has such an effect in the first place (Gloobe and Nathan 1971). Silberberg (1974*b*) treated mice with somatotrophic hormone during their growth period and found that STH had a slight spondylosis-inducing effect, characterized by a significant chondrocyte proliferation next to the growth area of the lumbar vertebrae, or in the remaining cartilage under this area. This chondrocyte proliferation occurred even without the prolapse of the nucleus pulposus. Furthermore, Silberberg (1974*a*) demonstrated that only mild spondylosis occurs in hypopituitary dwarf mice. The incidence of spondylosis, as will be discussed later in detail, is higher in young people and they are more severely affected. Therefore, it seemed worthwhile to study the problem of spondylopathy of diabetics in animal model experiments. Silberberg and Gerritsen (1976) studied spondylosis in healthy and diabetic Chinese hamsters. Animals of each group were killed at predetermined ages. Blood glucose, plasma insulin and ketone body tests were performed at predetermined times during the study. Pathological and histological examinations were performed on the head of the femur, thoracic and lumbar vertebrae of the animals. According to their results, spondylosis occurred more often and earlier in diabetic Chinese hamsters than in the age-matched controls.

The animal experiments support our radiological observations concerning the spine of diabetics. Growth hormone is suggested to be involved primarily in the pathomechanism of this process.

One of the greatest difficulties in judging diabetic bone changes is that some hormonal changes associated with diabetes or even inducing the disease (somatotrophic hormone, steroids) also influence bone development. Therefore, it is extremely difficult to judge whether a certain process is due to diabetes or to the associated hormonal disorder.

Summary

No substantial changes were detected in the matrix and mineral content of bones in diabetics. According to the studies of Frost (1963, 1964), in diabetes the dynamics of bone formation is disturbed. The size of the osteoid foci is increased, but their number is reduced, i.e., less new osteoid matrix is formed. Osteon formation time is prolonged.

Calcium is also involved in the carbohydrate metabolism. This ion is essential for the secretion of insulin and it also contributes to the action of insulin. However, no disorder of the calcium metabolism could be detected which might be responsible for the changes in carbohydrate metabolism, or which might be characteristic of diabetes.

Hormonal effects are responsible for diabetes associated osteopathy, primarily those of growth hormones. The experiments of Silberberg et al. (1976) showed a relationship between diabetes mellitus, somatotrophic hormone and frequent spondylosis.

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Chapter 2

Osteoporosis and diabetes mellitus

Earlier, diabetes was unanimously considered to predispose patients to osteoporosis (Albright and Reifenstein 1948, Berney 1952, Bartelheimer and Smitt-Rhode 1956), as osteoporosis occurred in about half of the adult patients with diabetes. In 1961 Kuhlencordt et al. discussed osteoporosis as a form of diabetic osteopathy. Therefore, it is not at all surprising that in modern textbooks and in several papers diabetes is listed among the causes of osteoporosis. Such data are reported even in some current papers. Arcangeli and Toccofondi (1970) and Efimov et al. (1972) report osteoporosis in 33%–67% of the diabetics, but the method they used for determining osteoporosis is not referred to. Neumann and Arnold (1970), examining patients with osteoporosis of the spine, found diabetes in 23%. Santiago et al. (1977) examined diabetic children, 25% of whom had cortical thickness below the normal values. Diankov et al. (1979), using different methods, found a significant loss of bone in juvenile diabetes and a moderate decrease in bone mineral content in patients with maturity-onest diabetes. Rizvi et al. (1977) carried out iliac crest biopsy in 40 patients with diabetes mellitus. In 25 cases moderate while in 4 cases mild osteoporosis were found.

Several factors were assumed to contribute to the development of diabetic osteoporosis:

1. In "asthenic diabetes" and in patients with decompensated metabolism, a nitrogen deficit occurs. In consequence, the protein content of the bone decreases. Earlier, many diabetics had decompensated metabolism, therefore, many authors considered this negative nitrogen balance to be the most important factor involved in osteoporosis.
2. Insulin deficiency results in reduced metabolic activity of the osteoblasts.
3. Diabetic acidosis results in increased osteoclastic activity.
4. The renal complication of diabetes (diabetic nephropathy) leads to secondary hyperparathyroidism.
5. Reduced secretion of sexual hormones.
6. Increased secretion of glycocorticoids.
7. Disorders of mucopolysaccharide synthesis, necessary for the formation of bone matrix.
8. Undernourishment of diabetics.
9. Decrease in the blood supply of bones due to diabetic angiopathy.

Photon absorption technique is a modern and precise method for determining bone mineral content. This technique is worth special attention. Levin et al. (1976) examined 35 insulin-treated patients with juvenile type diabetes and 101 adult diabetics with stable metabolism. The bone mass was significantly reduced in both groups. This reduction was the most pronounced in patients treated with oral antidiabetic drugs, while it was the least in the subjects receiving insulin therapy. This may be due to the favorable effect of insulin on the bone metabolism. Another explanation might be the role of the cyclic AMP system. The increase in the cyclic AMP level causes increased bone resorption. Insulin inhibits

adenylcyclase, reducing thus the cyclic AMP level. Consequently, the bone substance increases.

Ringe et al. (1976) examined 21 males under 50 years and 36 females under 45 years of age. In about half of the males and in approximately one third of the females the mineral content was found to be extremely low. Rosenbloom et al. (1977) observed a high frequency of bone density loss in a group of 196 insulin-dependent childhood (age 6–26 years) diabetics.

De Leeuw et al. (1976) completed their photon absorption studies with histomorphometric assays. They found low mineral content in only juvenile type diabetics.

The question arises as to whether the duration and severity of diabetes can influence the calcium content of the bones. According to Arcangeli and Toccofondi (1970), Heuck and Schmidt (1956), Levin et al. (1976) and Santiago et al. (1977), such a relationship cannot be established. Others (Hernberg 1952, Kuhlencordt et al. 1966, Neumann and Arnold 1970), however, emphasize the role of the duration of the disease. McNair et al. (1979) found bone loss in insulin-treated diabetics. They observed bone mineral loss in patients having the following risk factors: onset of diabetes before 21 years of age, ceased insulin secretion, high insulin requirement and severe hyperglycemia associated with raised urinary excretion rates of calcium and phosphorus. Rosenbloom et al. (1977) observed an inverse relationship of bone mass loss to duration of diabetes in childhood.

Among these contradictory data (which are due to the difference between radiological and clinical–pathological definitions of osteoporosis), it is not at all surprising to find several observations disputing the unambiguous relation between diabetes and osteoporosis. In 1952, Hernberg had stated that bone resorption in elderly diabetics was not greater than the degree of involutional osteoporosis in the control group. Gastineau and Power (1959) failed to find any link between calcium and carbohydrate metabolism in a patient suffering from severe osteoporosis. Menczel et al. (1972) did not observe a frequent coincidence of osteoporosis and diabetes in subjects between 55 and 64 years of age. Kelin and Frost (1964) measured the cortical thickness of the ribs of diabetics obtained from surgical specimens of autopsy material. No reduction in the cortical thickness, which might have indicated osteoporosis, was detected. The authors formed the opinion that diabetes slowed down the development of osteoporosis. Meema and Meema (1967) are in support of this concept. They measured the cortical thickness of the radius in diabetic women over the age of 65 years, and found it to be thicker than that of age-matched healthy females. In 1975 and 1976 at the Congress of the European Association for the Study of Diabetes, De Leeuw et al. (1976) reported that in maturity-onset diabetes, the calcium content of bones was significantly increased.

Total body calcium was measured as a parameter of bone mass by means of in vivo neutron-activation analysis. Roginsky et al. (1973), when applying this technique, found that the bone mass in the postmenopausal diabetic females is not significantly different from that in normal controls.

The author's data

The mutual deficiency in the above-cited studies is that they were all performed on a relatively limited number of patients. In our studies, the metacarpal index was determined on the basis of hand radiographs of 428 diabetics (Barnett–Nordin method), and 646 traumatologic patients without diabetes were used as controls.

The principle of the applied method is that in generalized osteoporosis the cortical thickness of the tubular bone is reduced. The degree of osteoporosis can be estimated by measuring the cortical thickness. The cortical index is determined by measuring the cortical thickness at a given level and dividing this value by the total width of the bone. The cortical index of numerous bones has been calculated. The assay of the second metacarpal bone is performed most frequently: on the dorsovolar picture of the right hand, always made at the same focus–film distance, the diameter of the bone and the width of the bilateral cortex are measured with 0.5-mm accuracy with a compass on graph paper. The measurements are made in the middle of the longitudinal axis as the cortex is usually the thickest here.

Our results are summarized in Table 1. The index, i.e. the calcium content of the bones increases in the control group until the age of 30–39 years. Beyond this age a decrease in the metacarpal index was observed, which was particularly marked in females due to postmenopausal porosis. The regression lines were plotted from 35 years onward; our calculations demonstrated that the age-linked decrease of the metacarpal index was statistically significant in males ($P < 0.05$) and strongly significant in females ($P < 0.001$). A significant sex difference was observed in the decrease of bone substance ($P < 0.01$). These observations in nondiabetic controls show that the metacarpal index characterizes the age-dependent changes in the calcium content of the skeletal system.

As our aim was to *compare the age-linked decrease of the metacarpal index in diabetics and nondiabetic population*, exclusively subjects over 30 years of age were examined. The mean values result in similar curves in both groups (Fig. 1). There are two significant differences: (*a*) in diabetic males over 50 years of age the bone substance does not decrease rapidly; and (*b*) in diabetic females the decrease starts one decade later than in the controls.

The regression lines of diabetics were also plotted. Over the age of 35 years the decline of the downward directed regression line was not significant in males ($P < 0.30$) and strongly significant in females ($P < 0.001$). Mathematical comparison (Fig. 2) showed no significant difference between the regression lines of diabetics and controls of either sex (males $P < < 0.30$, females $P < 0.08$).

Table 1

Metacarpal index in diabetic patients and controls

Age (years)	Control group						Diabetics					
	Males			Females			Males			Females		
	Total	Index		Total	Index		Total	Index		Total	Index	
		$\bar{x}$	SE		$\bar{x}$	SE		$\bar{x}$	SE		$\bar{x}$	SE
16–19	36	71±1.3		46	77±1.6		–	–	–	–	–	–
20–29	108	72±0.7		56	78±1.0		–	–	–	–	–	–
30–39	82	74±1.1		42	81±1.4		16	73±2.7		10	76±1.5	
40–49	48	73±0.9		36	78±1.7		42	71±1.5		36	79±1.2	
50–59	28	71±1.7		36	73±1.8		50	69±0.6		84	73±0.9	
60–69	34	65±2.1		46	67±1.6		40	68±1.5		80	66±1.2	
70–79	14	65±2.2		24	60±2.2		28	68±2.0		36	59±2.0	
80–	4	63±1.5		6	51±4.0		–	–	–	6	59±2.0	
Total	354			292			176			252		

x = mean values; SE = standard error.

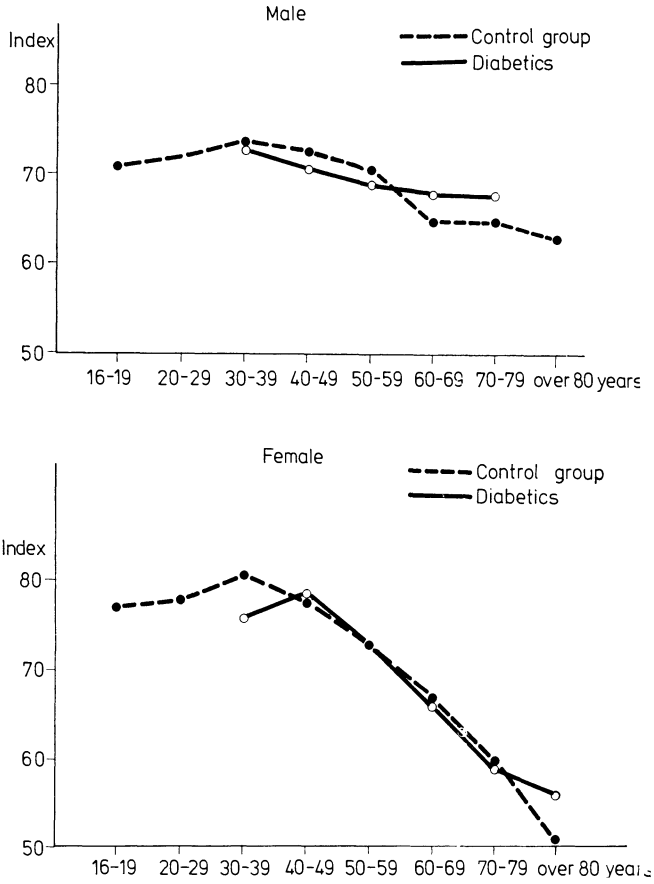

Fig. 1. Comparison of the metacarpal indices in diabetic patients and controls

The relation between the metacarpal index and the duration of diabetes was also examined. We compared the data of patients with diabetes diagnosed within 2 years and of those with a previous history over 10 years. No substantial differences were observed in the mean values.

The relation between the metacarpal index and the type of diabetes was also studied. The data of patients requiring insulin and those treated with oral antidiabetic drugs were compared. A slight increase of the metacarpal index was found in elderly males of the latter group, but otherwise the curves were similar.

We examined the incidence of spontaneous vertebral compression fractures in a large series of patients. Among 230 diabetics over 60 years of age compression fractures of nontraumatic origin were observed in the dorsal and lumbar spine in 19 cases (8.3%). According to the literature, the incidence in the normal population of vertebral compression without clinical symptoms, due to osteoporosis is higher than in our studies (Gerson-Cohen et al. 1953, Reshef et al. 1971, Rusch and Virtama 1972).

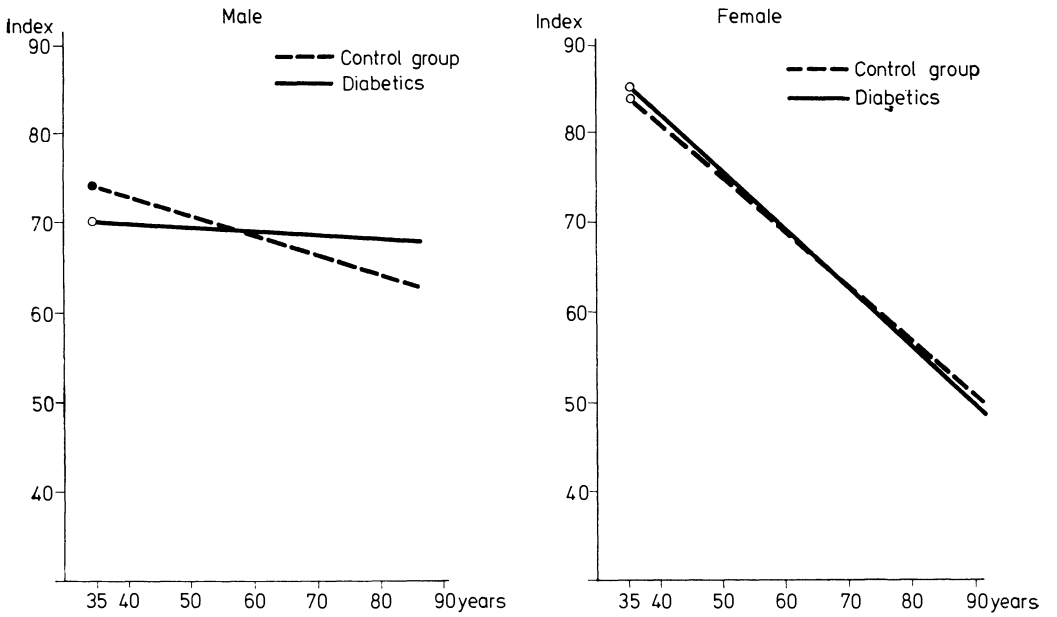

Fig. 2. Comparative regression lines in diabetic patients and controls
Equations:

control males	$y = 82 - 0.23\ (\pm 0.08)x$
diabetic males	$y = 73 - 0.078\ (\pm 0.086)x$
control females	$y = 105 - 0.60\ (\pm 0.09)x$
diabetic females	$y = 107 - 0.64\ (\pm 0.08)x$

Evaluation of the author's data

The most important conclusion of our studies is that the age-linked decrease in the calcium content of bones does not differ significantly in diabetics and healthy age-matched controls of both sexes.

What is the explanation of our findings, and how can the often contradictory data from the literature interpreted?

Before the insulin era, a great number of diabetics were encountered with severe osteoporosis. At present this stage can develop only in extremely neglected cases. Due to modern therapeutics no prolonged and severe metabolic disorders form in diabetes resulting in substantial decrease of bone matrix, decrease of osteoblastic activity or prolonged acidosis stimulating osteoclastic activity, nor does chronic undernourishment of diabetics occur today.

Precise assays performed by four research groups (De Leeuw et al. 1976, Levin et al. 1976, Ringe et al. 1976, Rosenbloom et al. 1977) using photon-absorption technique led to identical results only in juvenile type diabetes in which case the calcium content of the bones was reduced. This only indicates a tendency to osteoporosis without manifest radiographic and clinical symptoms.

In cases of maturity-onset diabetes, the situation is somewhat different. According to our studies, and in agreement with other authors, no osteoporosis develops, moreover the

calcium content of the bones is higher than in the controls. According to Kelin and Frost (1964), further to Meema and Meema (1967), diabetes slows down the development of involutional osteoporosis. When performing histological examinations, the aforementioned authors, as already discussed under pathophysiology, found that the cortical area of diabetic ribs was thicker than those of the controls. This phenomenon is ascribed to hormonal effects.

The relationship between the reduced production of sexual hormones and postmenopausal osteoporosis is well known. Hernberg (1952) attributes an important role to the reduced production of sexual hormones in the development of diabetic osteoporosis, but there are also observations demonstrating a normal or increased estrogen level in the majority of diabetic females in the menopausal period (Campagnoli et al. 1965). This observation may explain why the decrease of the bone mass starts a decade later in diabetic females than in healthy controls (Fig. 1).

Other workers believe there is a link between adrenocortical estrogen production and diabetes (Bruisma and De Waard 1959, De Waard and Oettle 1965). Increased estrogen production protects against postmenopausal osteoporosis. According to Holló's studies (1972), postmenopausal osteoporosis is due to reduced adrenocortical hormone production.

Hyperostosis frequently occurring in elderly diabetics is at the same time a protecting factor against osteoporosis. This phenomenon, as will be discussed later, is linked with somatotrophic hormone. In cases of increased growth hormone production (acromegaly), the cortex is thicker (Ikkos et al. 1974). This explains the higher cortical index of elderly males with mild diabetes, who had particularly marked hyperostosis.

Osteoporosis is frequently encountered in the course of idiopathic hemochromatosis. Monnier et al. (1979) examined diabetics with hemochromatosis. A deficiency was found in the hepatic production of 25-hydroxycholecalciferol which leads to decreased intestinal calcium absorption and thereby to bone rarefaction.

Summary

Earlier, authors often observed severe osteoporosis in diabetics, which was due to the negative nitrogen balance resulting in a decrease of protein matrix of the bones. Thanks to modern management of diabetes mellitus, today prolonged and severe metabolic disorders usually do not develop, thus, substantial decrease of the bony mass hardly ever occurs. In juvenile diabetes measurements by photon-absorption technique demonstrated a reduced mineral content, but radiographic and clinical symptoms did not indicate calcium deficiency.

In elderly patients, particularly in cases of "maturity type" diabetes, no significant difference in the decrease of calcium content of the bones was found in diabetics and healthy controls. Several studies reported an increased mineral content in the bones of elderly diabetics. This phenomenon is attributed to hormonal effects.

The influence of the duration, severity and management of diabetes on the bone calcium content remains a question of dispute. These factors seem to have no substantial effect. Further detailed studies are still needed in order to resolve this problem.

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Chapter 3

Hyperostosis and diabetes mellitus

Hyperostosis of the spine

In 1950, Forestier and Rotes-Querol described a disease characterized by calcification of the vertebral ligaments, which they named "hyperostose ankylosante vertébrale sénile." The disease was found in elderly males; thus, they assumed a relationship with the disorders of the prostate gland. In 1952, Ott observed similar changes in females, and introduced the term spondylosis hyperostotica, indicating that he regarded it as a form of spondylosis deformans. This designation is widely used in the literature, the English literature refers to "ankylosing hyperostosis" and "hyperostotic spondylosis." Other authors use the terms Forestier's disease or Forestier's spondylosis.

The final place of this disease among the abnormalities actually is still disputed. Pathologic studies by Forestier and Lagier (1971) and by Resnick and Niwayama (1976) proved that it differs from spondylosis. Forestier and Lagier have merely changed the name inasmuch as they omitted the adjective "sénile."

The pathologic process consists in the calcification of the anterior longitudinal ligament. Calcification also involves the paravertebral connective tissues and the peripheral portions of the intervertebral discs.

Hyperostotic spondylosis became a topic of renewed interest when attention was drawn to its relationship with endocrine disorders. In 1954, Boulet et al. discussed its association with diabetes mellitus in 12 patients. Later, supporting evidence was provided by studies performed on a large number of patients. Literary data are summarized in Table 2. Hyperostotic spondylosis was confirmed in 13%–49% of the diabetic patients. This percentage is significantly higher than the incidence in the normal population (Table 3). Table 4 reveals that disorders of the carbohydrate metabolism were observed in 12%–79% of the patients

Table 2

Incidence of hyperostotic spondylosis in diabetics

Authors		Total No. of diabetics	Hyperostotic spondylosis	
Ott et al.	1963	82	40	(49%)
Hajkova et al.	1965	101	40	(40%)
Schilling et al.	1965	50	11	(22%)
Julkunen et al.	1966	510	66	(13%)
Schoen et al.	1969	507	125	(25%)
Lequesne et al.	1970	52	15	(29%)
Andersch et al.	1970	1000	134	(13%)
Bossa et al.	1970	102	30	(29%)
Geyer	1973	150	30	(20%)
Own material		500	118	(24%)

Table 3

Incidence of hyperostotic spondylosis in nondiabetics

Authors		Incidence of hyperostotic spondylosis (%)	Age (years)
Vignon et al.	1961	5	Mean 77
Cassan	1963	6.5	
Julkunen et al.	1966	4	<60
Dahmen	1967	7.3	
Julkunen et al.	1968	1.6	30–60
Schoen et al.	1969	2.6	31–85
Andersch et al.	1970	2	<45
Bossa et al.	1970	8.3	<40
Lequesne et al.	1970	13	Mean 70
Julkunen et al.	1971	3.5 (males) 2.2 (females)	<40
Streda et al.	1971	4.9 (females)	25–85
Bregeon et al.	1973	5.4	<40
Pilosov et al.	1973	4.6	<40
Own material		3.1	<40
		6.5	<60

with hyperostotic spondylosis. A high incidence was reported by those authors who carried out detailed studies on the metabolism (e.g., Shoen et al. 1969).

Besides the tabulated data, Bywaters et al. (1966), Fiorio (1967), Frehner and Hohl (1961), Giordano (1972) (who suggests the designation "dysmetabolic hyperostotic spondylopathy"), Hajzok and Takac (1970) and Mayer and Frehner (1956) have reported on the association of hyperostotic spondylosis and diabetes mellitus. Efimov et al. (1972) and Waine et al. (1961) discuss the relationship between spondylosis deformans and diabetes. It should be mentioned that, in 1933, Hetényi in his book on metabolic disorders called attention to the high incidence of severe spondylosis in diabetics. Klunker (1964) was the

Table 4

Incidence of disturbed metabolism in hyperostotic spondylosis

Authors		Hyperostotic spondylosis	Manifest diabetes	Latent diabetes	Total	
Recordier et al.	1959	16				(56%)
Einaudi and Viara	1960	19		11		(60%)
Cassan	1963	43	10			(23%)
Ott et al.	1963	100	25	25	50	(50%)
Dahmen	1967	120	23	12	35	(30%)
Ott et al.	1967	160	35	52	87	(55%)
Julkunen et al.	1968	23				(17%)
Schoen et al.	1969	166	53	79	132	(79%)
Queiros et al.	1974	45				(31%)
Harris et al.	1974	34	4			(12%)
Resnick et al.	1975	21	6			(29%)

only author who failed to confirm a significant correlation between diabetes mellitus and spondylosis.

Author's studies and experience

The incidence of hyperostotic spondylosis, a disease of the elderly, is pronounced in patients over 40 years of age. A radiographic survey of 500 randomly selected diabetics over 40 years old included the following approaches:

1. Lateral view of the cervical spine.
2. Lateral view of the thoracic spine.
3. Lateral view of the lumbar spine.
4. Lateral view of the skull.
5. Sagittal view of the pelvis.

In many instances, the sagittal view of the skull and spine was also included. In the majority of cases (when anomalies of the spine were detected), radiographs of the hands, feet, and of the large joints of the extremities were also made. In the control group, 500 lateral projections of the thoracic spine were assayed in patients over 40 years. These patients were examined because of vertebral fracture suspected to be of traumatic origin, and diabetes mellitus was absent from their medical history.

In accordance with the accepted criteria we considered spinal changes positive if ventral ligamentous calcification was observed on at least three successive vertebrae. Statistical analysis was performed using the χ^2 test.

Analysis of the control group

In agreement with the literature we found the incidence of hyperostotic spondylosis increasing with age. There were 36 positive cases observed in the control (traumatologic) group. The youngest subject was 53 years old. These patients were called in for further examination. Their medical history was recorded, fasting blood and urine glucose levels were tested and,

Table 5

Incidence of hyperostotic spondylosis in traumatological material and results of carbohydrate metabolic studies

Age (years)	No. of patients	Hyperostotic spondylosis	Results of carbohydrate metabolic tests in x-ray positive cases			Corrected data		
			No. of patients examined	Manifest diabetes	Chemical diabetes	No. of nondiabetic patients	Hyperostotic spondylosis	
40–49	85	–	–	–	–	85	–	
50–59	181	5	5	2	2	177	1	(0.6%)
60–69	153	14	11	4	4	145	6	(4.1%)
<70	81	17	12	3	6	72	8	(11.1%)
Total	500	36	28	9	12	479	15	(3.1%)

Note: Eight patients with hyperostotic spondylosis did not report for the examination.

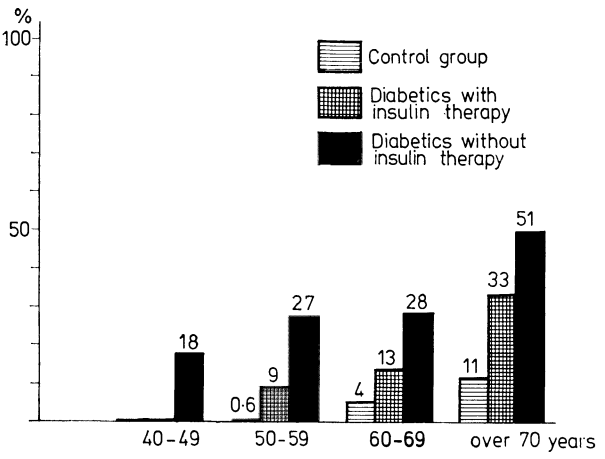


Fig. 3. Incidence of hyperostotic spondylosis in the various patient groups

if negative, glucose tolerance tests were made. Of the patients, 28 responded to our appeal. In 9 cases manifest diabetes, and in 12 other cases a diabetoid blood-sugar curve (chemical diabetes), were confirmed. Thus, disturbed carbohydrate metabolism was found in 21 cases.

The ideal controls would be subjects in whom diabetes could be ruled out with certainty. However, we have no patient material with such spinal radiographs at our disposal. Not counting the diabetic cases we found when glucose tolerance tests were performed in the total number of cases, "corrected data" were obtained which approach the figures of the ideal control group (Table 5). These data are presented in Fig. 3. In the nondiabetic series hyperostotic spondylosis actually occurred only with old age, as we found only one patient under age 60 with this disorder.

The incidence of hyperostotic spondylosis in nondiabetic patients over the age of 40 is 3.1%. Considering exclusively the cases over 60 years of age the incidence rises to 6.5%.

In patients with hyperostotic spondylosis only 6 had normal blood glucose levels. They were all males, and 4 of them had prostate gland disease (three cases of hypertrophy and one carcinoma). As the original description by Forestier and Rotes-Querol (1950) reported ligament calcification in elderly males suffering from prostatic disorder, they assumed ascending prostatitis was involved. This etiology can be rejected with certainty, but a mutual hormonal origin of the two diseases may be assumed. Several authors report the frequent association of hypertrophy of the prostate and diabetes mellitus: 6%–9% of the patients with prostatic hypertrophy also have diabetes (Corrodi et al. 1974). These data must, however, be evaluated with great care, as it may also be possible that old age is the link between these diseases.

Analysis of data in diabetic patients

Among the 500 nonselected diabetic patients over 40 years of age, hyperostotic spondylosis was found in 118 cases (23.6%). The sex and age distribution of our patients is listed in Table 6. The incidence of the disease naturally rises with age. There was a slight prevalence of males, but the sex distribution showed no statistically significant difference ($P > 0.20$). We failed to find male dominance in our patients, as emphasized by several other authors.

Hyperostotic spondylosis did not occur in the 40- to 49-year-old controls, 7 diabetics were detected in this group, and the youngest patient was 42 years old.

Table 6

Age and sex distribution in hyperostotic spondylosis in diabetes mellitus

Age (years)	Males		Females		Total No. of diabetics	Total No. of hyperostotic spondylosis
	Diabetics	Hyperostotic spondylosis	Diabetics	Hyperostotic spondylosis		
40–49	28	5	35	2	63	7 (11.1%)
50–59	126	28	76	14	202	42 (20.8%)
60–69	61	18	122	26	183	44 (24%)
<70	25	13	27	12	52	25 (48.1%)
Total	240	64 (26.7%)	260	54 (20.8%)	500	118 (23.6%)

Comparison of the diabetic and nondiabetic population clearly indicates that the incidence of hyperostotic spondylosis is significantly increased in all age groups. In addition, spondylosis was present at an earlier age in diabetics than in nondiabetics. Silberberg and Gerritsen's (1976) experiments support our clinical observations. Chinese hamsters with spontaneous diabetes were examined. The histological changes detected in the spines of the animals were similar to those of humans. They found that the incidence of spondylosis was significantly increased and its onset was accelerated in the diabetic animals. Blood glucose level and ketoacidosis did not influence the development of spinal changes.

Radiographic features of hyperostotic spondylosis

Hyperostotic spondylosis is confirmed radiologically by means of lateral radiography of the spine. In order of frequency the thoracic, cervical, and lumbar spine are affected.

Hyperostotic spondylosis occurs most frequently in the lower section of the *thoracic spine*. At the onset, only a thin linear or somewhat thicker calcification appears, involving only a few segments (Fig. 4). Later, a calcified band appears along the anterior longitudinal ligament, fusing the anterior plates of the vertebral bodies as well as the discs (Fig. 5). In the more advanced stage of the disease the total ligament and the adjacent connective tissue are calcified, and the vertebral bodies become fused by synostosis (Figs 6 and 7).

A radiolucency beneath the deposited bone is visible. Calcification is thicker at the level of the intervertebral discs, thus the wavy appearance (Fig. 7) is sometimes associated with almost regular thickenings (Fig. 6). In the sagittal view the defects appear on the right side, at least in the majority of cases (Fig. 8). The vertebral bodies are generally flat.

Reports on the involvement of the cervical spine are far less frequent (Luschnitz and Lange 1972, Spilberg and Liebermann 1972, Wackenheim and Dirheimer 1970). In our material, only 9 such cases occurred, and these mostly involved the lower cervical segments (Figs 9 and 10). The changes occurring in the initial stage are best studied at the cervical spine. In front of the intervertebral discs a linear shadow appears (Fig. 11), following the direction of the ligament. The size and radiolucency of this calcified shadow grows (Fig. 12). Later, the margin of the vertebrae becomes elongated and a triangular or irregularly shaped thick calcification develops adjacent to the elongated margin, thereafter, osseous bridges develop (Fig. 13). This is an extremely slow process, and therefore difficult to follow. Figures 13a and b compare the changes developed after 2 years. Circumscribed ossifications on the

anterior longitudinal ligament are not rare in the cervical spine, particularly at the level of the 5th, 6th, and 7th segments. However, ossification is unusual in the cranial section of the neck (Fig. 14), and a continuous calcification developing from the isolated calcified ligament segment is even less common (Figs 9 and 10). This is probably due to the wider range of motion of the cervical spine.

Involvement of the *lumbar spine* seems to be extremely rare. In fact the "flowing" calcification pattern visible in the thoracic or cervical sections does not occur. In cases of typical thoracic manifestation of hyperostotic spondylosis, pointed candle-flame-like outgrowths extending proximally (rarely caudally) appear on the anterior face of the lumbar vertebrae (Fig. 15). The calcified osteophytes broadly cover the anterior surface of the vertebral bodies (Fig. 16). These osteophytes unite, forming coarse and thick, bizarre-shaped calcifications (Figs. 16 and 17).

An important radiographic sign is that the height of the intervertebral discs is maintained. The small joints are free (Fig. 18). The hyperostotic vertebrae may be mildly porotic.

In our patients, all three sections of the spine were radiographically examined, and the relation between the abnormalities was studied. The following conclusions were drawn:

1. Defects of the thoracic spine are often isolated. Extremely extended thoracic hyperostosis was often accompanied only by minimal spondylotic changes in the cervical and lumbar sections.

2. However, isolated hyperostotic spondylosis of the cervical or lumbar spine did not occur. These changes were generally associated in the form of extended thoracic hyperostosis.

Clinical picture of hyperostotic spondylosis

Most authors agree that, in spite of the extensive radiological changes, the patients usually have few complaints. Our own examinations confirmed this, too. In patients with hyperostotic spondylosis, the incidence of back pains was lower than in age-matched patients suffering from other diseases. This is due to the fact that hyperostotic spondylosis is not a disease of discopathic origin, because calcification occurs at the anterior part of the vertebral bodies, which does not give rise to radical symptoms or pain. A decreased range of motion rarely causes major complaints, and the patient seldom seeks medical help. Therefore, it is not at all surprising that hyperostotic spondylosis is frequently diagnosed accidentally.

Due to the anatomical situation of the spine and esophagus, dysphagia may occur in cases of cervical involvement (Balla 1964, Lecomte et al. 1969, Meeks and Renshaw 1973, Ratnesar 1970, Schnier 1972). Govoni (1973) found a total of 77 cases in the literature and in his own experience. Figure 9b shows such a case. In severe cases, removal of the osteophytes is indicated (Carlson et al. 1970).

As diabetes itself may cause dysphagia owing to diabetic visceral neuropathy (lesion of the vagus nerve), the problem is even more complicated. These symptoms are designated as diabetic dysphagia. According to our studies, in some cases Forestier's disease may be involved in the pathogenesis of diabetic dysphagia (Forgács 1974).

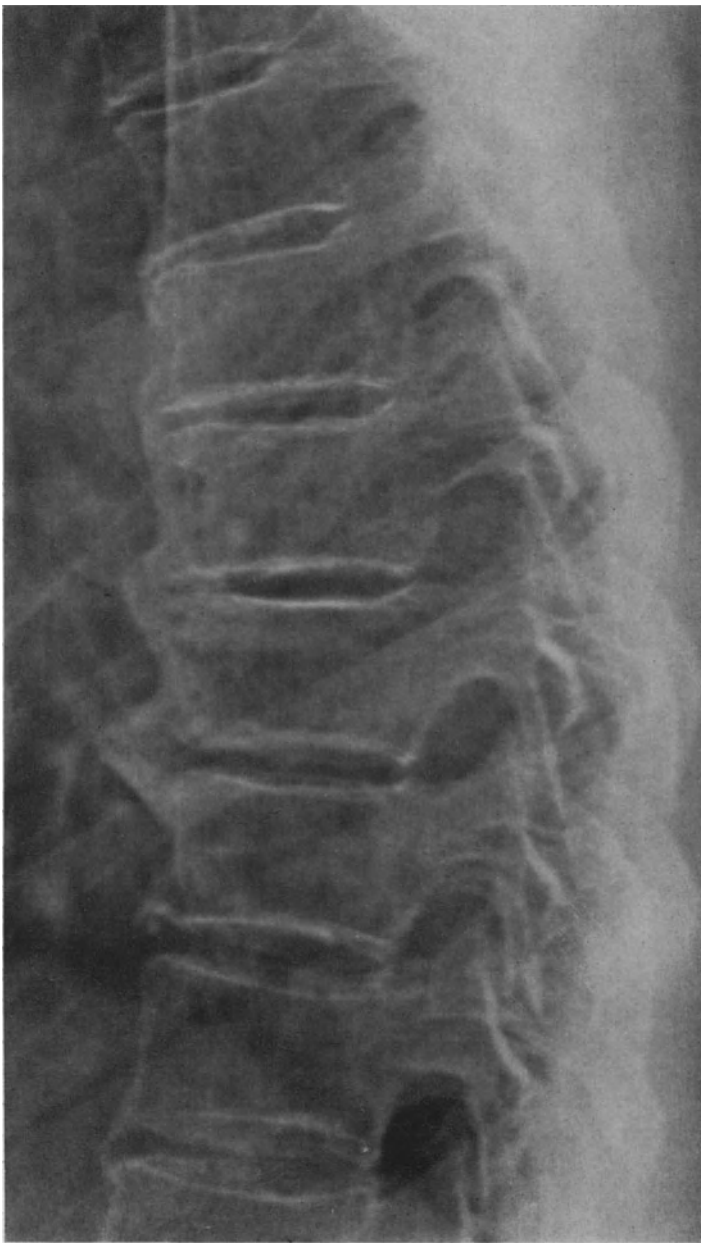
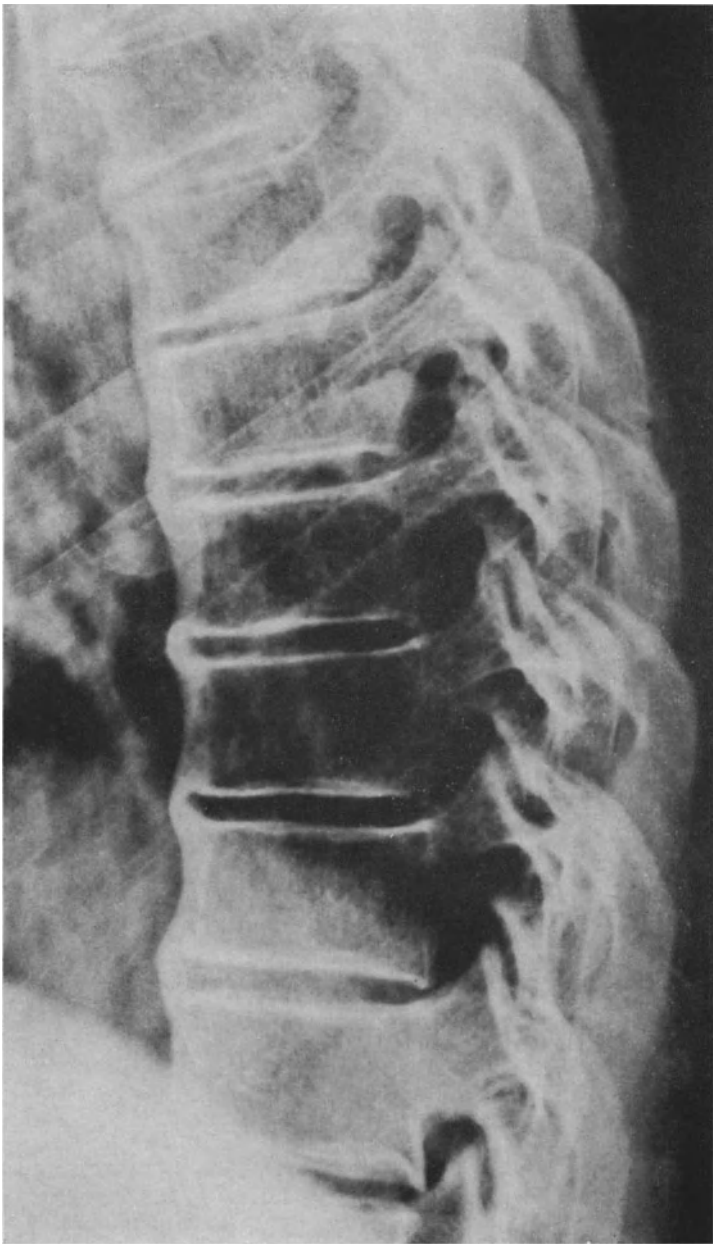


Fig. 4. Calcification extends along the anterior margins of the vertebral bodies and ntervertebral spaces between D8 and D11. Typical localization of the *initial stage of hyperostotic spondylosis*

Fig. 5. Narrow, ribbon-like calcification along the anterior longitudinal ligament



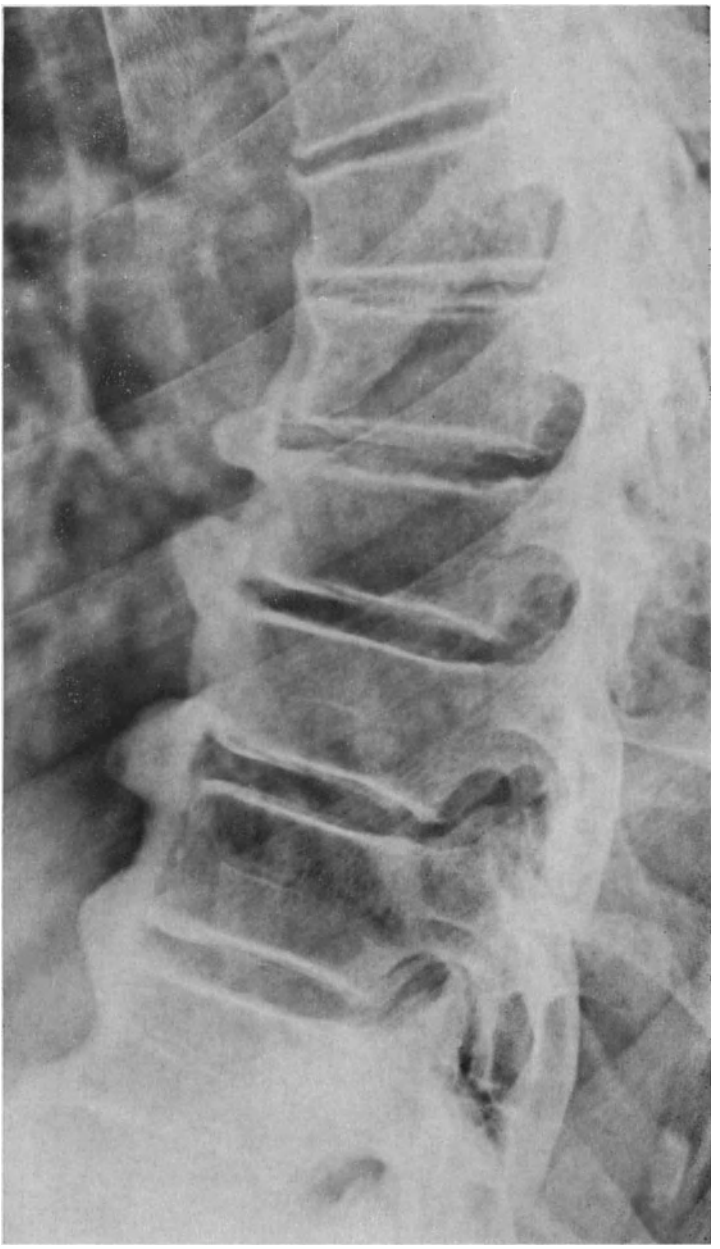
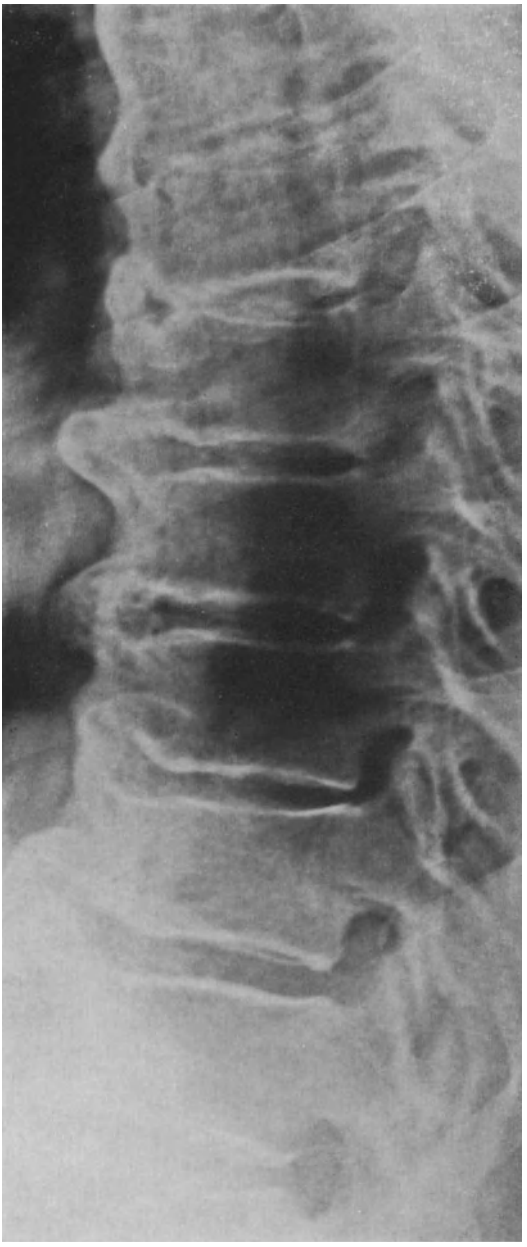


Fig. 6. The anterior longitudinal ligament is calcified caudally to D7 with almost regular thickenings in front of the discs. Flattened vertebral bodies. Persistent vascular canals on the caudal thoracic vertebrae. *Advanced stage of hyperostotic spondylosis*

Fig. 7. The whole anterior longitudinal ligament is calcified. The anterior margins of the vertebral bodies are indistinguishable. Calcified bands, wavy due to their widening in front of the intervertebral discs. *Advanced stage of hyperostotic spondylosis*



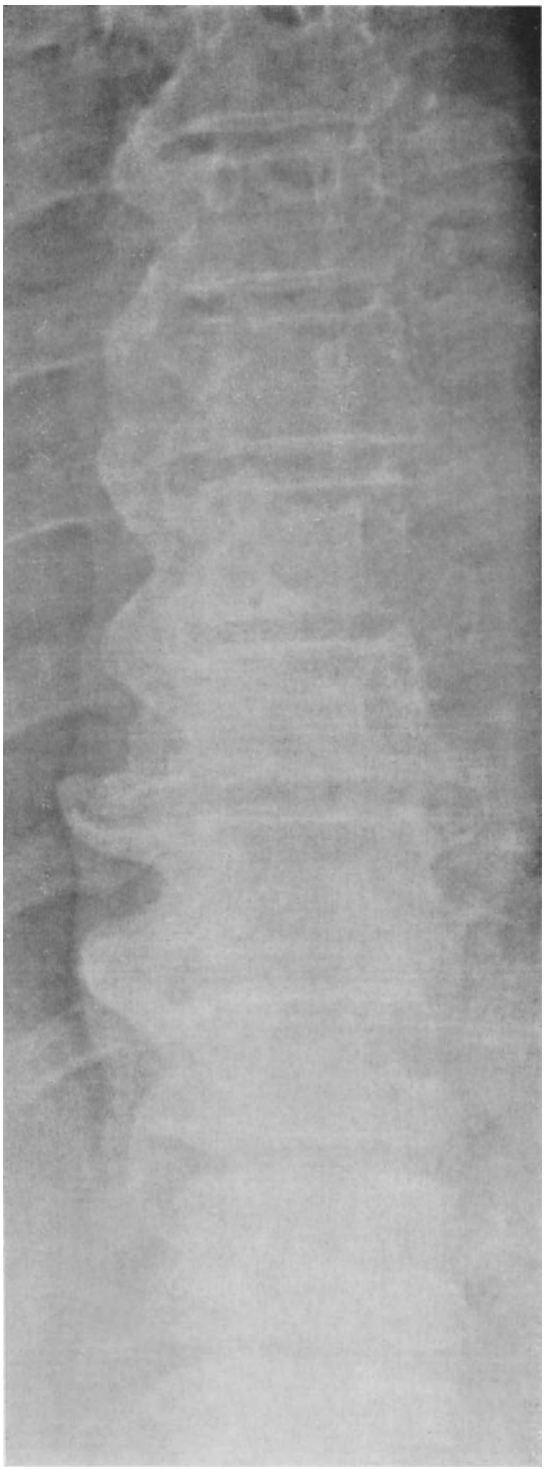
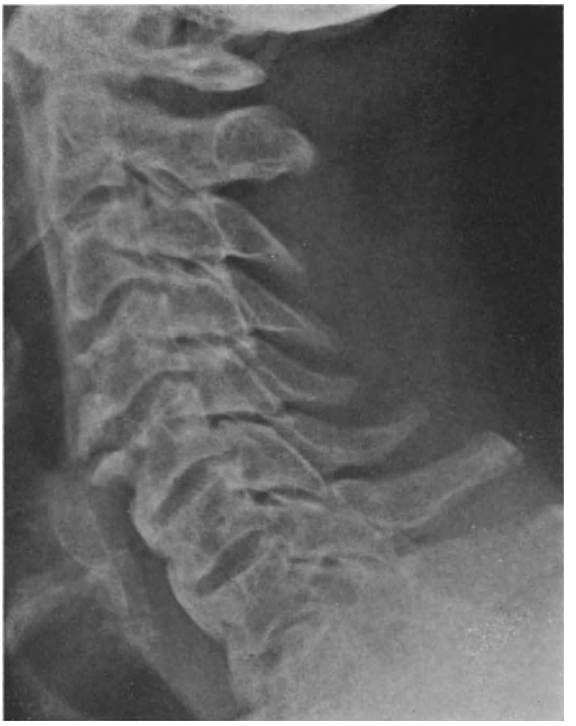


Fig. 8. Sagittal view of the thoracic spine. Ligamentous calcification generally on the right side

Fig. 9**a.** Large anterior spurring at the level of C4–C5. Extensive ossification along the anterior margins of C5–D1. The intervertebral disc spaces are maintained



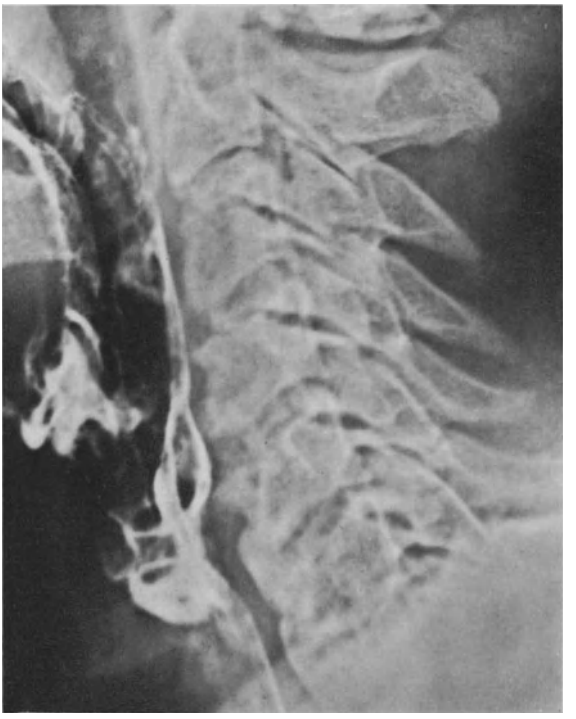


Fig. 9**b.** Swallowing of the contrast material in the hypopharynx shows its dislocation at the level of C4–C5 due to the bony mass. The patient complained of difficulties in swallowing. *Dysphagia caused by hyperostotic spondylosis*

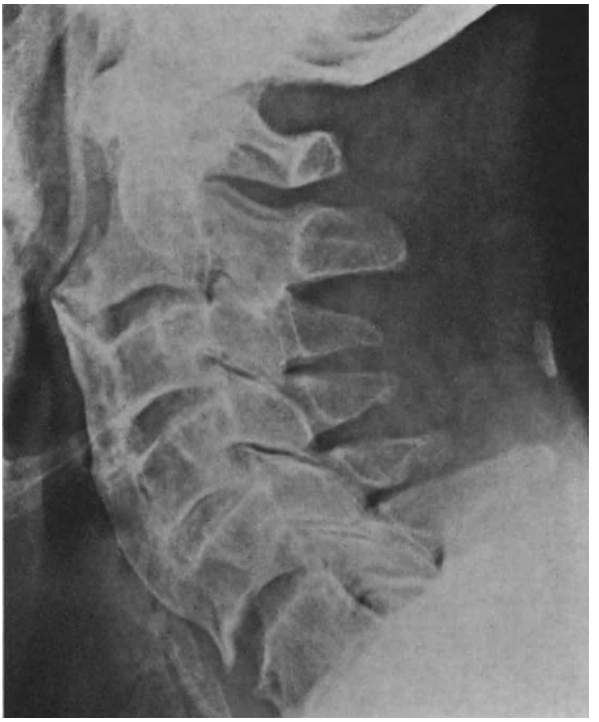
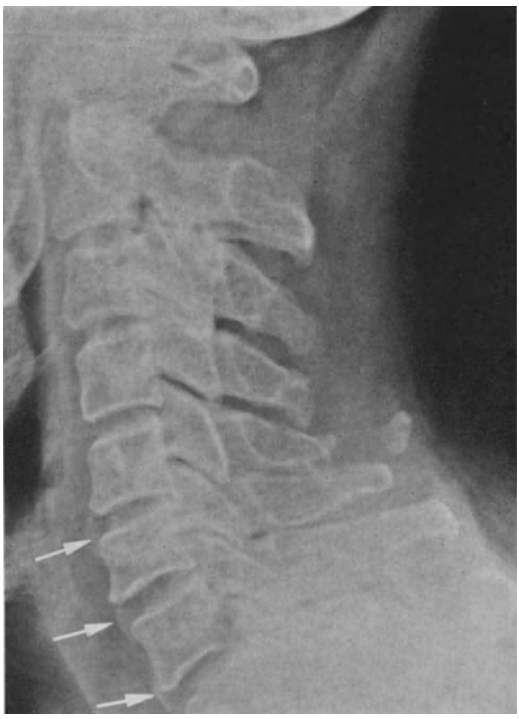


Fig. 10. Continuous thick calcification between C2 and C5. The extensive ossification along the anterior margins of the vertebral bodies resulted in ankylosis. Radiolucency beneath the deposited bone at the margins of C3–C5. *Advanced stage of hyperostotic spondylosis*

Fig. 11. Thin linear calcifications in front of the intervertebral discs between C5–C6 and C6–C7. The anterior longitudinal ligament is also calcified at about the inferior aspect of C7. The height of the intervertebral space is maintained. *Initial form of hyperostotic spondylosis.* Circumscribed calcification of the nuchal ligament at the level of C5



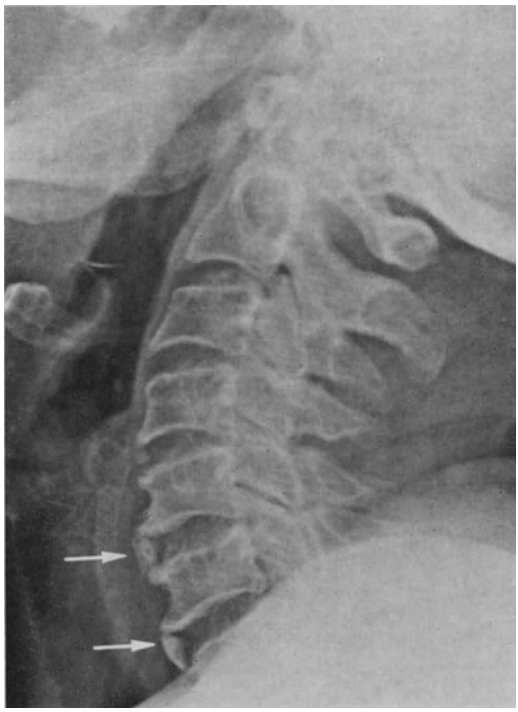


Fig. 12. Elongated and thickened margins of C5 and C6 vertebral bodies. Shapeless, thick calcification attached to the margins of the vertebrae in front of the intervertebral discs between C5–C6 and C6–C7. *Initial form of hyperostotic spondylosis*

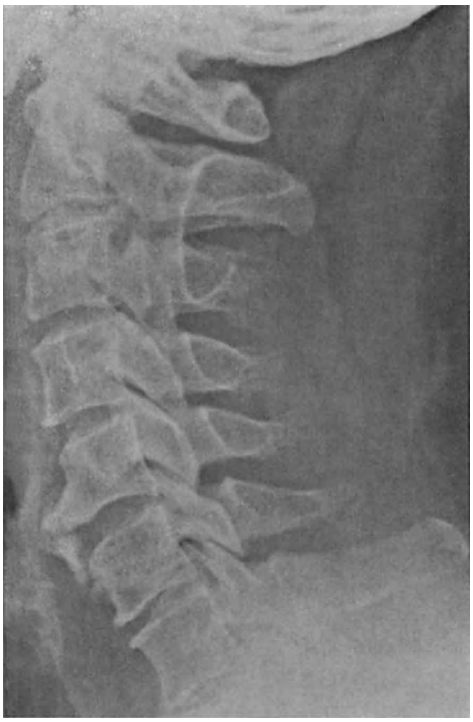


Fig. 13**a.** Large anterior spur on the lower anterior aspect of C5. Underneath, in front of the vertebral disc, massive calcification. Smaller outgrowth on the anterior aspect of C6, and on the margins of C4, C6, and C7

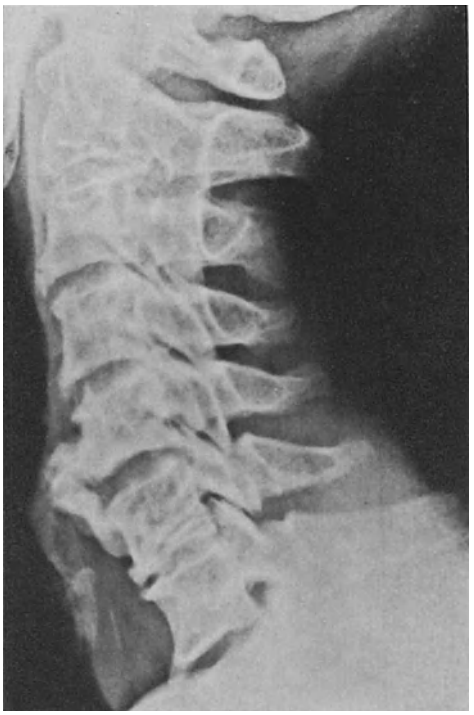
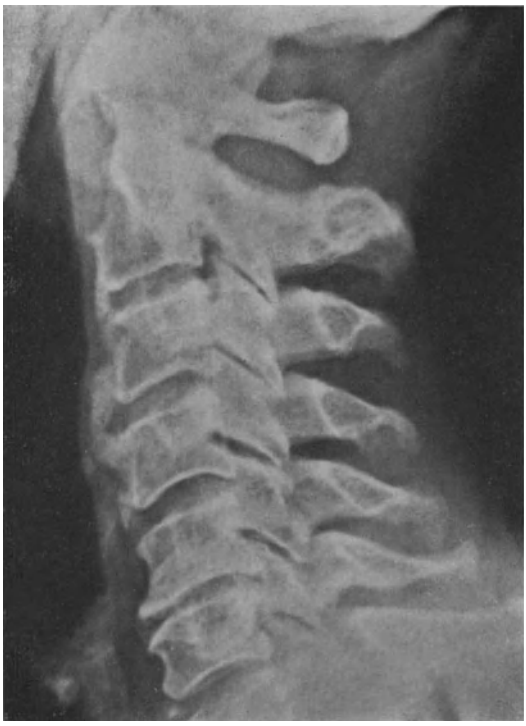


Fig. 13**b.** Two years later, progression of the process. Thick osseous bridge between C5 and C6. Under the elongated anterior margin of C3, a well-defined long triangular outgrowth is visible. The margins of all the other vertebrae are also thickened when compared to the previous x-ray picture. The height of the discs is relatively maintained. *Hyperostotic spondylosis on the cervical spine*

Fig. 14. *Rare form of hyperostotic spondylosis*. The upper cervical spine is affected. Thick calcified band in front of C2–C4. Calcification of the ligament also on the inferior edge of C4. Anterior spur on the neighboring edges of C5 and of C6. Between these vertebral bodies the disc was flattened, indicating that hyperostotic spondylosis was associated with simple spondylosis. Calcification at the attachment site of the nuchal ligament behind the spinous process of C7



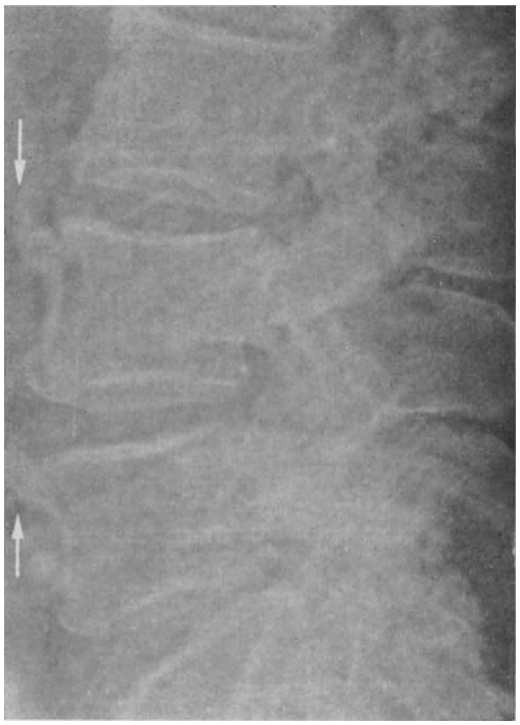


Fig. 15. Detail of the lateral aspect of the lumbar spine. "Candle-flame"-like osteophytes extending superiorly from the anterior–superior edges of L4–L5. *Initial stage of hyperostotic spondylosis in the lumbar spine*

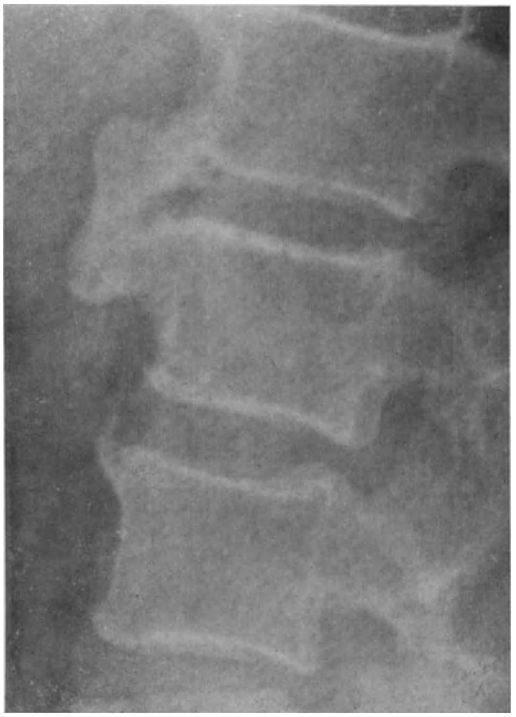
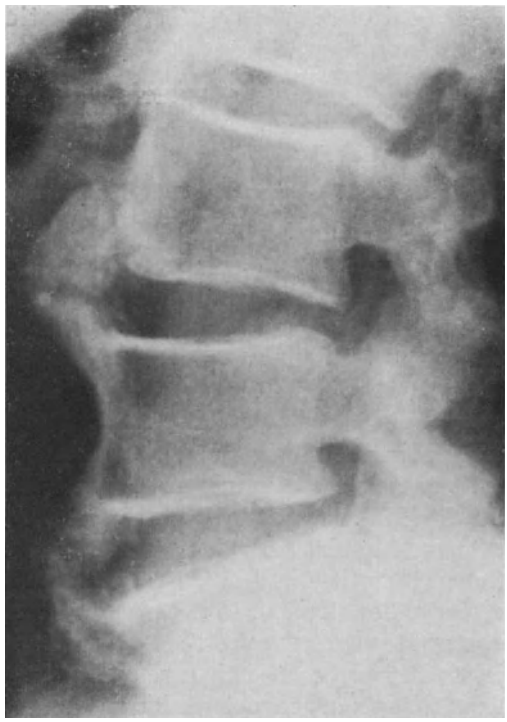


Fig. 16. Detail of the lateral view of the lumbar spine. Adjacent osteophytes fuse with each other, a large irregular osseous bridge between L1 and L2. Calcification extended to the anterior surfaces of the vertebral bodies. Ligamentous calcification on the anterior superior margins of L3 and L4. *Hyperostotic spondylosis in the lumbar spine*

Fig. 17. Irregular, extensive new bone formation at the lumbar level. *Advanced stage of hyperostotic spondylosis of the lumbar spine*



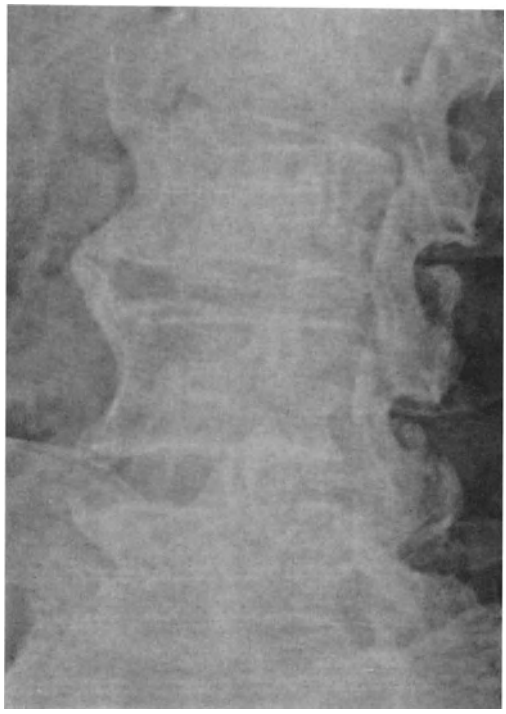


Fig. 18. Picture taken by Dittmar's technique. Continuous ligament calcification along most of the lumbar spine. Unaffected small joints

Differential diagnosis of hyperostotic spondylosis

1. Hyperostosis associated with gross changes of the spine (e.g., kyphoscoliosis, and posttraumatic conditions) is excluded from this group.

2. Hyperostotic spondylosis is similar to spondylosis deformans, but the two can definitely be distinguished, as for example, Resnick and Niwayama's newest (1976) radiographic and pathologic studies have shown. Simple spondylosis due to degeneration of the intervertebral disc is not, or only extremely rarely, associated with continuous ligamentous calcification and then only in a late stage, when several discs are considerably flattened. In hyperostotic spondylosis the height of the discs is maintained; a "flowing" ossification is visible corresponding to the state of the anterior ligament, which covers broadly the anterior surface of the vertebral bodies already at the initial stage. Based on radiological findings, clear-cut forms can be differentiated, but both may occur together in the elderly.

3. Most authors stress the importance of differentiating hyperostotic spondylosis from *ankylosing spondylitis* (Bechterew's disease). These two diseases are distinguished on the basis of their characteristic clinical and radiological features (Lackner 1958, Pazredka and Streda 1975). Hyperostotic spondylosis is a disease of the elderly, without severe clinical symptoms or signs of inflammation. The site and form of ligament calcification also differ (less regular than in Bechterew's disease). The small joints are free, and the intervertebral discs are not calcified. In Bechterew's disease, the vertebrae are often cubical in shape, in contrast to the flat vertebrae in hyperostotic spondylosis. Certain changes in the sacroiliac joints may also occur in hyperostotic spondylosis, but these can be definitely differentiated from changes in spondylarthritis ankylopoietica by careful analysis of the roentgenograms.

4. Calcification of the ligaments in *psoriatic spondylarthritis* resembles Bechterew's disease (Bywaters and Dixon 1965, Kálózdi et al. 1974, Killebrew et al. 1973, Koó et al. 1977, Sundaram and Patton 1975, Theiss et al. 1969). Beardwell (1969) found a similar picture associated with keratosis punctata plantaris (tylosis).

5. Reiter's syndrome (conjunctivitis, urethritis, arthritis) is often accompanied by ligamentous calcification (Bálint 1966, Cliff 1971, Sundaram and Patton 1975).

6. Spinal hyperostosis and ligamentous calcification have been described in hypoparathyroidism (Adams and Davies 1977, Bart and Forgács 1975), in Hodgkin's disease (Duncan 1973) and in fluorosis (Singh et al. 1962).

Cranial hyperostosis

Several authors have reported a high incidence of hyperostosis frontalis interna in diabetics (Table 7). Besides the tabulated data, Boulet and Mirouze (1954), Martin (1969), and Messerer and Franke (1973) have performed studies on the subject. Lengyel and Horváth (1971) examined the gerontological aspect of hyperostosis frontalis and found that 5.8% of their patients had diabetes.

Cranial hyperostosis has four types of radiological manifestations:

1. Hyperostosis frontalis interna: this is the most frequent and best known form.
2. Hyperostosis fronto-parietalis.
3. Nebula frontalis.
4. Hyperostosis calvaria diffusa.

Table 7

Incidence of hyperostosis frontalis interna in diabetes mellitus

Authors		Males			Females		
		Diabetics	Hyperostosis frontalis interna		Diabetics	Hyperostosis frontalis interna	
Schoen et al.	1969	109	9	(8%)	134	45	(34%)
Andersch et al.	1970	200	29	(15%)	200	100	(50%)
Streda et al.	1971				61	35	(57%)
Own material		240	13	(5%)	260	73	(28%)

According to our observations, frontal hyperostosis associated with diffuse thickening of the vault of the skull occurs only in diabetics (Fig. 19). On the radiographs of the skull besides hyperostosis, widened paranasal sinuses were often visible (Fig. 20).

Cranial hyperostosis is more frequent in females, while the incidence of hyperostotic spondylosis is higher in males, but in our experience both disorders may arise simultaneously. Analyzing the relationship between the two abnormalities (Table 8), we found the incidence of frontal hyperostosis to be four times higher in diabetics with hyperostotic spondylosis than in the group without spinal disease. The difference between the two groups was statistically significant ($P < 0.001$).

Frontal hyperostosis is a cardinal symptom of the Morgagni-Stewart-Morel syndrome. The existence of this syndrome is a matter of dispute, and is as yet unsettled (Marlet 1974). Accepting the existence of this syndrome, we can conclude on the basis of our studies that hyperostotic spondylosis also belongs to this group of symptoms. We examined approximately 100 patients with Morgagni syndrome (Forgács and Rosinger 1973). The incidence of Morgagni syndrome was low in males, hyperostosis of the spine was observed in all affected males and in about half of the female patients.

Table 8

The relationship between hyperostosis frontalis interna and hyperostotic spondylosis

	Diabetics without hyperostotic spondylosis			Diabetics with hyperostotic spondylosis			Total		
	No. of cases	Hyperostosis frontalis interna		No. of cases	Hyperostosis frontalis interna		Diabetics	Hyperostosis frontalis interna	
Males	176	4	(2.3%)	64	9	(14.1%)	240	13	
Females	206	36	(17.5%)	54	37	(68.5%)	269	73	
Total	382	40	(10.4%)	118	46	(39%)	500	86	(17.2%)

Other manifestations of hyperostosis

In the large number of patients under our care we observed that hyperostotic spondylosis is often accompanied by hyperostotic changes of various localization. Literary data, although detailed studies were not performed, indicate that in diabetes mellitus and/or in hyperostotic spondylosis certain hyperostotic changes occur frequently.

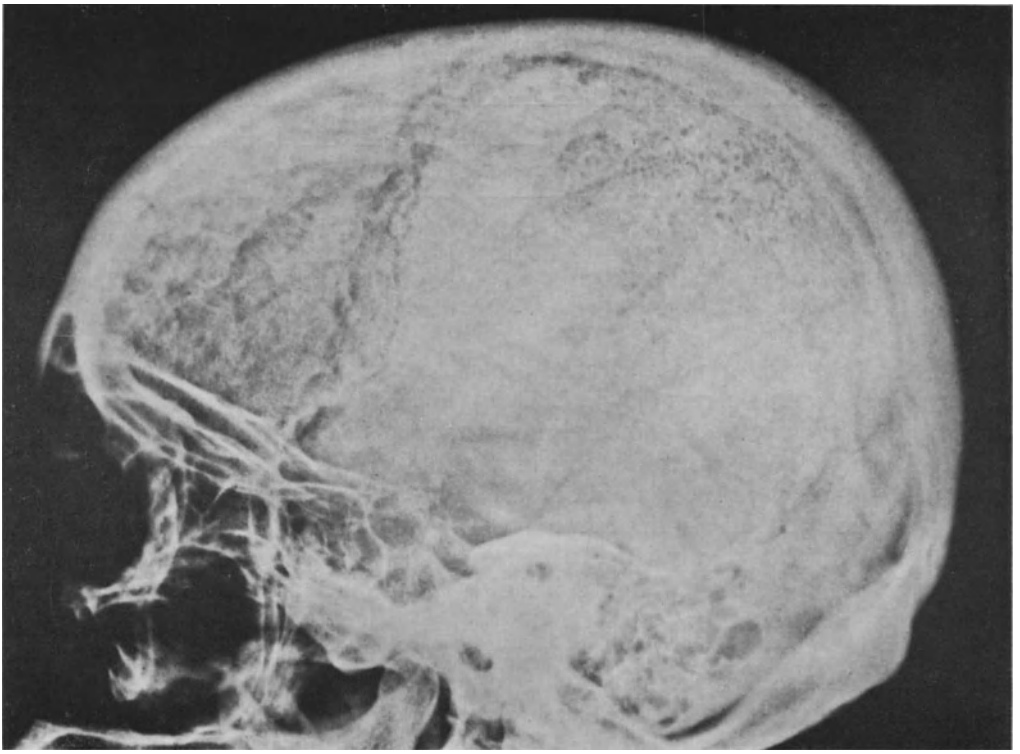
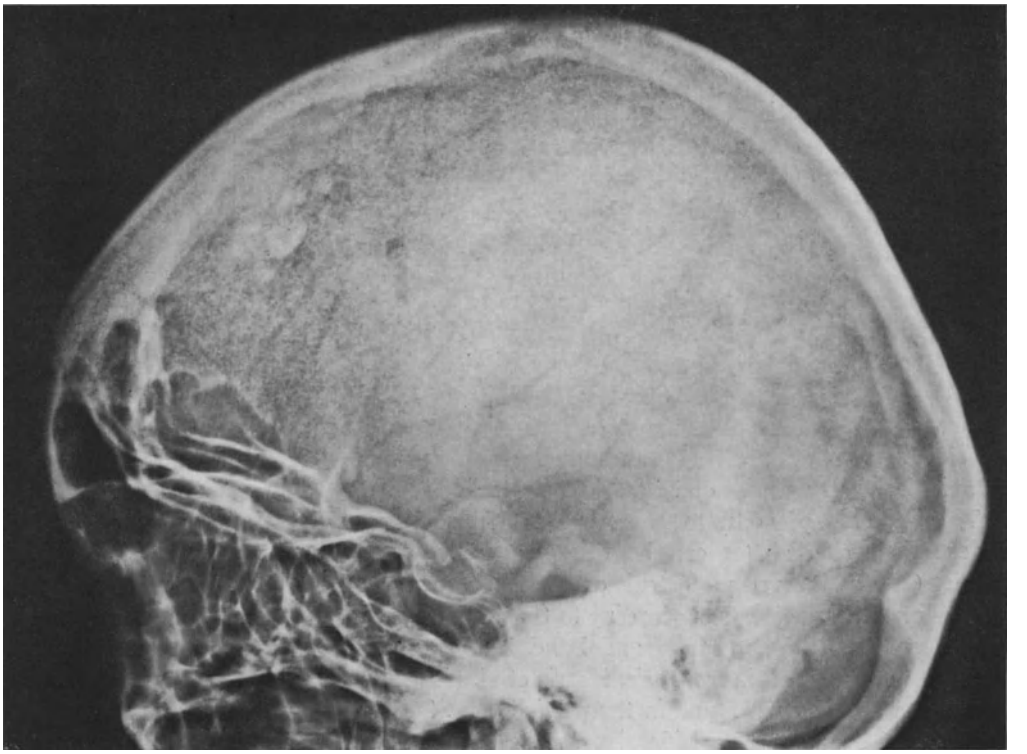


Fig. 19. Diffuse, irregular thickening of the vault of the skull with internal frontal hyperostosis. *Hyperostosis calvaria diffusa*



Aig. 20. Partly continuous and partly nodular calcified densities on the inner table of the frontal bone. Freas of higher density on the parietal bones. Extensive, pneumatized sinuses. The body of the sphenoid bone is also pneumatized

First, we shall discuss observations related to diabetes. Already in 1954, Boulet et al. reported a high incidence of exostoses of the feet and thickening of the sternocostal joints in diabetics. Bossa et al. (1970) observed periarticular calcification, particularly on the feet, but also in the soft tissues of the knee, shoulder and thigh. Andersch and Arzberger (1971) described the calcification of the long plantar ligament in elderly patients with diabetes. Pappalardo et al. (1975) found osteophytosis in the calcaneum of 80% of his diabetic patients and, in one-third of these patients hyperostosis was also confirmed in the spine. Oldberg (1978) found Heberden's nodes in 59 cases of 100 postmenopausal diabetic women. Among 62 women with hyperostosis frontalis interna, 57 had Heberden's nodes. Diabetes mellitus seems to foster the appearance of sternoclavicular osteoarthritis (Silberberg et al. 1960, 1976). Berker and Dinitz (1974), Bianchi and Ricci (1967), Mirouze (1965) and Waine et al. (1961) reported data supporting the relationship between degenerative articular changes and diabetes. According to Streda and Hajkova (1973), diabetes in itself does not predispose to arthrosis associated with osteophyte formation, nevertheless, these changes often develop in cases when diabetes and hyperostotic spondylosis occur together or in the case of spinal defects without diabetes.

This latter study leads us to the other side of the problem: what other hyperostotic changes independent of diabetes can be observed in hyperostotic spondylosis? Forestier and Lagier (1971) observed periostosis on the flat bones, particularly on the pelvis, and osteophytes on the large joints. According to their studies, which have since been complemented by newer observations (Lagier and Band 1978), these new bone formations differ from osteophyte formation in arthrosis. Harris et al. (1974) also reported new bone formations which were most often found in the pelvic bones. Sutro et al. (1956) observed generalized tendon and ligamentous calcification on the spine and extremities. Dihlmann and Freund (1968) studied sacroiliac defects in 50 cases of hyperostotic spondylosis. Calcification of the articular ligaments was observed in 21 cases. Dihlmann used the term "osteoplastic diathesis" for these cases. Fischer and Stecker (1972) observed the hyperostosis of the costal articular heads, and Laczay (1973) observed the thickening of the costovertebral joints.

Although no uniform concept has been accepted as yet about etiology, several authors observed the simultaneous manifestation of paraarticular calcifications of various localizations and types (Bobkó et al. 1966, Dihlmann 1967*a*, Lagier and Band 1978, Lazarus and Galloway 1973, Sutro et al. 1956, Szántó 1975).

Resnick et al. (1975) performed detailed examinations on the whole skeletal system. Subjected to the examination were 21 patients with Forestier's disease. Hyperostosis was detected in the pelvis of all patients; further, in the extremities on the ulnar olecranon (in 12 cases), at the insertion of the patellar ligament (in 6 cases), on the calcaneus (in 16 cases), and on the dorsal surface of the foot (in 15 cases). These lesions together with other types of calcification are considered to be extraspinal manifestations of Forestier's disease, and the designation diffuse idiopathic skeletal hyperostosis (DISH) is suggested for them.

In our patients, we also observed other types of hyperostosis associated with hyperostotic spondylosis (Forgács 1972, 1973, 1974).

Both in the review of the literature and in our own observations, the various forms and variously localized hyperostotic changes often seem to occur simultaneously. In these cases there seems to be a predisposition to diffuse hyperostosis. In this respect, hyperostotic spondylosis is not an independent disease, but a partial phenomenon of this process. Generally, calcification of the ligaments and tendons is observed, being most striking at the sites of insertion. These defects often develop in the elderly and can be well differentiated from

osteoarthritic calcifications. The clinical picture is helpful in differential diagnosis: this type of calcification is generally painless.

Almost all forms of hyperostotic changes frequently occur isolated in single ligaments adjacent to some large joint. Due to mechanical and local factors, they are particularly frequent in the lower extremities. These abnormalities are not related to metabolic disorders. Nevertheless, a metabolic disorder may be suspected in the background of diffuse hyperostosis, as the majority of these patients also suffer from diabetes.

The radiological forms of appearance of hyperostotic defects are as follows.

Cervical hyperostosis

Calcification of the nuchal ligament is a frequent radiological finding (Figs. 11, 12 and 14). The calcification may be circumscribed, generally situated at the caudal section of the neck, or the ligamentous insertion itself is calcified. In the latter case thickening and spur formation of the external occipital protuberance are visible.

Calcification of the *stylohyoid ligament* results in the styloid process syndrome in some cases.

The radiographic signs and clinical importance of the calcification of the *posterior longitudinal ligament* have only recently been discussed (Kataoka 1977, Op den Orth 1975). For some unknown reason, this type of abnormality occurs more frequently in Japan. Roentgenograms disclose dense ossification posterior to the vertebral bodies, and symptoms are most often observed when the ossification occupies more than 60% of the sagittal diameter of the cervical canal (Ono et al. 1977). In serious cases, surgical intervention (posterior decompression) is suggested. Several of the reported patients had diabetes (Hiramatsu and Nobechi 1971).

Arlet et al. (1976) observed concomitant occurrence of posterior longitudinal ligamentous calcification and Forestier's disease and, as did the aforementioned authors, they also found neurological symptoms.

Hyperostosis in the thorax

Widening of the sternocostal joints and calcification of the costal cartilage are characteristic. These are particularly well visible on the first costal cartilage. Calcification may also appear on the sternum (Fig. 21).

Hyperostosis of the pelvis

Changes occurring in the sacroiliac joint are of great importance, as these may be mistaken for sacroilitis in ankylosing spondylitis (Dihlmann 1967*b*). The various degrees of calcification of the capsular ligament result in pseudoankylosis of the joint (Figs. 22 and 23). Paraarticular osteophyte formation along the inferior portion of the sacroiliac joints is often visible (Fig. 24). The changes are frequently unilateral or asymmetric.

Irregularly shaped calcifications due to the ossification of tendon insertions are often visible on the *lateral margin of the ileum*, particularly adjacent to the anterior iliac crest and above the acetabulum (paraacetabular osteophyte) (Figs. 22 and 24). Calcification of the *iliolumbar ligament* is also frequent (Figs. 22 and 23).

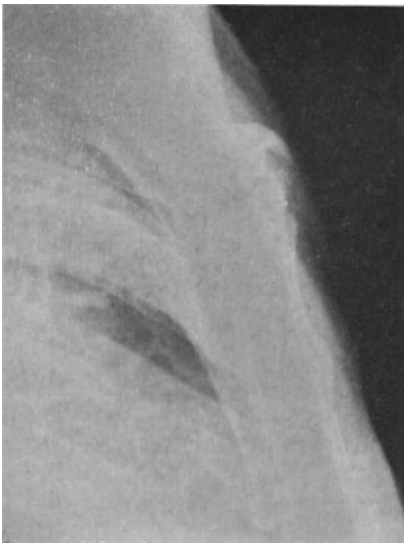


Fig. 21. Lateral view of the sternum. Beak-shaped calcification situated on the manubrium at the sternal angle

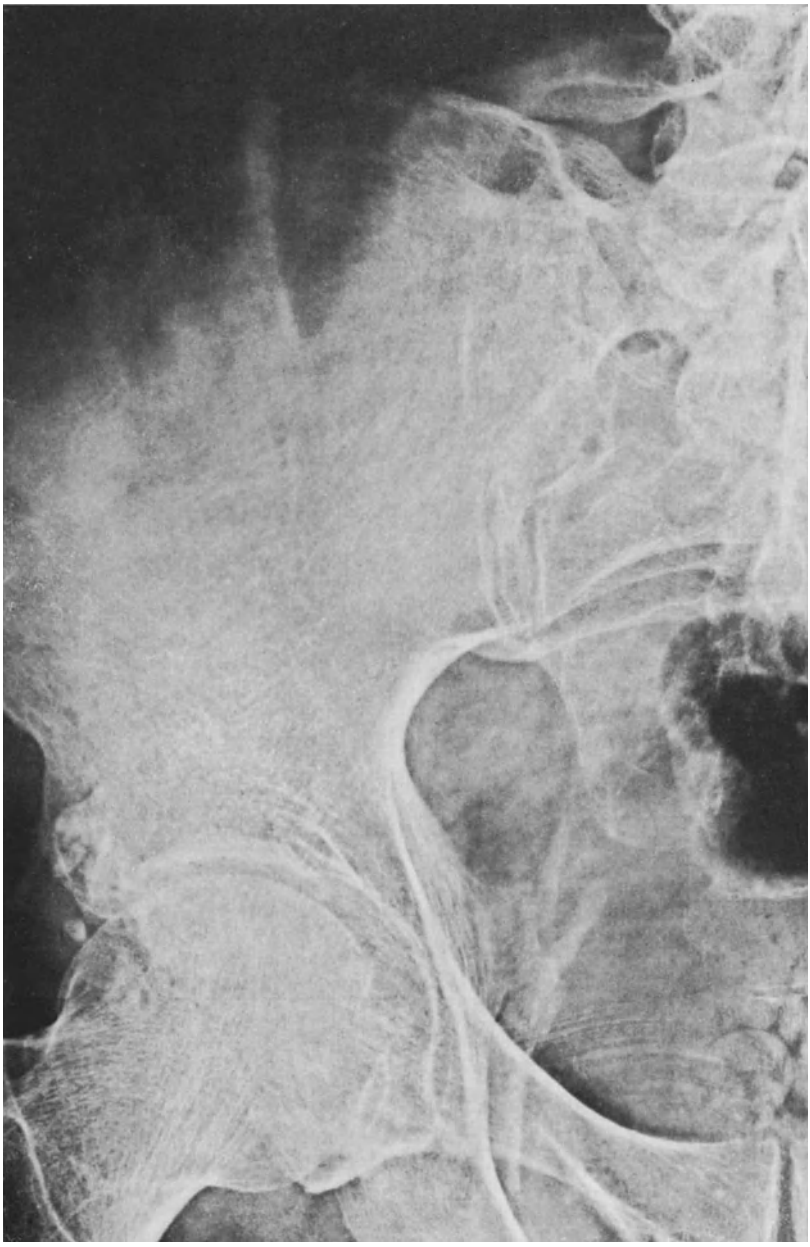


Fig. 22. Pelvis of a patient with hyperostotic spondylosis. The iliolumbar ligament is calcified. The sacroiliac space is hardly visible; the calcified sacroiliac ligaments form an osseous bridge at the caudal part of the joint. Large paraacetabular osteophyte and calcification in the caudal recesses of the hip joint capsule. Calcification of the sacrotuberous ligament appears extending superiorly from the ischium as a calcified band. Ischial spine thickened due to calcification of the ligamentous attachment; rare forms of ligamentous calcification

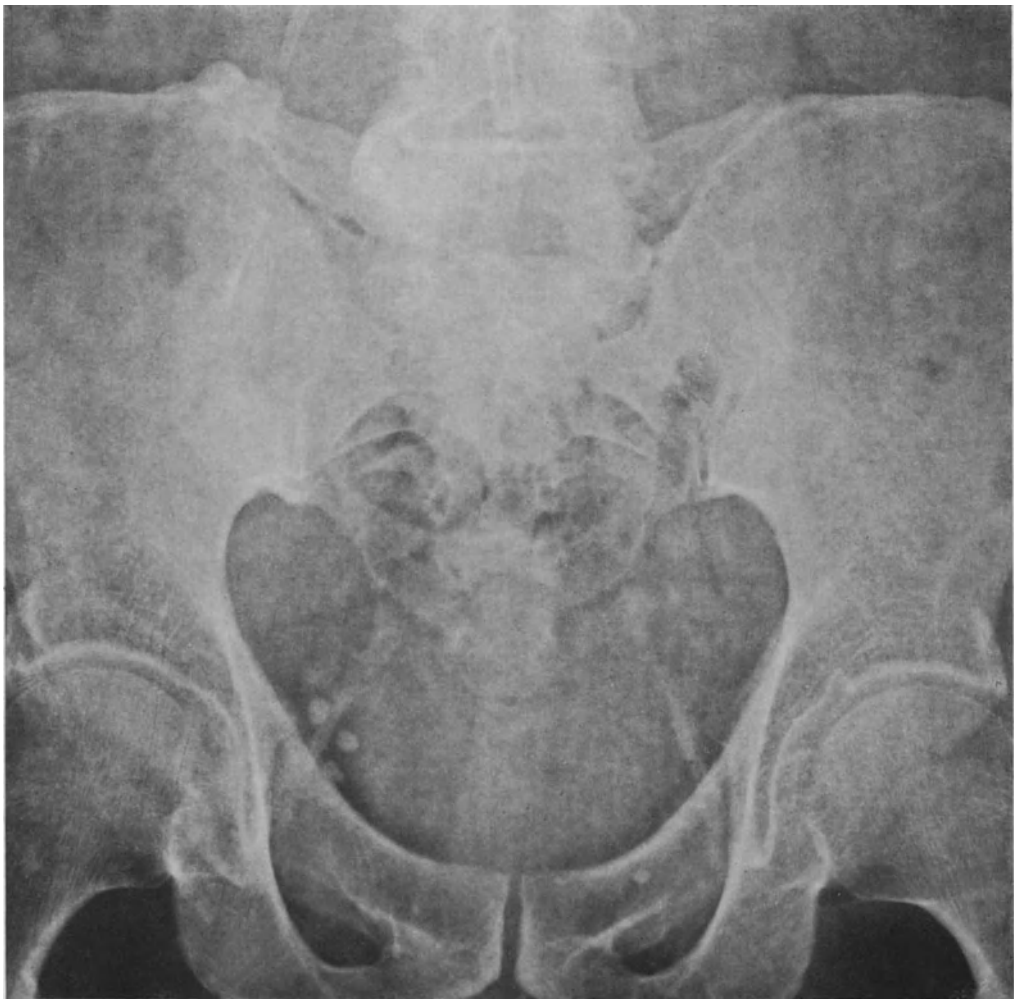


Fig. 23. Ossified iliolumbar ligaments on both sides. Calcification of the sacroiliac ligaments. Symmetrically calcified sacrotuberous ligaments

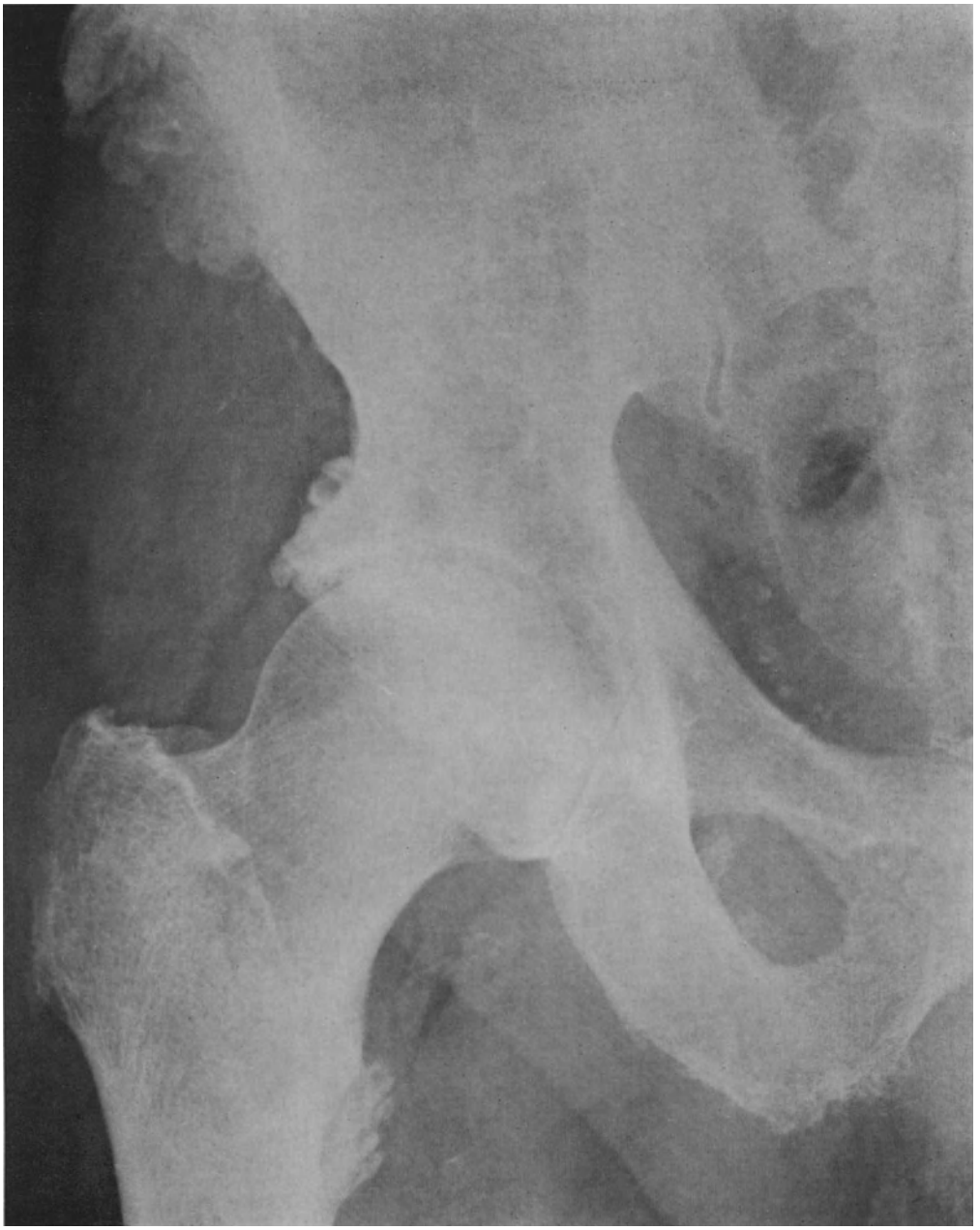


Fig. 24. Irregular outgrowth of bone extending from the iliac crest and the lateral margins of the ilium. Paraarticular osteophyte along the inferior portion of the sacroiliac joint. The sacroiliac space has almost disappeared

In our material calcification of the *superior pubic ligament* resulting in an osseous bridge across the superior margin of the symphysis pubis occurred only in 4 cases (Fig. 25).

Calcification of the *sacrotuberous ligament* is also very rare (Figs. 22, 23 and 24). The latter two forms of ligamentous calcification have been observed exclusively in diabetics.

Osseous outgrowths often appear on the *trochanters* at the site of the adhesion of muscles (Figs. 24 and 26).

Hyperostosis of the extremities

On the extremities, hyperostosis appears in the form of paraarticular calcification and periosteal appositions.

Paraarticular calcifications are the result of calcium deposition in the capsular ligaments or of the adjacent insertions. Calcification of the patellar ligament (Fig. 27) and the Achilles tendon (Figs. 28 and 29) are typical forms. Similar changes occur around the elbow joint (Fig. 30), the shoulder joint (Fig. 31), and on the plantar surface of the calcaneus (Figs. 27 and 29). These changes are often encountered in routine radiographic practice. The concurrent manifestation of several forms of hyperostosis in one patient is characteristic of diabetes (Figs. 24–30).

This holds also true for *periosteal appositions*. Appositions appear on the metacarpal bones of the hand and foot and on the diaphyses of the phalanges. These are finer on the hand (Fig. 32) and cruder on the foot bones, and sometimes the bone is thickened (Fig. 33). The unguicular processes are thickened, and exostosis-like signs appear on the distal phalanges (Fig. 34).

Its radiographic appearance distinguishes it from osteoarthrosis. The articular surfaces are intact, subchondral cysts do not occur, and arthrotic pains are absent. Similarly to hyperostotic spondylosis, hyperostosis of the pelvis and extremities is often detected only when radiography is carried out for some other reason; for example in trauma. The disease is often accompanied by real osteoarthrosis which has an extremely varied radiographic picture.

Relationship between hyperostosis and metabolism

In the previous chapter we discussed in detail that the incidence of hyperostotic spondylosis – often in association with other forms of hyperostosis – is high in diabetics. The next question to be discussed is to which types of diabetes are these changes associated.

The data from the literature are extremely contradictory. Andersch et al. (1969, 1970) observed that, in males, hyperostosis is associated with the labile and, in females, with the stable form of diabetes. Several authors agree that the degree of severity, or the duration, of diabetes does not influence the incidence of hyperostosis, moreover, hyperostosis has often been observed to accompany mild diabetes.

The incidence of hyperostotic spondylosis was compared in insulin-dependent and non-insulin-dependent cases. Patients with an unstable metabolism belonged to the insulin-dependent group, while those with a stable metabolism belonged to the latter.

Table 9

The incidence of hyperostotic spondylosis according to the type of diabetes

Age (years)	Type A		Type B	
	No. of cases	Hyperostotic spondylosis	No. of cases	Hyperostotic spondylosis
40–49	24		39	7
50–59	69	6	133	36
60–69	46	6	137	38
<70	9	3	43	22
Total	148	15 (10.6%)	352	103 (29.3%)

Type A: insulin-dependent diabetes; Type B: non-insulin-dependent diabetes.

Among 118 diabetics with hyperostotic spondylosis, only 15 needed chronic insulin treatment. Detailed analyses revealed that in patients who received oral treatment or those who had to control a diet alone (Type B), the incidence of hyperostotic spondylosis was almost three times higher than in the group treated with insulin (Table 9). The difference between the two groups was statistically highly significant ($P < 0.001$).

Pyknic and/or acromegaloid features were characteristic properties of diabetics with associated hyperostosis. Adult or old-age onset of diabetes, and a lack of disposition to ketoacidosis, were also characteristic. However, heart complaints and hypertension were frequently found in these patients, and were often more difficult to manage than the mild diabetes itself. Peripheral macroangiopathy was also found in a considerable number of patients. Hypercholesterinemia, hyperlipidemia, and hyperuricemia were frequent laboratory findings. The values of the calcium and phosphorus metabolism were normal.

We have also studied the relationship between hyperostotic spondylosis and the duration of diabetes. Of the 103 diabetics treated with oral drugs or diet, bone abnormalities were revealed in 38 newly diagnosed patients. Moreover, bone hyperostosis was often detected prior to the diagnosis of diabetes. Analysis of the control group also suggested this possibility, since in 21 cases the radiographic findings indicated diabetes, and this diagnosis was in fact confirmed later.

However, in the insulin-treated group hyperostosis was always confirmed only many years after the onset of diabetes (over 12 years, on the average). No newly diagnosed cases of diabetes occurred in the group of patients suffering from hyperostotic spondylosis.

Pathogenesis of hyperostosis

The role of growth hormone

In Ott's opinion, hyperostotic spondylosis develops from persisting fetal connective tissue, which due to mechanical, inflammatory, or hormonal effects transforms into osseous tissue, viz., a pathological ossification takes place. The majority of authors studying the relationship between hyperostotic spondylosis and diabetes emphasize the role of growth hormone overproduction (after menopause?). Our observations showing hyperostotic spondylosis

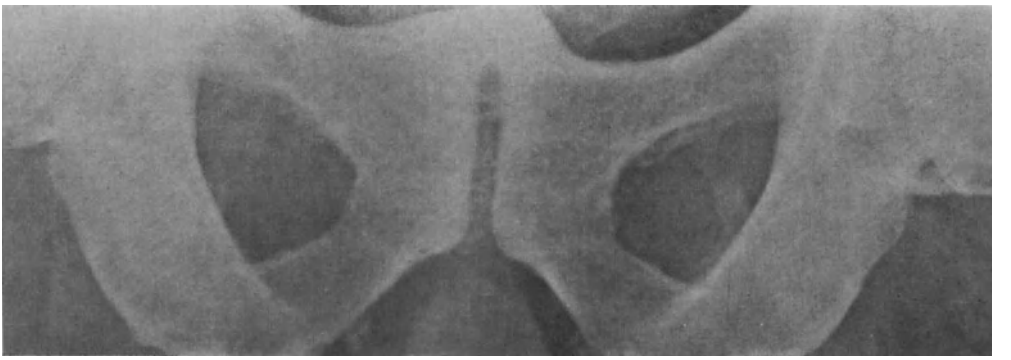


Fig. 25. Ossification of the superior pubic ligament. Calcification at the attachment of the sacrotuberous ligament on the tubercle of the ischium

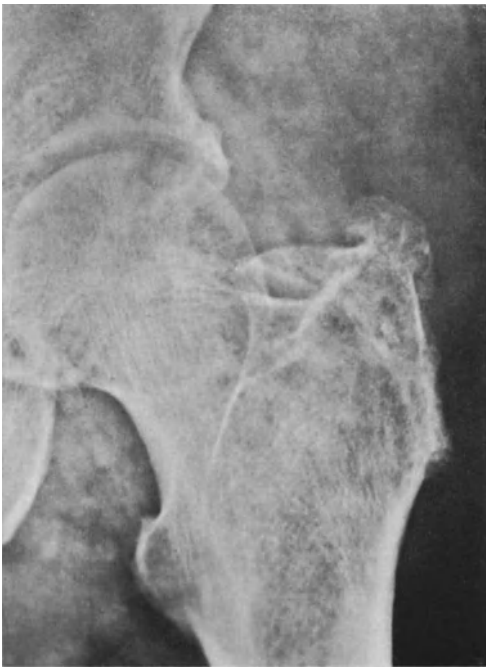


Fig. 26. Club-shaped calcified protuberance on the greater trochanter. Calcification in the wall of the femoral artery

Fig. 27. Calcification of the quadriceps and patellar tendons. Note the prominence of the tibial tuberosity at the ligamentous attachment

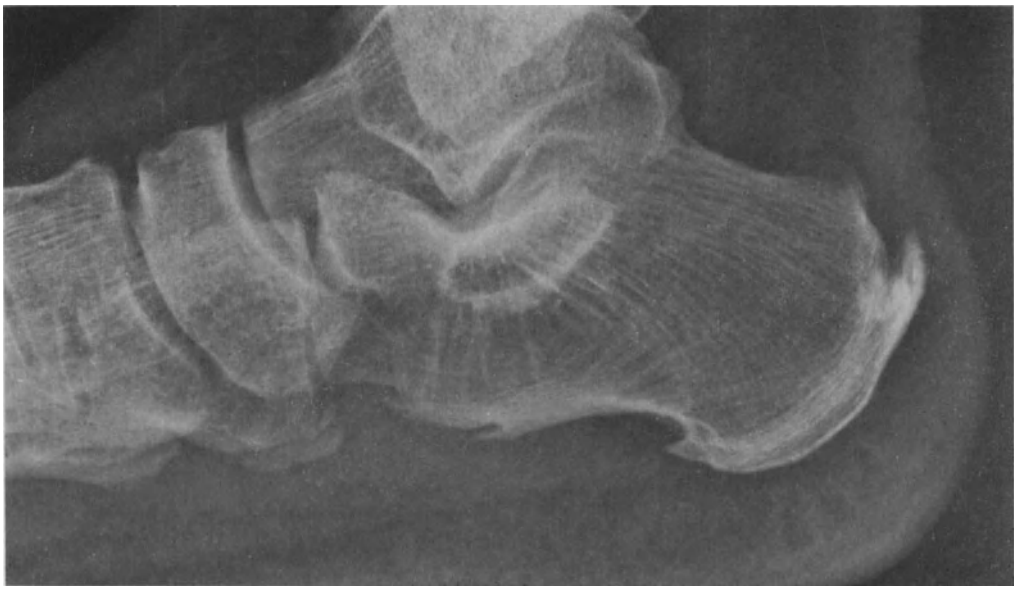


Fig. 28. Calcaneal spurs along the posterior (Achilles tendon attachment) and the inferior surfaces, with ossification adjacent to the cuboid and bones of the forefoot. Calcification of the dorsal pedal artery at the level of the Chopart joint

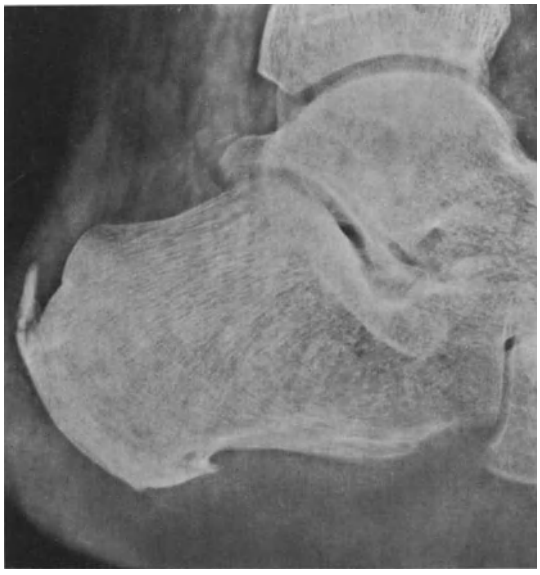


Fig. 29. Lateral view of the heel. Extensive calcification along the posterior surface of the calcaneum. Exostosis-like osteophyte on the plantar surface

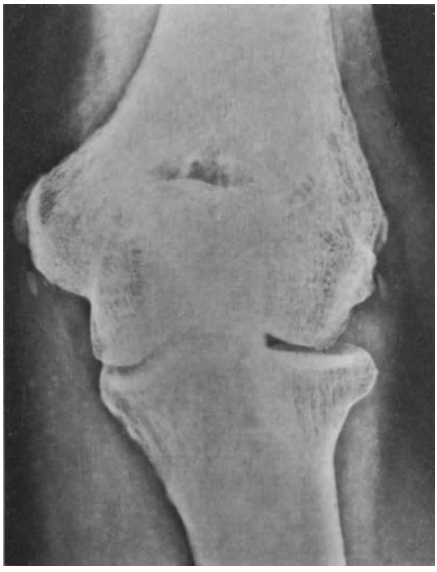


Fig. 30. Elbow. Irregular calcifications adjacent to the thickened epicondyles of the humerus and in the soft tissue

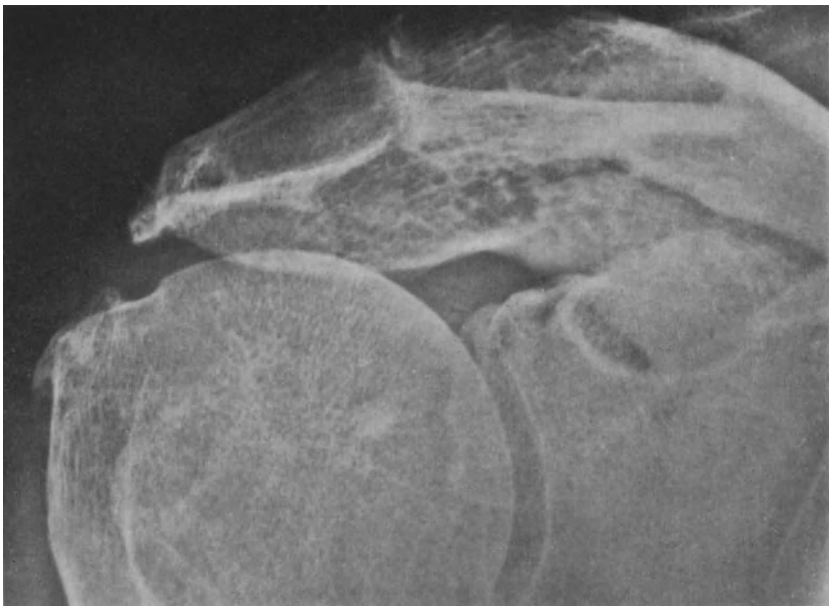


Fig. 31. Prominence and osseous irregularity along the greater tubercle in the shoulder joint

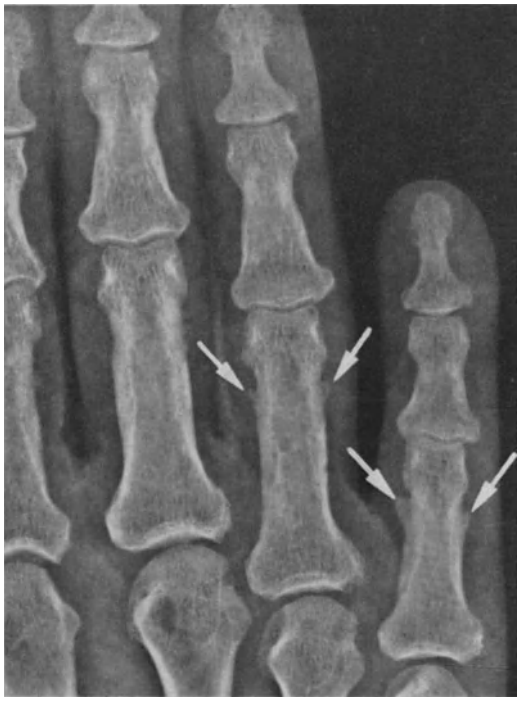
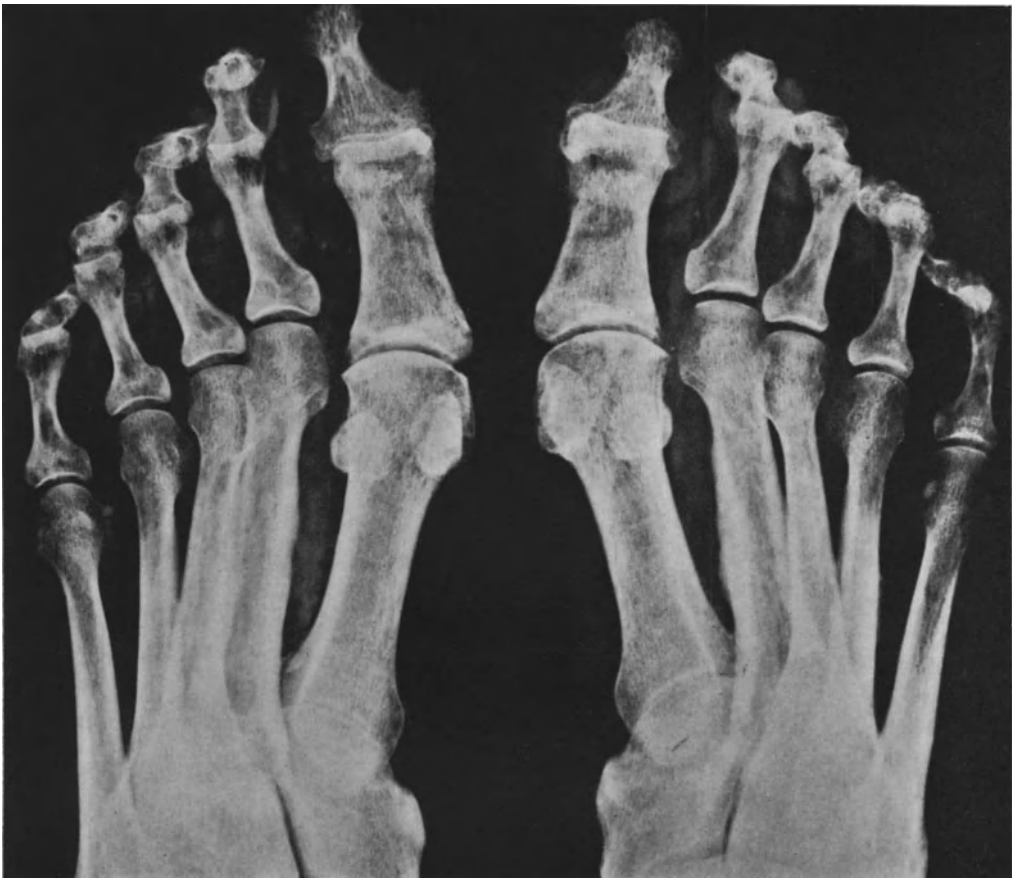
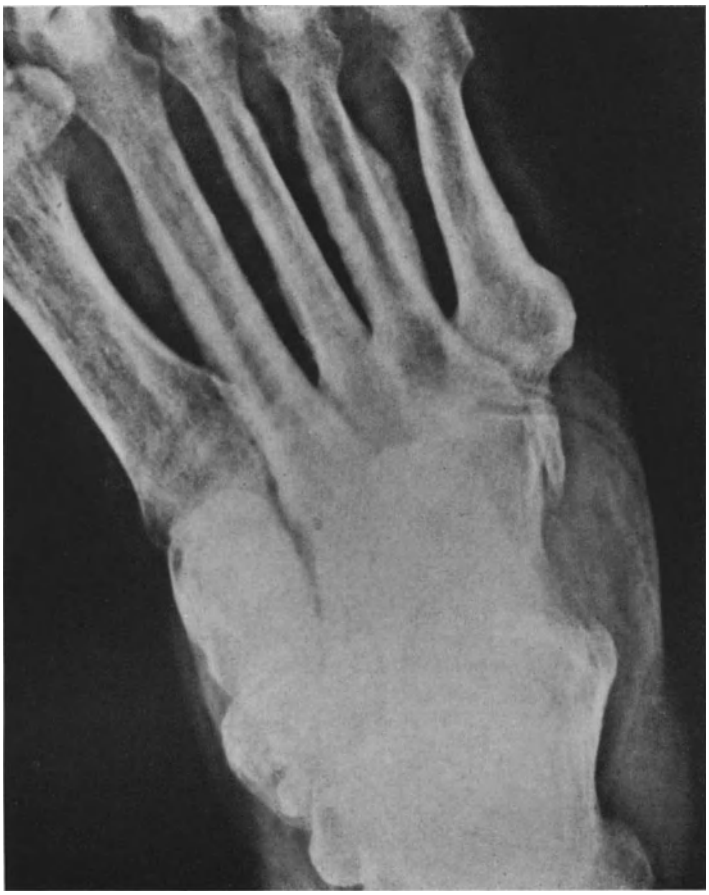


Fig. 32. Peculiar protuberances in the proximal phalanges of the hand



a

Figs. 33**a** and **b.** Comparative pictures of the feet and lateral view of the right foot. Cortical thickenings on the diaphysis of the metatarsals. New bone formation at the lateral margin of the cuboid



b

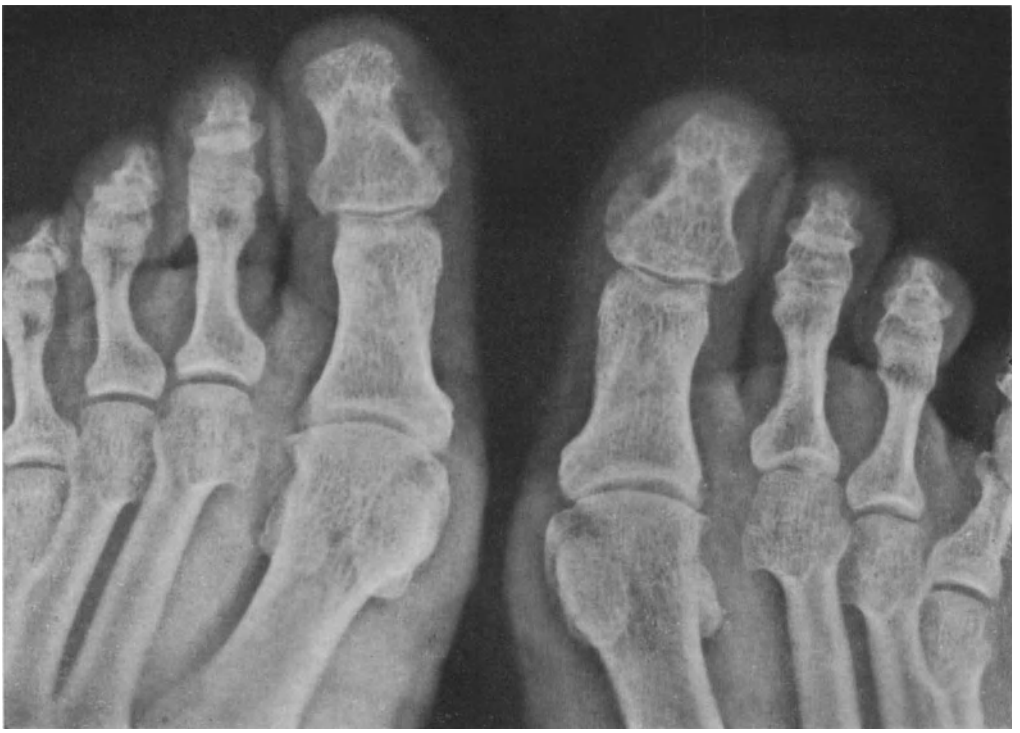


Fig. 34. Symmetric, exostosis-like outgrowth on the terminal phalanges of the big toes

to be part of a diffuse hyperostosis support this concept as the various localizations of hyperostosis prove that a process involving the entire organism is concerned.

The skeletal system of acromegalic patients provides indirect evidence. Recently, many authors have discussed the radiographic features of acromegaly (Anton 1972, Bluestone et al. 1971, Erbe et al. 1975, Garusi 1964, Gonticas et al. 1969, Juliani and Mauri 1962, Julkunen et al. 1966, Lang and Bessler 1961, Silinkova-Malkova and Köbel 1970, Siegelman and Jacobson 1970, Vanderdorp et al. 1967). The radiographic picture of hyperostosis in diabetics described above appears to show many similarities to the radiographic signs described on the skull, spine, pelvis, and extremities of acromegalic patients. In animal experiments, severe early arthrosis was induced by administering somatotrophic hormones (Silberberg and Silberberg 1960).

Generally, spondylosis is explained by some local cause. The degeneration of the intervertebral discs forms the basis of the disease. Fibrotic proliferation of the annulus fibrosus and prolapse of the nucleus pulposus reduce the stability of the spine. The periosteum is elevated due to the increasing fibrotic tissue mass. This means an abnormal stress on the cartilage and ossification sites of the vertebral discs, resulting in cartilaginous or osseous (or both) overgrowth. Histological examinations verified these phenomena in hyperostotic spondylosis (Forestier and Lagier 1971, Pazredka and Streda 1975, Vernon-Roberts et al. 1974). However, potentially cartilage and bone forming foci can also be induced by systemic stimuli. Mainly the anterior pituitary hormones are known to have such an effect (Silberberg 1973, 1974). In diabetes – as already discussed in Chapter 1 – the disorder of mucopolysaccharide synthesis and the consequent decrease of mucopolysaccharides results in a relative condensation of collagen, and this explains the tendency to enhanced calcification and subsequent ossification.

The question arises as to whether the growth hormone level of patients suffering from hyperostotic spondylosis is elevated. In 1973, Bregeon et al. examined the hormone level of 10 such patients; in 1974, Harris et al. investigated the same parameter in 5 patients. No significant difference was found. We determined the fasting serum growth hormone level in 52 of our patients, by using radioimmunoassay (the assay was performed by Dr. G. Gács). On the basis of their spinal radiographs, our patients were divided into groups. Although Table 10 shows that the group with hyperostotic spondylosis had the highest somatotrophic hormone levels, and these proved statistically significant, the difference cannot be considered biologically significant.

Thus, regarding the role of growth hormone, in many respects we can only rely on hypotheses. A change of sensitivity of the connective tissues to somatotrophic hormone is one

Table 10

Fasting serum growth hormone level in various groups of spondylosis

	Males	Females	Total	Growth hormone		Mean blood glucose values (mg%)
				Mean value (ng/ml)	SE	
Group I	12	6	18	5.1	1.0	151
Group II	7	10	17	3.1	0.5	164
Group III	9	8	17	1.4	0.3	136

Group I: hyperostotic spondylosis; Group II: spondylosis deformans; Group III: minimal or mild spondylitic changes.

of these. Although direct evidence of hormonal effect is lacking, many data support the possibility that hyperostotic spondylosis and other hyperostotic changes – frequently encountercd in diabetics – are not related to the disturbance of the carbohydrate metabolism, but to hormonal changes accompanying or inducing diabetes. Some of our other observations also support the notion that bone abnormalities are not directly related to diabetes: there was no correlation between the duration and degree of severity of diabetes, and hyperostosis. Optimal management of diabetes did not halt the progress of the bone processes. These patients generally do not have insulin-dependent diabetes.

Naturally, a detailed study of the hormonal status in a large number of patients might change the concept outlined above, but such a study has not yet been conducted. Therefore, all other factors must also be considered which might play a role in the development of hyperostosis.

The role of vertebral dysplasia

Rubens-Duval et al. (1972) found signs of dysplasia in 90% of patients with hyperostotic spondylosis. Based on this finding, they assumed that spinal hyperostosis develops on the already abnormal vertebra. Signs of dysplasia were: flat vertebral bodies, irregular endplates, Schmorl's nodes, persisting vascular canals. In elderly patients, particularly if accompanied by kyphosis, these were evaluated as residual symptoms of Scheuermann's disease.

Diagnosis of dysplasia is not an easy task; the symptoms are not uniformly interpreted. According to Schoen et al. (1969), diabetes itself predisposes to vertebral dysplasia. Fülöp (1961), reporting 9 cases of "hyperostosis vertebrae," found signs of dysplasia in only one case.

Such radiographic findings were observed in 40%–45% of our patients belonging to various groups (controls, diabetics, patients with and without hyperostotic spondylosis). Scheuermann's disease is undisputedly involved in the development of spondylosis. We also observed that spondylosis always accompanied the residual symptoms of Scheuermann's disease. Nevertheless, other factors are also necessary for the development of hyperostotic spondylosis.

The role of mechanical factors

Rupture of the annulus fibrosus is assumed to play a decisive role in the development of spondylosis. Recently, the role of physical work has also been stressed (Billekamp 1972). According to literary data, and our experience, the incidence of hyperostotic spondylosis did not differ in manual and nonmanual workers (Forestier and Lagier 1971, Fülöp 1961, Julkunen et al. 1971). Moreover, according to Smith et al. (1955) this process is related to the relative immobility of the spine in the elderly.

Although, even at present, some authors contend that intervertebral disc injury is the cause of hyperostotic spondylosis (Pazredka and Streda 1975), the other forms of hyperostosis associated with spinal diseases cannot be explained by this mechanism.

We can approach the truth somewhat better if we study the role of mechanical factors in the development of different forms of hyperostosis. In the thoracic spine, where there is only a small range of motion, generally continuous ligamentous calcification develops,

while this is rare in the mobile cervical and lumbar spine. The alterations are much more pronounced in the lower than in the upper extremities, due to the weight-bearing stress on the former.

The role of obesity

Forestier had observed that most of the patients with hyperostotic spondylosis are fat, and this correlation has been confirmed by others (Geyer 1973, Hajzok and Takac 1970, Julkunen et al. 1971), who emphasized the role of obesity in the development of the disease. However, hyperostotic spondylosis often occurs also in nonobese diabetics, especially in thin males. In our opinion, obesity is not the cause of hyperostosis but a frequently associated symptom.

The role of complex metabolic disorder

Due to the complex metabolic disorder in diabetes, tissue metabolism declines and may result in degenerative processes. Bossa et al. (1970) emphasize the harmful effect of hyperlipidemia and angiopathy upon the connective tissues.

Two observations support the role of metabolic factors: hyperostosis occurs more frequently in juvenile diabetes of long duration than in the control group, even in cases of insulin-deficient diabetes when there is no reason to assume the effect of somatotrophic hormone; hyperostotic alterations are often associated with severe vasosclerosis.

Summary

In hyperostotic spondylosis (Forestier's disease) the anterior longitudinal ligament is calcified. The abnormality causes few clinical symptoms, and can be distinguished by its characteristic radiographic features. Its occurrence is age-linked. In diabetics the incidence of hyperostotic spondylosis was significantly higher in all age groups. In addition, spondylosis was present at an earlier age in diabetics than in nondiabetics. We examined 500 nonselected diabetics over the age of 40 years, and confirmed spondylosis in 118 of these patients (23.6%), while the incidence was 3.1% in the control group.

Hyperostotic spondylosis is not a disease in itself, but represents a predisposition to diffuse skeletal hyperostosis. Other hyperostotic defects are often found, the most frequent forms being hyperostosis frontalis interna (Morgagni's syndrome), calcification of the pelvic ligaments, paraarticular calcifications, and periosteal appositions at the tendon insertions on the extremities.

Hyperostosis and diabetes form a characteristic entity, where diabetes is usually not a severe, insulin-dependent form, but a maturity-type diabetes which is relatively easy to control. The abnormalities are very similar in many respects to the bone changes in acromegaly. Presumably, the overproduction of somatotrophic hormone may play a major role in the pathogenesis. However, an elevation of somatotrophic hormone level has not yet been unambiguously proven.

Schoen's (1969) question as to whether or not spondylosis hyperostotica deformans is a diabetic osteopathy seems to be answered: hyperostotic spondylosis is not a specific complication and hyperostosis is not a consequence of diabetes. A frequent common occurrence, however, can be proven. The radiographic features frequently appear prior to the metabolic disorder, and sometimes only radiographic examination draws attention to diabetes. In 75% of the patients with hyperostotic spondylosis, a disorder in the carbohydrate metabolism can be detected. This means that if a radiograph is made for any reason and diffuse hyperostosis is revealed, laboratory examinations must be performed to test the carbohydrate metabolism.

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Chapter 4

Diabetic osteoarthropathy

The term diabetic osteoarthropathy (DOAP) has been used to describe destructive-lytic bone changes, which are severe late complications of diabetes mellitus affecting primarily the pedal bones and only exceptionally others.

Diabetics frequently complain about discomfort or disorder in the feet; for example, Whitehouse and Block (1964) reported ischemic, neuropathic, and infectious complications of the feet in 16% of their diabetic patients. In a recent study Faerman et al. (1979) found 66 (14%) among 447 patients to have foot lesions. These changes may involve the soft tissues, bones, or both. The designation "diabetic foot" is a well-known term in the literature and diabetic osteoarthropathy also belongs to this category.

Many synonyms are used to describe this disease. Some authors use the term *diabetic arthropathy*, while others, who consider bone destruction of primary importance, call it *diabetic osteopathy*. The designations referring to the origin of the disease are *diabetic Charcot joint*, *diabetic pseudotabetic joint*, *diabetic neuroarthropathy*, *and diabetic neurogenic osteolysis*. In our opinion, the term diabetic *osteoarthropathy* is the most appropriate. Also, our histological examinations support this designation, because both the articular cartilage and bones are involved.

Diabetic osteoarthropathy belongs to the category of neurogenic bone diseases. The most frequent causes of these disorders are tabes dorsalis and diabetes mellitus. In 1966, Eichenholz, studying a series of 68 patients with neuropathic joints, found 34 cases to be due to syphilis, 12 due to diabetes mellitus, and the others had various other etiological factors in the background. Today, syphilis is a disease in retreat, but as the incidence of diabetes seems to be rising, the frequency of DOAP cases is also expected to rise. Although there are no exact data available, we assume that, at present, diabetes mellitus is the principal factor responsible for neurogenic bone diseases.

The occurrence of diabetic osteoarthropathy

Jordan was the first to describe this condition in 1936, although Bailey and Root reported 17 cases in 1947; case reports were still being published in the 1970s. Table 11 presents the case reports from the literature. In 1969, according to Dinkel, the total number of cases was 90. Since then there is a rapid increase in incidence: Kraft et al. (1975) observed 22, Gondos (1968, 1972) 32, and Sinha et al. (1972) reported 101 cases based on 20 years of experience in the Joslin Clinic. Clouse et al. (1974) found 30 cases between 1959 and 1969, and 60 between 1969 and 1973.

What is the explanation for this rapid increase in the number of DOAP cases?

1. A rising incidence of diabetes mellitus.

Table 11

Cases of diabetic osteoarthropathy reported in the literature

Authors		No. of compiled cases
Muri	1949	24
Parsons and Norton	1951	29
Beidelman and Duncan	1952	23
Sheppe	1953	37
Martin	1953	37
Bolen	1956	29
Bloch-Michel et al.	1959	53
Petersen	1960	89
Fritz	1960	50
Rouillard et al.	1961	103
Boehm	1962	52
Grönberg and Saarme	1969	86
Dinkel	1969	90

2. DOAP is a late complication, appearing after long-term insulin treatment. At present, an increasing number of juvenile diabetics treated with insulin reach an old age, thus, more patients "have a chance" to develop DOAP.

3. The clinical symptoms of DOAP are generally mild, and not at all characteristic; in most cases no x-ray examination is made and therefore the disorder escapes detection. In the light of these findings, in 1952 Martin proposed the routine x-ray examination of the feet of patients with diabetic neuropathy. Today, this suggestion is under reconsideration.

4. Accumulation of knowledge results in more precise diagnosis and cases previously often diagnosed as osteomyelitis, bone tuberculosis, tumors, etc., are now correctly recognized to be associated with diabetes.

Accordingly, the increase in the number of DOAP cases is to be expected. Furthermore, it remains an important task to recognize and reveal the existing cases.

The incidence of this complication in diabetes mellitus is summarized in Table 12. The great scatter can be ascribed to the absence of standard criteria in the patient selection.

Our own material is pooled from several diabetic outpatient centers and various hospital departments in Budapest. We found a 0.2%–0.5% incidence of DOAP, which approaches the figures of Bailey and Root (1947), Mazovetsky et al. (1974), and Sinha et al. (1972), who made their assessments on excessive material. These data and the high incidence of diabetes mellitus (1%–2% of the total population) show that the incidence of DOAP is not at all as low as many authors like to state. For example, in Hungary several hundreds of such complications may occur.

Table 13 also shows the increasing tendency toward DOAP. A total of 178 cases reported in 74 papers were analyzed. Between 1936 and 1966 there were 87, and 91 were reported between 1966 and 1977. Adding our own cases to the latter group, this equals 122 cases. In the latter period, many papers were published discussing the cases from other aspects, too (for the relevant clinical data of diabetics with osteoarthropathy see Table 14).

Table 12

Literary data regarding the incidence of diabetic osteoarthropathy

Authors		No. of diabetics	DOAP	
Bailey and Root	1947	20.000	17	(0.08%)
Martin*	1953	150	9	(6%)
Copland**	1954	400	19	(4.8%)
Lippman and Grow	1955	110	2	(1.8%)
Koluchenko and Kudryaisev	1964	100	17	(17%)
Pogonowska et al.	1967	242	7	(6.8%)
Klümper et al.	1968	134	10	(7.5%)
Velickov and Djanov	1971	177	28	(15.8%)
Friedman and Rakow***	1971	22	17	(77%)
Naim	1971	300	5	(1.6%)
Sinha et al.	1972	68.000	101	(0.15%)
Mazovetsky et al.	1974	1.366	9	(0.7%)
Mynte	1974	130	8	(6.2%)
Lippmann et al.	1976	500	12	(2.4%)

* Patients with diabetic neuropathy. ** Author considered these changes due to inflammation, however, according to presented data these were cases of DOAP; *** Patients with severe diabetic neuropathy.

Specific features of diabetic osteoarthropathy

The age and sex distribution was analyzed on the basis of 268 cases (Table 15). Sex distribution showed no substantial difference. The incidence of DOAP was the highest in the age group of 50–60 year old, in males a high rate was also observed between 40 and 49 years of age. Therefore, the average age of the males (49.9 years) was lower as compared to the affected females (52.1 years). The mean age of our patients was higher than the average reported in literature (the average age of males was 62.9 years, and that of females 61.6 years).

The youngest patient, reported by Szijj and Bakay (1970), was 19 years old. Heik (1974) mentions 3 childhood cases, without any detailed description of these patients. To determine the relationship between the duration of diabetes mellitus and DOAP (Table 16), 255 cases were subjected to detailed study. (The differences between the totals in Tables 15 and 16 are due to the lack of data in the analyzed case reports.)

DOAP is a late complication. In 73% of the cases compiled from the literature and in 77% of our cases, DOAP developed later than ten years after the onset of diabetes. The average duration of diabetes before DOAP developed was 12.4 years in males and 17.7 years in females. In our patients, it was 16.5 years in males and 12.6 years in females.

The question arises as to whether DOAP may accompany latent diabetes, or whether the bone lesions develop before the manifestation of diabetes. According to Ellenberg's studies, diabetic neuropathy also appears with latent metabolic disorders. Five cases (4 males and 1 female) were reported in which DOAP preceded manifest diabetes. Arnott et al. (1971) and Lièvre et al. (1969) published detailed descriptions of their cases.

Table 13

Some important data on the cases of diabetic osteoarthropathy reported in the literature

Authors		No. of cases	Sex	Age (years)	Duration (years)	Therapy	Retinopathy	Nephropathy	Neuropathy	Localization
Jordan	1936	1	F	56	14	Insulin			+	A
Takáts	1945	1	M	28	15	Insulin			+	A – Knee
Morris	1947	1	F	52		Insulin		–	+	TM
Bailey and Root	1947	17	F	29	20		+	+	+	MP
			F	67	19		+	–	+	TM
			F	63	15		–	–	–	TM
			M	63	11		–	–	+	TM
			F	56	14		+	+	+	TM
			M	59	11	Insulin	+	+	+	TM
			M	30	7		+	+	+	T
			M	63	14		+	–	+	TM
			F	61	2		–	–	–	TM
			M	43	11		+	–	+	T
			F	52	13		+	–	–	TM
			M	69	6		–	–	+	TM
			F	55	14		+	+	+	TM
			F	61	8		+	–	+	TM
			F	69	7		+	–	+	TM – MP
			F	45	18		–	–	+	TM – MP
			F	62	5		–	+	+	MP
Foster and Basset	1947	2	M	23	10	Insulin	+		+	TM
			M	29	17	Insulin	+		+	A
Hindemith	1949	1	M	24	7	Insulin	+	–	+	A
Muri	1949	1	M	49	18	Insulin	+	+	+	A
Cozen	1950	1	M	26	11	Insulin			+	T
Lister and Maudsley	1951	1	M		2	Insulin			+	MP
Knutsson	1951	4	F	30					+	A
			F	28					+	A
			M	34	10				+	A
			M	63	19				+	A
Beidelman and Duncan	1952	4	M	43	14	Insulin	+	+	+	T
			F	54	22	Insulin	+	–	–	TM
			M	49	12	Insulin	+	–	–	TM
			F	43		Insulin		–	+	TM – MP – IP
Zsebők	1952	1	F	66					+	TM – IP
Benard et al.	1953	1	M	61		Insulin	–		+	TM – MP
Cram	1953	2			8		+		+	TM
				59					+	A
Sheppe	1953	1		58	17	Insulin	+		+	MP
Boulet et al.	1954	5	M	45	10	Insulin				MP
			M	46	9	Insulin			+	MP
			M	49		Diet			+	MP
			F	58	8	Insulin			+	MP
			M	60	10	Diet			+	MP
Nantes	1954	1	M	39	10	Insulin	–	–	+	TM
Gocke	1955	1	F	32	14	Insulin			+	TM

Table 13 (continued)

Authors		No. of cases	Sex	Age (years)	Duration (years)	Therapy	Retinopathy	Nephropathy	Neuropathy	Localization
Bolen	1956	1	F	39	19	Insulin	−	−		TM
Murazt	1956	2	F	35	20	Insulin		+	+	TM
			F	35	16	Insulin		+	+	TM
Gottlob	1957	2	F	60	9	Insulin			+	MP
			F	67	9	Insulin			+	MP
Jacobs	1958	3	F	68	14	Insulin			+	TM − MP
			M	57	20	Insulin			+	TM − MP
			M	30	14	Insulin			+	A
Kardos and Varró	1958	1	M	36	12	Insulin			+	A
Ochsenschläger	1958	1	M	57	6	Insulin		−	+	TM − MP
Sheppe and Wheeling	1959	1			26					TM
Aagenes and Hagensen	1959	2	F		17	Insulin	+	+	+	T
			F		20	Insulin	+	+	+	TM
Prestinari	1959	1	F	61	20	Insulin			+	T
Bloch-Michel et al.	1959	1	F	30		Insulin	+	+	+	A
Petersen	1960	2	M	30	20	Insulin	+	+		A
			F	62	12	Insulin	+	+		A − TM
Degenhardt and Goodwin	1960	2	M	35	15	Insulin	+	+	+	TM
			F	75	9	Diet				TM
Contamin and Deuil	1960	1	M	62		Insulin	+	+	+	TM
Rouillard et al.	1961	1	F	54	9	Insulin	+	−	+	A
Bossi et al.	1961	5	M	60	12	Insulin	+	+	+	TM
			F	70	11	Insulin	+	+	+	MP − Knee
			F	64	5	Insulin	+	+	+	MP
			F	71	25	Insulin		−	+	TM
			F	58	11	Insulin	+	−	+	
Naide and Schnall	1961	1	F	45	17	Diet			+	MP
Boehm	1962	1	M	44	16	Insulin	+		+	TM
Galmiche and Pocher	1962	1	M	48	12	Insulin	+	−	+	T
Azérad et al.	1963	4	M	46					−	MP
			M	54					+	MP
			F	78	5	Insulin			+	MP
			F	55	15	Insulin			+	MP
Agnoli and Bonamini	1963	1	M	55	4	Oral			+	MP
Feiereis	1964	1	F	22	15	Insulin	+	+	+	T − MP
Hiltner	1964	1	F	60	10	Insulin			+	T
Rouillard et al.	1964	4	M	53	2	Insulin	+		+	MP
			F	58	10	Insulin			+	TM
			F	78	15	Oral			+	TM − MP
			F	35	25	Insulin	+	+	+	T
Pomeranze and King	1965	1	F	67	23	Oral				IP
Heiple and Cammarn	1966	2	M	44	8	Insulin	+	+	+	T
			F	62	11	Insulin	+	+	+	

Table 13 (continued)

Authors		No. of cases	Sex	Age (years)	Duration (years)	Therapy	Retinopathy	Nephropathy	Neuropathy	Localization
Buia and Lensi	1966	7	M	71	15	Insulin			+	MP – IP
			M	52	15	Insulin			+	MP
			M	56	12				+	MP
			M	60	20	Insulin			+	MP
			F	55	17	Insulin			+	MP
			M	56	21	Insulin			+	MP
			F	49	19	Insulin			–	IP
Rathery	1968	9	M	55	13	Insulin				T
			F	59	16	Insulin				T
			M	55	25	Insulin	+	+	+	TM
			F	67	10	Insulin	+	+	+	T
			M	29	14	Insulin	+		+	T – Knee
			F	53	20	Insulin			+	TM
			M	55	2	Oral				T
			F	48	6	Insulin				T
			M	54	15	Oral	+			TM
Lièvre et al.	1969	1	M	46		Diet			+	A – IP
Schwartz et al.	1969	1	M	61					+	MP
Dinkel	1969	1	M	66	5					TM
Belser	1969	6	M	65	9	Insulin	+	+	+	TM
			F	67	20	Insulin	+		+	TM – MP
			F	57	17	Insulin			+	MP
			F	67	14	Insulin			+	MP
			M	62	2	Oral			+	TM
			F	58	47	Insulin			+	MP
Fiorio	1969	1	F	65		Insulin			+	TM – IP
Grönberg and Saarme	1969	4	F	38	30		+	+	+	MP
			M	40	18		+	–	+	TM
			F	69	37	Insulin	+	–	+	MP
			M	51	37	Insulin	+	–	+	
Feldman et al.	1969	1	M	63	14	Insulin	+		+	T
Róna and Kóczé	1970	1	F	27	15	Insulin				T
Amtrup	1970	1	F	28	14	Insulin	+		+	MP
Szántó and Kapui	1970	1	M	55	13	Insulin	+	+	+	MP
Szijj and Bakay	1970	1	F	19	10	Insulin	+	+	+	T
Steinberg	1971	2	M	48		Oral			+	MP
			M	56		Insulin			+	MP – IP
Arnott et al.	1971	1	M	50		Oral	–		+	T
Mau	1971	4	M	74	22		+		+	T
			F	25	15				+	A
			F	24	12	Insulin			+	TM
			M	28	6					TM
Bruni et al.	1971	1		52	10	Insulin			+	TM
Southward	1971	5	M	64	6	Oral			+	MP
			M	49	15	Insulin			+	T
			M	43	13				+	
			F	63						MP
			F	69	21					A
Friedman and Rakow	1971	1	F	59	10				+	MP

Table 13 (continued)

Authors		No. of cases	Sex	Age (years)	Duration (years)	Therapy	Retinopathy	Nephropathy	Neuropathy	Localization
Mitra et al.	1971	1	F	42	10	Insulin	+	+	+	MP
Sandrow et al.	1972	4	F	48	12					TM
			M	55						TM
			F	62	12					T
			F	52						TM
Götze	1973	1	M	41	1	Insulin	+		+	TM
Shagan et al.	1973	1	F	47	9	Insulin		−	+	A − TM
Lippard	1973	6	F	51	4					MP
			M	46	5	Oral	+			IP
			M	51	1	Insulin				MP − IP
			M	48	1					MP − IP
			M	57						IP
			F	43	10	Insulin				
Clouse et al.	1974	5	M	36	21				+	MP
			M	61	30				+	T
			M	59	30	Oral			+	IP
			M	58	3	Insulin			+	MP
			M	72	24	Insulin			+	MP
Mazovetsky et al.	1974	1	F	28	20	Insulin				A − MP
Rosenberg	1976	1	F	51	30	Insulin	+	−	+	MP − IP
Fritz	1960	1	M	42	13	Insulin	+	+	+	A − IP
Ohlsen	1963	2	F		10	Insulin	+	−	+	T
			F		12	Insulin	+	+	+	TM
Lippmann et al.	1976	12	F	59	15				+	T
			M	53	10	Oral			+	T − TM
			M	53	15	Oral			+	T
			M	61		Insulin			+	T
			F	37	21		+		+	A
			M	25	12	Insulin				A
			F	44	18		+		+	TM
			F	47	13				+	MP
			M	77			+		+	TM
			F	67					+	A
			F	55	15	Oral			+	T
			M	26	5	Insulin				T
Naim	1977	5	M	68	14				+	
			M	72	16				+	
			M	58	6				−	
			F	71	14				+	
			F	56	11				+	

M = male; F = female; A = ankle joint (often together with other tarsal bones); TM = tarsometatarsal joints (in some cases together with the proximal tarsal bones); MP = metatarsophalangeal joints; IP = interphalangeal joints.

Table 14

Clinical and radiological data of patients with diabetic osteoarthropathy

Sex	Age (years)	Duration of diabetes (years)	Therapy	Retinopathy	Nephropathy	Neuropathy	Oscillation	Calcification of arteries in the leg	Localization
M	60	12	Insulin	−	−	+	Decreased	+	Knee, ankle, tarsus
M	64	25	Insulin	+	+	+	Decreased	+	Tarsus, 3rd TM
M	60	21	Insulin	+	+	+	Decreased	+	1st MP
M	61	14	Oral	−	−	+	Decreased	+	1st MP, 2nd IP
F	59	15	Oral	+	−	+	Normal	+	1st MP
F	66	14	Oral	+	+	+	Decreased	+	1st MP
F	65	11	Oral	+	+	+	Decreased	+	1st MP
F	59	2	Insulin	−	−	+	Normal	−	2nd and 3rd MP
F	59	19	Insulin	+	+	+	Normal	+	2nd and 4th MP
F	48	12	Insulin	+	−	+	Normal	−	3rd MP
F	79	15	Insulin	+	−	+	Decreased	+	3rd and 4th MP
F	58	13	Insulin	+	−	+	Decreased	−	5th MP
M	77	32	Insulin	+	−	+	Decreased	+	5th MP
M	55	18	Insulin	−	−	+	Normal	+	5th MP
M	55	13	Insulin	+	−	+	Normal	+	1st and 4th MP
M	75	10	Insulin	−	−	+	Decreased	+	1st to 3rd MP, 3rd IP (toe)
M	66	8	Oral	+	−	+	Decreased	+	Bilateral 5th MP, 1st IP (toe)
F	57	9	Insulin	+	−	+	Normal	−	5th MP, 4th to 5th IP (toe)
F	56	16	Insulin	+	−	+	Normal	−	2nd and 3rd MP, 2nd IP (toe)
F	63	13	Insulin	+	−	+	Decreased	+	1st and 2nd MP, 2nd IP (toe)
F	58	9	Insulin	+	−	+	Normal	+	1st MP, 1st IP (toe)
M	69	20	Insulin	+	+	+	Decreased	+	2nd to 4th MP, 2nd and 3rd IP (toe)
F	77	18	Oral	+	−	+	Decreased	−	1st IP (toe)
M	53	15	Insulin	+	−	+	Decreased	+	Bilateral 4th MP, 4th IP (toe), 2nd and 3rd MP
F	70	10	Insulin	+	−	+	Decreased	+	Bilateral 3rd and 5th IP (toe)
M	72	12	Oral	+	+	+	Decreased	−	5th IP (toe)
F	52	16	Insulin	+	−	+	Normal	−	Bilateral 5th IP (toe)
F	77	8	Oral	−	−	+	Normal	+	2nd and 3rd IP (toe)
F	42	12	Insulin	−	−	+	Normal	−	3rd IP (toe)
M	51	14	Oral	−	−	+	Decreased	+	5th IP (toe)

TM = tarsometatarsal joint; MP = metatarsophalangeal joint; IP = interphalangeal joint.

Table 15

Sex and age distribution of patients with diabetic osteoarthropathy

Age (years)	Total of reported cases		Sinha et al. 1972	Total of cases in literary data	Own material		
	Males	Females			Males	Females	Total
>20	–	1	–	1	–	–	–
20–29	9	7	7	23	–	–	–
30–39	8	9	16	33	–	–	–
40–49	19	12	16	47	–	2	2
50–59	25	25	35	85	4	8	12
60–69	18	23	25	66	6	4	10
70–79	5	6	2	13	3	4	7
Total	84	83	101	268	13	18	31

Other diabetic complaints are also frequent. Peripheral neuropathy is of interest from the point of view of our subject. We found clinical symptoms indicating peripheral neuropathy in 143 case reports. Neurological disorders can always be recognized on careful examination.

There are 52 such cases reported in which positive or negative findings with respect to all three important complications of diabetes (retino-nephro-neuropathy) were present. Of these in 27, all three complications occurred simultaneously. We observed similar complications in 8 of our 31 patients. Thus, among 83 cases, "triopathy" was observed in 35 (42.2%). Root et al. (1954) introduced the term triopathy, which they encountered in 3.1% of the diabetic patients. Comparison of these data also indicates the high incidence of other complications in DOAP-accompanied diabetes. Therefore, when DOAP is confirmed, one should think of other simultaneously arising complications.

Data with respect to the characteristics of metabolic disorders in diabetics are difficult to assess accurately because their description by different authors is far from being uniform. However, the case reports indicate an unstable carbohydrate metabolism, ketoacidosis, hypo- and hyperglycemia in the majority of patients. Most patients required insulin therapy

Table 16

Distribution of patients with diabetic osteoarthropathy according to the duration of diabetes

Duration of diabetes (years)	Total of reported cases		Sinha et al. 1972	Total of cases in literary data	Own material		
	Males	Females			Males	Females	Total
0–5	15	6	5	26	–	1	1
6–10	16	16	12	44	2	4	6
11–20	36	46	50	132	8	13	21
<21	9	10	34	53	3	–	3
Total	76	78	101	255	13	18	31

(100 cases), and oral antidiabetics were sufficient in only 14 cases, while only 5 patients could be kept merely on a well-controlled diet.

Of our patients 22 were given insulin and 9 received oral antidiabetic drugs. DOAP occurred in 4 of the regularly and well-controlled insulin-treated patients, whose carbohydrate metabolism was stable. In our other DOAP cases, there was no apparent metabolic imbalance. In our opinion, DOAP in these cases was due to an error in treatment or to the lack of disciplined cooperation by the patient (irregular injection of insulin, dietetic errors). These patients were often inadequately controlled, they could not be kept in balance with oral antidiabetics for months or years preceding bone changes. They should have been treated with insulin.

Therefore, osteoarthropathic complications generally occur more frequently in diabetics with chronic metabolic decompensation.

Changes in the soft tissues and clinical findings in diabetic osteoarthropathy

In DOAP the clinical symptoms are much milder than would be expected on the basis of radiological findings. This explains why DOAP is often revealed only after severe irreversible bone changes have developed.

The clinical symptoms and soft tissue changes have been classified into four groups, indicating the degree of bone involvement.

Neurological symptoms (Group I)

The signs of peripheral diabetic neuropathy are present in every case and each stage of DOAP. Their detailed description can be found in all current textbooks on neurology. These symptoms are paresthesia and often reflex disorders (Beardwood and Schumacher 1964). An early and permanent sign is the loss of sensation to vibration.

The neurological manifestations are varied: 11 of our 31 patients complained of numbness, formication, insensitivity, and shooting pains. In the other patients, only neurological examination revealed these symptoms. In two subjects we observed muscular atrophy of the lower extremities, which also indicates neuropathy (Julien et al. 1974).

Sometimes the bone lesions develop without any visible soft tissue changes. Zsebők (1952) pointed out that it is the bone process and not the soft tissue lesions that are of primary importance in cases of trophoneuropathies. Martin's (1952) proposal to subject diabetic neuropathy to regular radiological examination is also based on this concept. Furthermore, it explains why DOAP is often only an accidental finding of a routine x-ray examination. Sinha et al. (1972) report 21 and we observed 4 such cases among our patients (Fig. 40).

Skin involvement is closely related to neurological and circulatory disorders. Lithner (1976*a*,*b*) distinguished four types of skin lesions on the foot:

1. erythema (with or without necrosis),
2. purpura or pigmentation,
3. yellow nails,
4. skin atrophy.

These skin lesions, according to Lithner's (1976*c*) observations, indicate the presence of bone disorders. In 27 of his 70 patients with erythema, radiography revealed bone destruction. However, radiologically verified bone lesions occurred in only 4 of 61 patients without skin symptoms.

Loose joints, articular swellings (Group II)

These symptoms include the loosening of the articular capsule and ligaments, pathologic mobility of the joint. The metatarsophalangeal joint is the site of predilection.

Owing to the appearance of loose joints and to the diabetic innervation disorder of the long flexor and extensor muscles, a simultaneous contraction develops, resulting in dorsal flexion and subluxation in the metatarsophalangeal and interphalangeal joints. Naturally, this is seen on x-ray pictures.

In other cases, the soft tissue surrounding the joint is swollen. Although painless articular swelling is the characteristic finding, literary data report patients with symptoms of "acute arthritis." Frequently, neither the physician nor his patient attach importance to this swelling that shows no signs of inflammation, although very often this means the onset of a process leading to severe bone destruction.

According to Classen et al. (1976), radiographic signs appear 6–12 months after the clinical symptoms. In the 10 cases they examined with ^{99}Tm, an increased activity was found months before the manifestation of radiographic symptoms.

Soft tissue ulcer, gangrene (Group III)

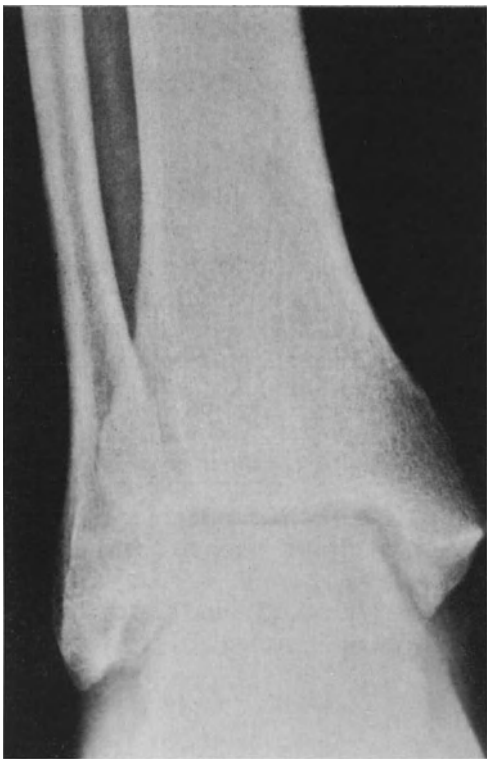
Diabetes is the most frequent cause of neurotrophic *ulcers* of the *plantar surface* (Table 17). As early as 1806, Garco drew attention to the frequent occurrence of plantar ulcer in diabetics. This is one of the symptoms of diabetic peripheral neuropathy (Ellenberg 1968, Harrison and Favis 1976). Martin (1954) reported data on the incidence of this symptom: 8 of 150 patients with diabetic neuropathy suffered from an ulcer on the plantar surface of the foot.

Plantar ulcers are often associated with bone destruction and it is in fact unusual to find these ulcers unaccompanied by bone changes. On examination of the case reports mentioned 16 of our patients had plantar ulcer. In the last 10 years, we have found only two diabetics who had ulcer of the plantar surface without osteopathy. The ulcers develop on the weight-

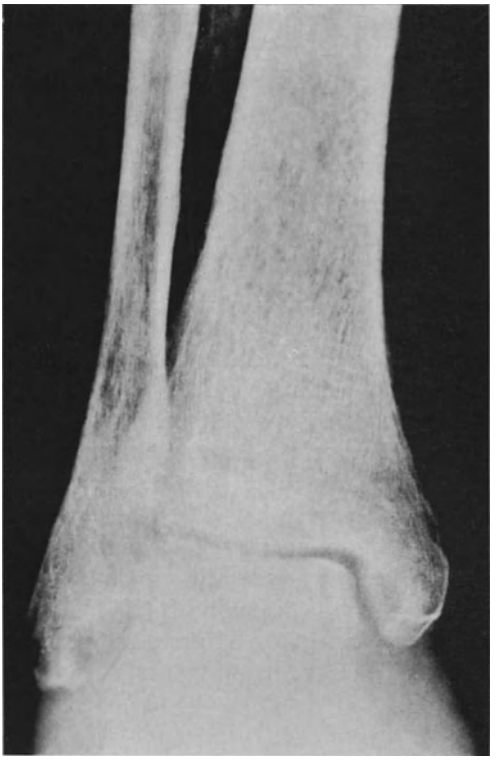
Table 17

Incidence of diabetes mellitus in patients with plantar ulcer

Authors		No. of plantar ulcers	No. of diabetics
Kelly and Coventry	1958	47	23
Classen	1964	45	40
Thivolet and Perrot	1970	32	11
Total		124	74 (59.7%)



a



b

Fig. 35. Case 1. The patient was regularly seen at the outpatient diabetic clinic. He was hospitalized because of deep vein thrombosis in the left leg. Medical history revealed plantar ulcer on the right foot, which healed completely half a year before. The ankle was found to be swollen, and was thought to be the consequence of thrombosis

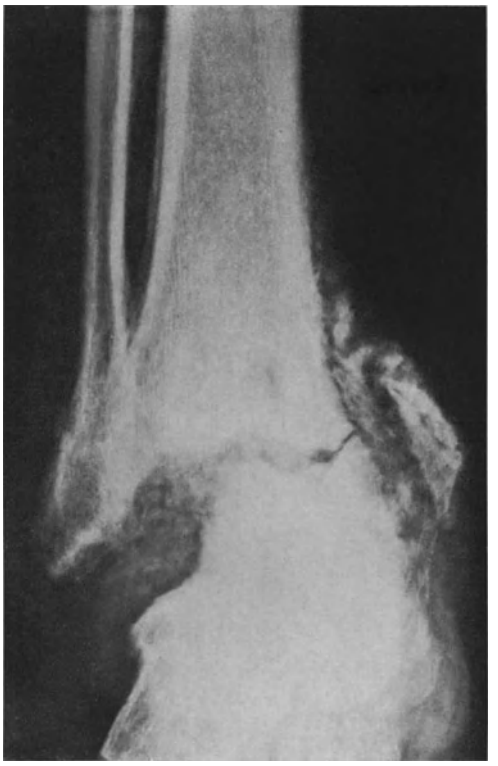
Fig. 35**a.** Five days after hospitalization, the bony structure of the ankle is perfectly normal

Fig. 35**b.** The patient recovered from thrombosis, but the ankle remained swollen; therefore, a new radiograph was made. Mild demineralization adjacent to the ankle joint. At the level of the apex of the internal ankle the contour of the talus is indistinct. Calcified blood vessel below the internal ankle

Fig. 35**c.** The patient returned home and resumed normal activities. He did not complain of pains in the feet although he had to stand all day during his work. Two months later the patient returned to the hospital because his ankle had deformed. Severe destruction of the ankle joint. Destroyed and fragmented articular surfaces of the shin bones as well as most of the proximal tarsal bones. Several fragments among the bones. The internal ankle was separated, fragmented, and displaced medially together with the tarsus. Markedly sclerotic, inhomogeneous articular surfaces. Periosteal reaction on the crural bones. At the level of the medial ankle a calcified artery can be seen, curve-shaped because of dislocation

Fig. 35**d.** Orthopedic consultation recommended surgical intervention, but the patient did not give his consent. One month later the x-ray picture revealed increased dislocation of the tarsus. Ankylosis developed between the distal part of the crural bones. Most of the fragments have been resorbed. Periosteal appositions became pronounced. Compared to the previous x-ray picture these signs are evidence of the onset of healing

Fig. 35**e.** A few months later, pronounced deformation of the ankle joint with a progressed periosteal ossification and partial ankylosis. The fractured internal ankle linked the tibia with the tarsus as an osseous bridge



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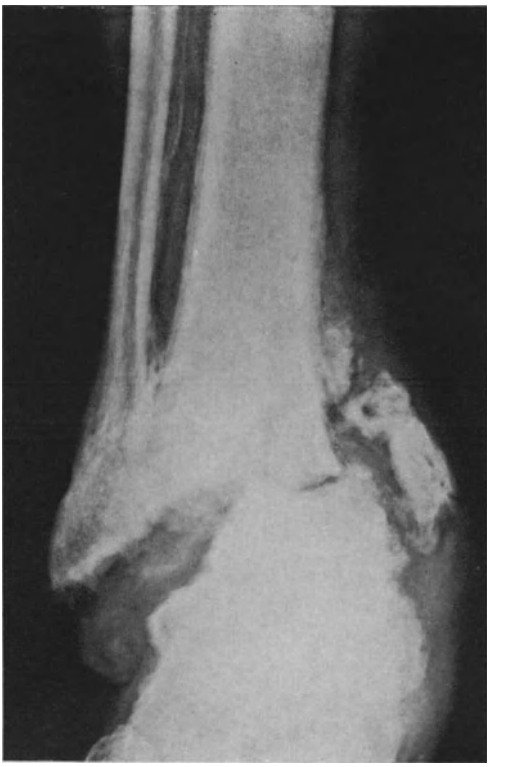

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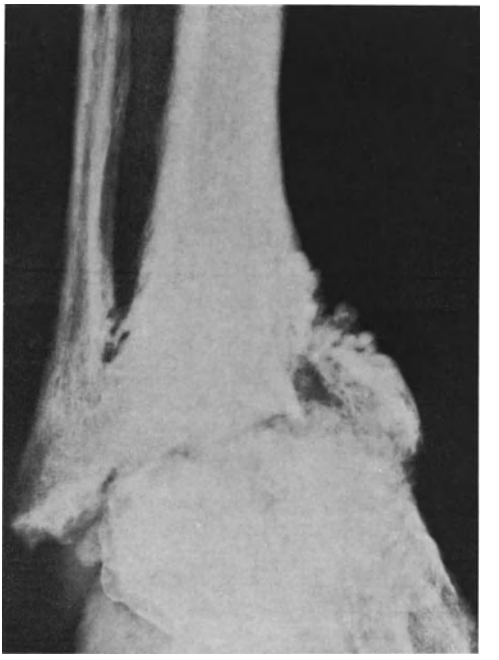

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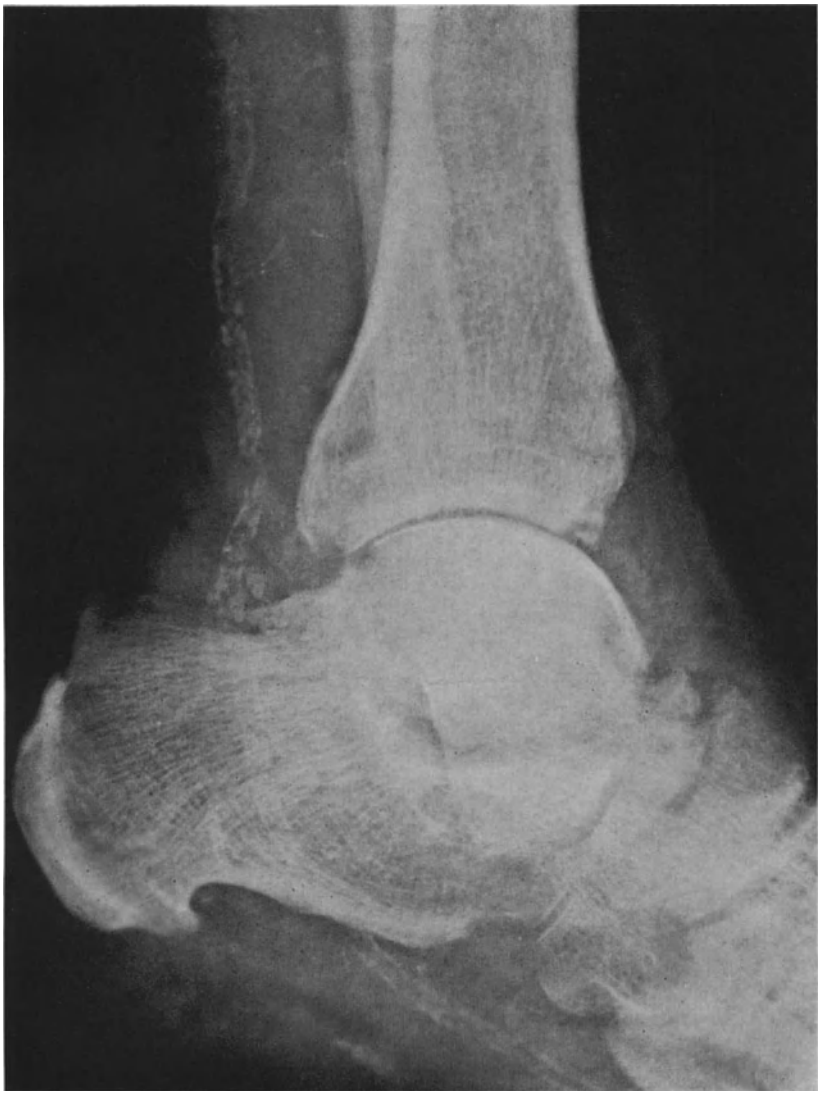
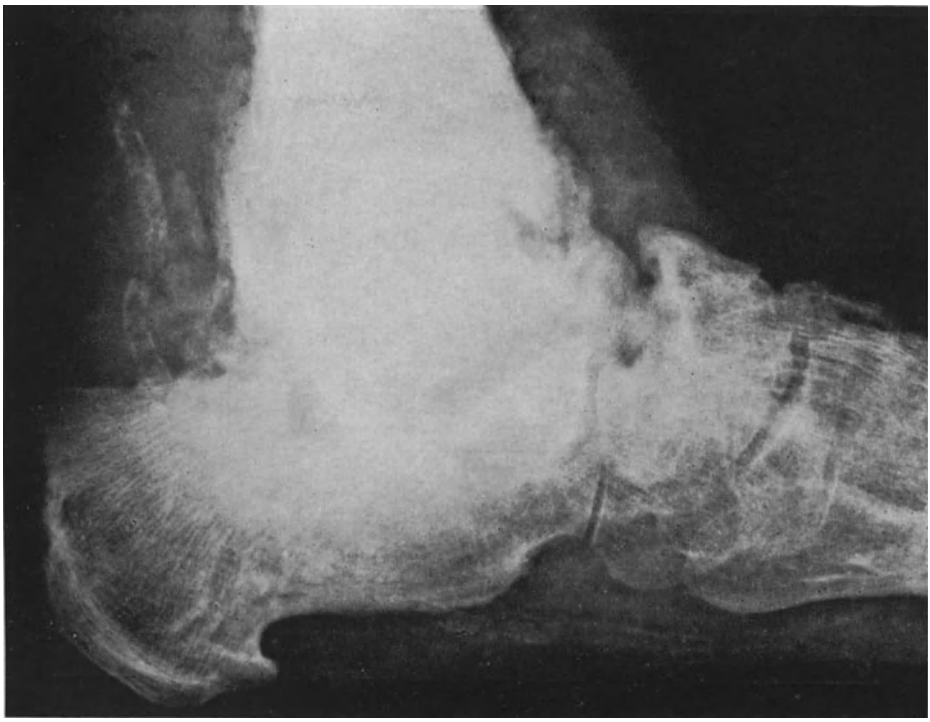


f

Fig. 35f. The process can also be followed in the lateral views. The destruction started on the anterior part of the talus, adjacent to the talonavicular joint. Bone defect with an indistinct edge. Irregular structure of the bones in the posterior part of the subtalar joint already at this stage

Figs. 35g and h. Marked erosion and fragmentation in the subtalar joint. The bones gradually slipped toward each other. Osteosclerosis, metaplastic soft tissue calcification ("hypertrophic arthropathy"). Large contrast between the sclerotic bones caused by arthropathy and the porotic structure of the other bones. Thickened tubercle of the calcaneus and an exostosis on the plantar surface. Severe, calcified arteriosclerosis involving the posterior tibial artery, the smaller arteries on the foot, and to a lesser extent the anterior tibial artery



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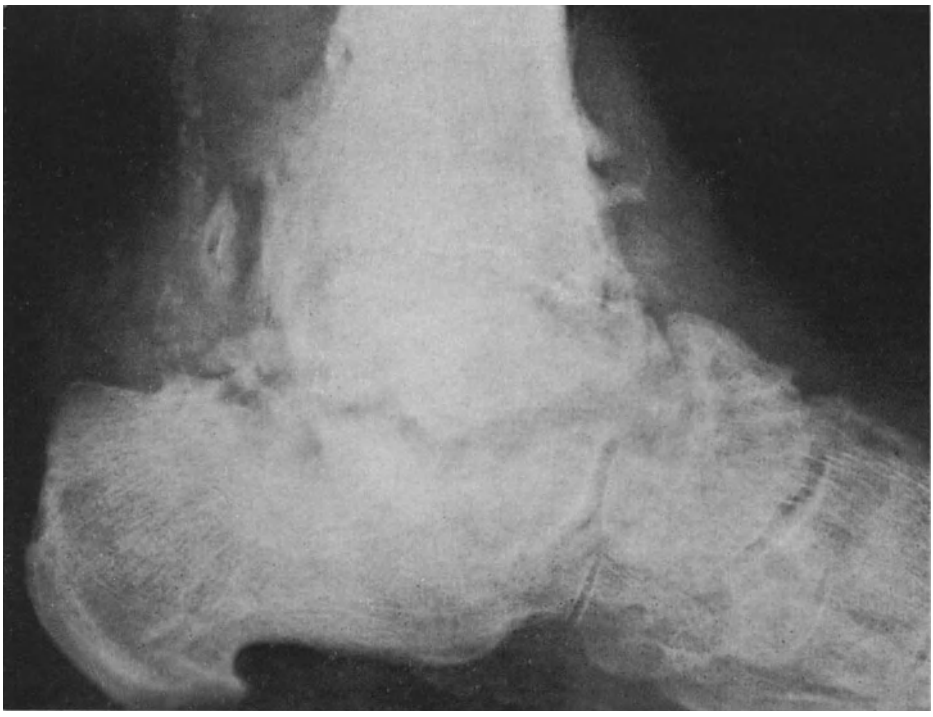

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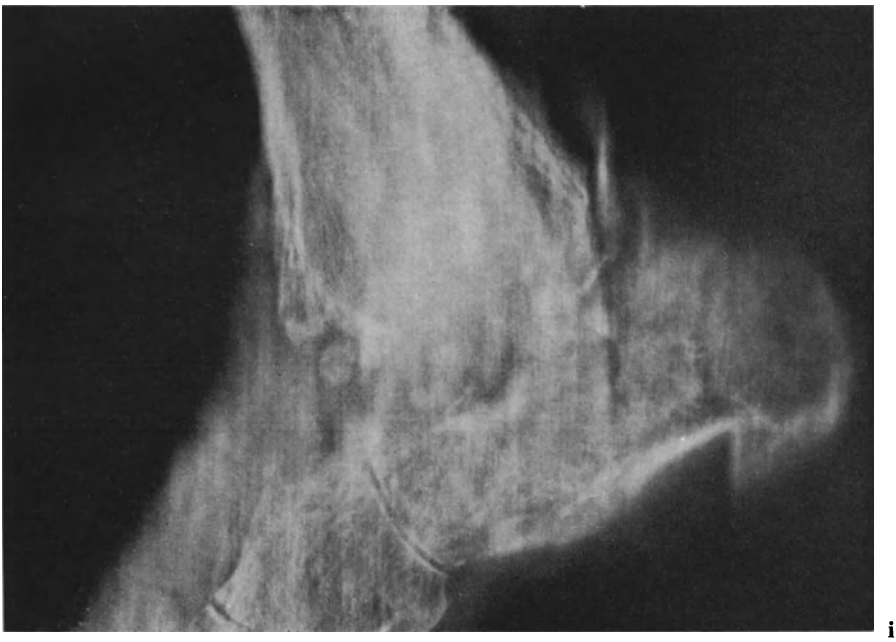

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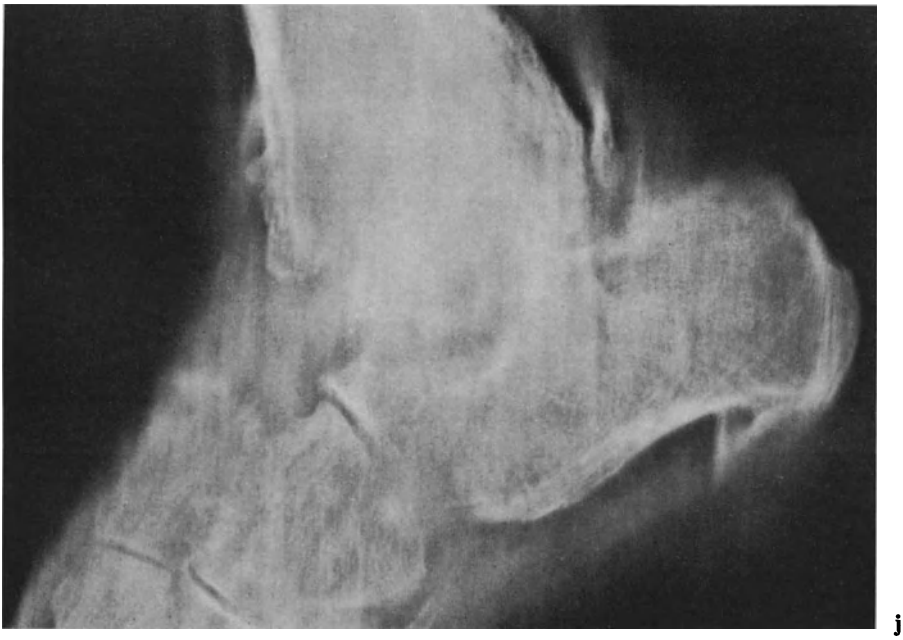

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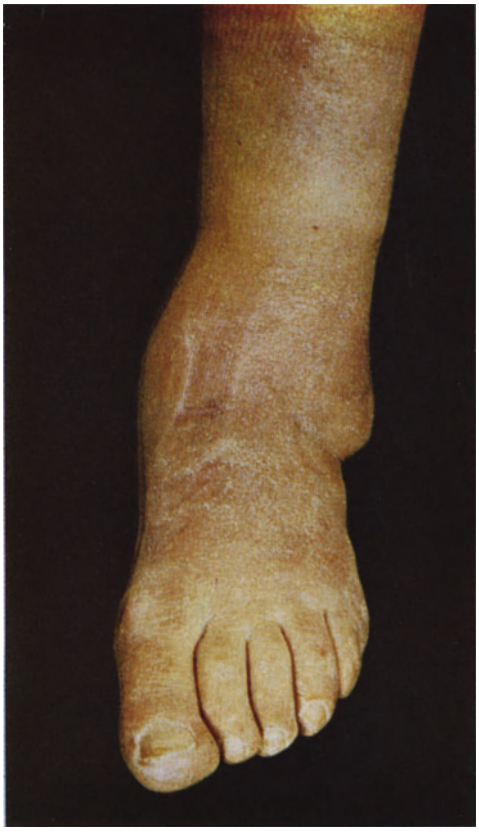
Figs. 35**i** and **j**. Ankle. Lateral view. Tomogram. In spite of sclerosis and hypertrophy, osteolysis is the basis of the process. The talus is almost completely destroyed, the process has extended to the navicular bone, calcaneus, moreover, to the upper part of the cuboid

Figs. 35**k** and **l.** Marked deformity of the ankle joint. Shortened extremity. The foot medially dislocated. Pathologic skin fold below the external ankle due to the slipping of the bones. The patient was given a walking splint and thus became capable of resuming work



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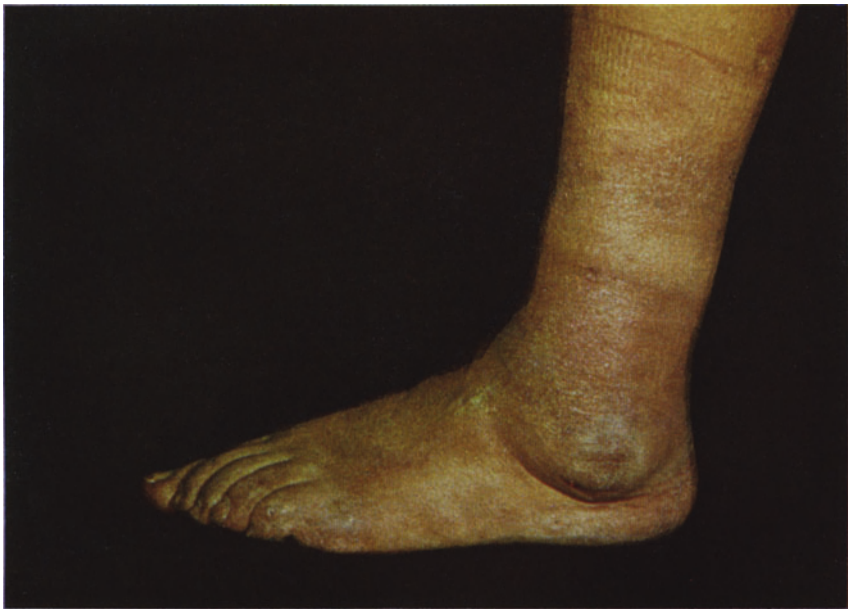

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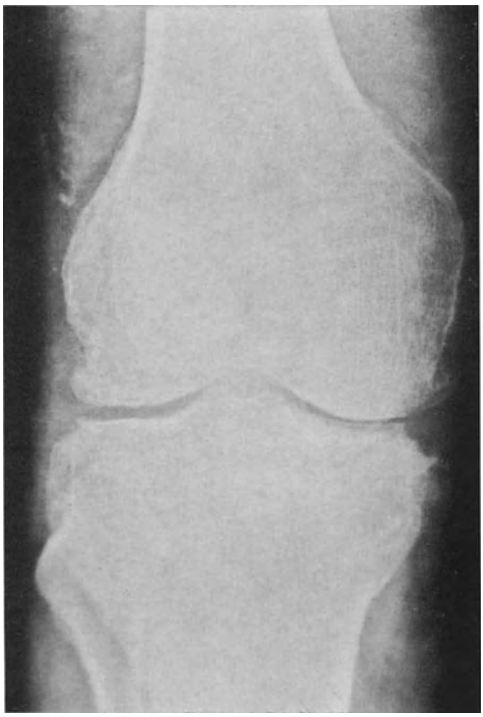

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Fig. 35**m.** Slight swelling of the knee with ankle deformity. Marked bone defect at the edge of the medial condyle of the tibia extending to the articular surface

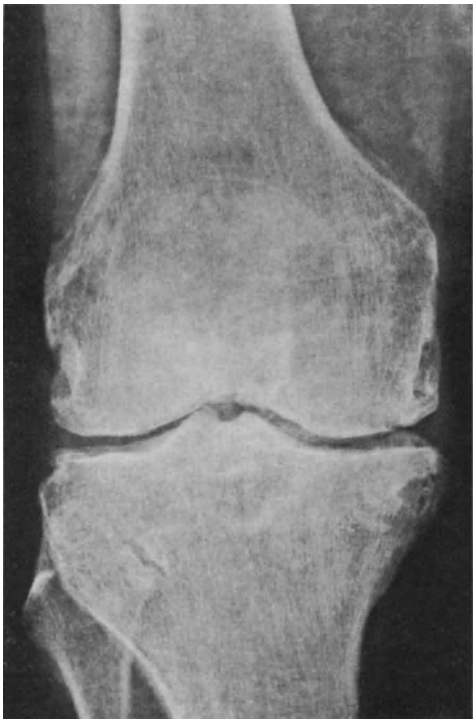

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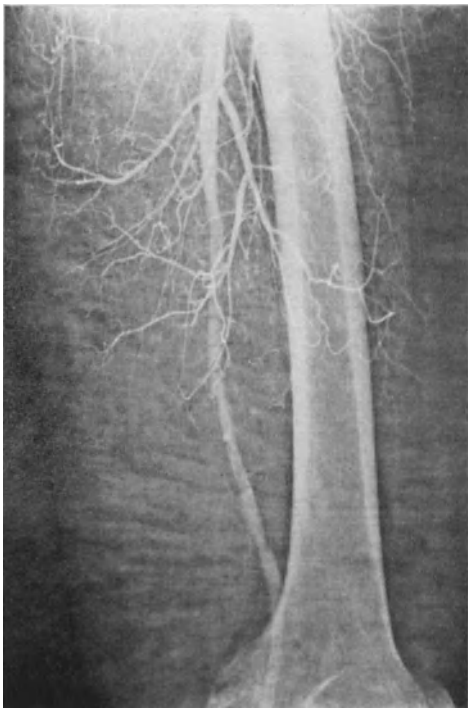
Fig. 35**n.** Half a year later the patient's knee gradually improved. Anterior and lateral views of the knee. The lytic area is refilled. Radiographic signs of arthrosis deformans



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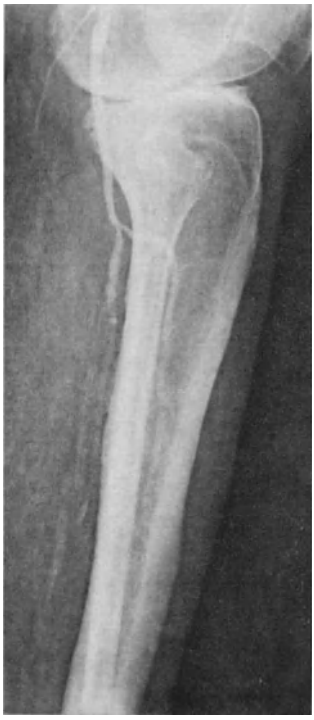


Figs. 35o and **p.** Femoral angiography. Multiple stenoses of the superficial artery and its segmental occlusion at the level of Hunter's canal. The posterior and tibial artery and the peroneal artery were obstructed, blood flow was observed only through the anterior tibial artery and the dorsal artery of the foot. Accordingly, the dorsal artery of the foot was well palpable

bearing plantar surfaces; as confirmed also by the measurements of Stokes et al. (1975). The earliest change is recurrent callus formation despite regular foot care. In most cases, a painless, sharply outlined, slightly oozing ulcer is visible (Figs. 38c, 39i, and 43i). Rarely, the ulcer develops on the dorsal surface of the foot or on the inner surface of the toes (Fig. 43j). Ulcer and bone destruction often develop simultaneously and on the same site. A typical example is when the metatarsal capitulum above the ulcer is affected (Fig. 39i). In our experience the two processes may change independently from each other, and the healing of the ulcer does not indicate recovery from osteopathy (Fig. 43). This phenomenon also supports the necessity and importance of regular radiographic checkup in this disease.

The ulcer can become a source of infection. Simultaneous occurrence of gangrene and DOAP is not a rarity either. Several cases are known in which DOAP developed on the partially amputated leg because of gangrene (Fig. 50). The simultaneous occurrence is no indication for extending the amputation; on the contrary, as will be discussed later, the concomitant occurrence indicates a better prognosis.

Deformities (Group IV)

In the advanced stage of DOAP, the soft tissues, deprived of their supporting structures, undergo contraction; consequently, the structure of the foot changes and severe deformities develop. According to Harrison and Faris (1976), the deformities of the foot are due to diabetic neuropathy and atrophy of the small foot muscles, making weight-bearing impossible.

Due to the destruction of the tarsometatarsal joints, the foot shortens, the medial contour becomes smooth, and the arch of the foot collapses. As a consequence, a "cubic"-shaped foot and "rocker-bottom sole" develop. The ankle joint may also be considerably deformed: due to the overlapping of the bones the leg becomes shorter, the foot partially dislocated, and pathologic skin folds appear under the external ankle (Figs. 35k and l). In cases of metatarsophalangeal or interphalangeal forms, contraction of the toes and pathologic skin folds can be observed.

From the above review of clinical symptoms and soft tissue changes, the following practical conclusions should be drawn:

1. When examining diabetic patients, their feet must also be carefully examined.
2. When symptoms listed in Group I are observed, it is advisable to carry out an x-ray examination. For routine purposes, a comparative dorsoplantar radiogram of the feet is sufficient.
3. When symptoms belonging to Groups II and III are found, radiography is obligatory. If the result is negative, regular control is necessary, as these patients are at high risk to develop DOAP.
4. In cases where symptoms belong to Group IV, bone destruction is an obvious finding. x-ray examination often reveals the final stage of the process.

Localization of diabetic osteoarthropathy

Table 18 summarizes literary data and our own findings regarding the localization of DOAP. The classification is somewhat arbitrary, as in metatarsal forms the proximal metatarsal bones are also often affected. When various joints were affected in one patient, these were listed separately; thus, in our series, 41 different localizations were observed in 32 patients.

In 60% of the 330 various localizations, the tarsometatarsal and metatarsophalangeal joints were affected. The tarsus, ankle, and interphalangeal joints were rarely involved.

The proximal parts of the foot were rarely affected in our patients. The interphalangeal form was frequent and, as a matter of fact, not rare as the summarized literary data indicate. Probably, as these changes are not very striking, they often remain unnoticed and are not reported. Other authors mention the involvement of the toes (Gondos 1968, Pogonowska et al. 1967).

Bilateral abnormalities were observed in 4 of our cases. In the literature, bilateral involvement and, sometimes, nearly symmetric localization have also been reported. Thus, in every case of DOAP, comparative radiograms must be made of the feet. This is an agreement with the clinical observation that in one-third of the cases with diabetic foot, both feet are affected (Baddeley and Fulford 1965).

Table 18

Localization of diabetic osteoarthropathy

Localization	Total of reported cases	Miller and Lichtmann 1955	Sinha et al. 1972	Total of literary data	Own data
A	24	1	12	37 (11.2%)	1
T	31	1	47	79 (23.9%)	2
TM	58	9	34	101 (30.6%)	1
MP	54	8	34	96 (29.1%)	21
IP	15	2	—	17 (5.2%)	17
Total	182	21	127	330 (100%)	42

A = ankle; T = tarsus; TM = tarsometatarsal joints; MP = metatarsophalangeal joints; IP = interphalangeal joints.

The stages and radiological symptoms of diabetic osteoarthropathy

DOAP can be diagnosed only by x-ray examination. The responsibility of the radiologist is enormous due to the discrepancy in the majority of cases between the patients' complaints, clinical findings, and the radiologically determined condition.

Numerous x-ray signs have been described. These are generally discussed according to their type or their order of frequency. Fochem (1971), Pogonowska et al. (1967), and Reinhardt (1974*a*,*b*) have attempted to give a classification of these symptoms.

Based on the x-ray picture and localization, most authors discuss two forms under various designations. Boulet et al. (1954) speak about pseudotabetic and pseudogout forms. Others

use the terms hypertrophic (sclerotic) and atrophic (mutilating) forms. More recently, Kraft et al. (1975) used the latter. They divided DOAP into the Charcot (destructive) and the bone-absorption (mutilating) type. The former occurs rarely and is typically found on the tarsus. It is considered to be true form of Charcot arthropathy. The latter is typically localized in the metatarsophalangeal joints.

However, the question arises as to whether such a sharp distinction between the two forms is justified; the two forms may turn into each other, they may occur concomitantly, and blood circulation also influences their development. A very important fact to be considered is that whichever type develops, the basic process is always osteolysis. If the lysis is associated with secondary sclerosis, the hypertrophic form will manifest itself. Precise analysis will reveal osteolysis in these cases, too (Figs. 35i and j).

Scarce and contradictory data are available regarding the duration and stages of DOAP. According to Gondos (1968, 1972), the intermittent course of activity is the most characteristic feature. Norman et al. (1968) analyzed the rapidly progressing cases. Rathery (1968) attempted to classify the single stages. According to this, neurological symptoms occur in the first stage, pathological fractures and lysis occur in the second, and a "cube" foot develops in the third. In 1966, Eichenholtz described three stages: (1) development, (2) coalescence, and (3) reconstruction.

Based on the follow-up of our patients and analysis of literary data, we distinguish three stages in the course of DOAP. (Diabetic osteoarthropathy cases see Figs. 35–53.) In the majority of cases, these stages are clearly separated, sometimes they may overlap, but even then they are distinguishable on the basis of their characteristic x-ray signs (Table 19).

Table 19

Radiological signs of diabetic osteoarthropathy

1st stage Initial symptoms	Circumscribed porosis Subluxation Cortical defect
2nd stage Progression	Osteolysis Fragmentation Fractures Periosteal reaction
3rd stage Healing	Filling of cortical defect "Pointed" bone Development of arthrosis deformans Ankylosis Total restitution

Stage I—Initial symptoms

Osteoporosis

Osteolysis can undoubtedly develop also in bones of normal density. However, in our experience lesions leading to rapid and severe destruction are characterized by circumscribed porosis at the onset of the process (Figs. 35b, 37a, and 42a). Lysis appearing in the vicinity

of porosis is a sign of progression (Figs. 43a–c). Osteoporosis is often subchondral (Clouse et al. 1974) and gradually turns into osteolysis. Actually this is not true osteoporosis, but an increased dissolution of lime salts (halisteresis); nevertheless, in the clinical sense, it is regarded as osteoporosis.

This form of osteoporosis must not be mistaken for diffuse osteoporosis of the foot. The latter is due to circulatory disorders, particularly frequent in diabetes. Circumscribed osteoporosis may be considered the radiographic sign indicating the onset of DOAP.

Cortical defect

This is a radiographic sign often mentioned and discussed in detail by Pogonowska et al. (1967). The cortical defect may persist without clinical symptoms for a long time, in other cases it may turn into osteolysis. In our experience, these two forms are characteristic of the onset of DOAP and can be differentiated by their radiographic features.

Type a starts as a juxtaarticular cortical defect in bones of normal density. A sharply demarcated, often half-moon shaped bone defect of variable depth develops. Most often the head of the 1st metatarsus is involved, but other metatarsal heads may also be affected (Figs. 45a,b, 47a, and 50). Multiple defects may occur, too. The fine cortical defects occurring in the metatarsophalangeal joints also belong to this group. Figures 35m and n display a "gnawed-out" defect on the tibial condyle.

These lesions have a good prognosis. They may persist for years without any progress; moreover in some cases the defects are gradually filled out (Figs. 35n, 38b, and 42a, b). In our patients, this type of defect never turned into osteolysis. However, the classic form of DOAP frequently developed in the adjacent joint (Figs. 43 and 47).

Type b is not a real cortical defect, but rather a cortical rupture, an osteolysis starting near the cortical area. An irregularly shaped defect with an indistinct border appears in porotic surroundings, gradually turning into osteolysis (Figs. 35f, 37a,b, and 41).

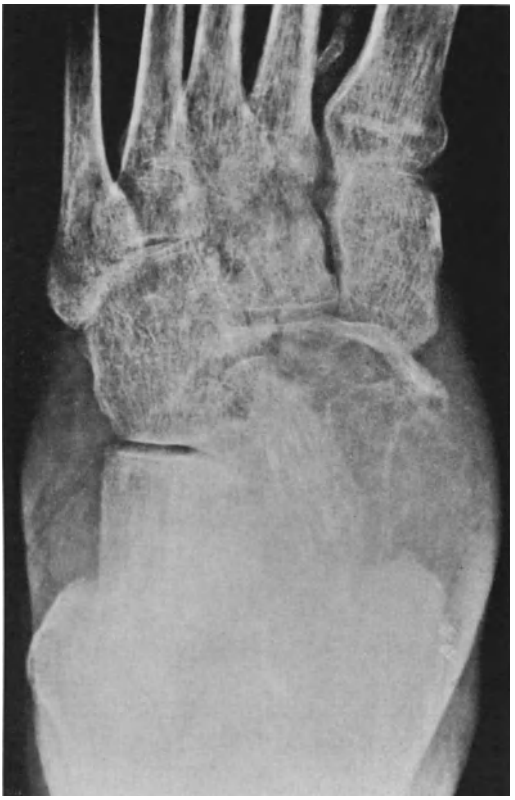
Subluxation, dislocation

This radiographic symptom has often been described. Sinha et al. (1972), for example, report finding this symptom in 27 of their patients. According to our observations, this symptom may occur in all three stages of the disease. The cause, x-ray picture and significance of the three forms vary.

Type a, developing in the otherwise intact joint, is an extremely important sign, as it warns about the risk of DOAP. In one patient (Case 8), it was clinically confirmed that bone destruction developed in the place of a 2nd metatarsophalangeal dislocation observed earlier (see Group II clinical symptoms) (Figs. 39a and b). Cortical defects are often accompanied by subluxation (Figs. 45 and 47). Sometimes, subluxation occurs in the joint adjacent to the osteolysis (Figs. 40b and c).

Type b. At the stage when osteolysis occurs, the bones are often dislocated due to the destroyed articular surfaces (Figs. 35c, 37c,d, 39a,b, 41, 46a,b, and 47b,c).

Type c. In the course of recovery, the residual deformities are partly due to dislocations (Figs. 35e, 37g, 44, and 48).

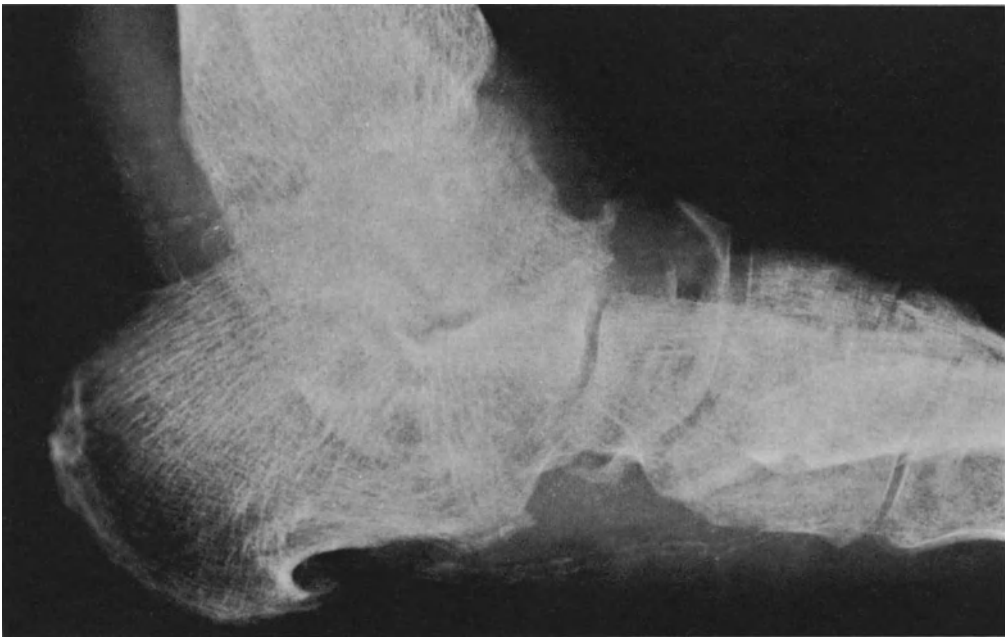


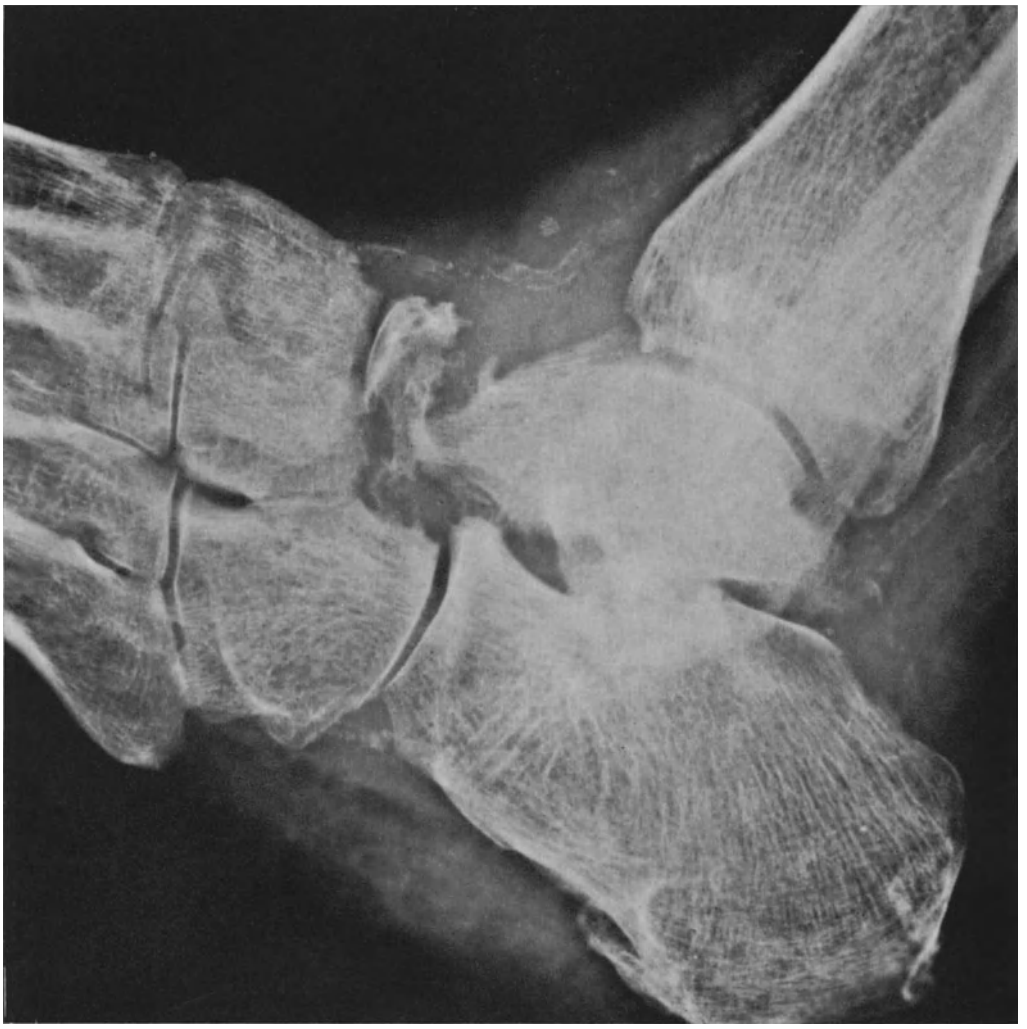
a

Fig. 36. Radiographs of Case 2. His diabetes was poorly controlled with oral antidiabetic drugs instead of insulin. The patient's feet were swollen. A slightly painful ulcer developed on the dorsal surface of the foot, through which bone fragments and pus came out

Figs. 36**a** and **b.** Two-directional picture of the tarsus with an enormous deformation of the navicular bone. Only the distal margin of the bone remained intact, the other parts underwent erosion. Destroyed anterior part of the talus. Extensive sclerosis in the arteries of the foot. Thick exostosis on the plantar surface of the calcaneus

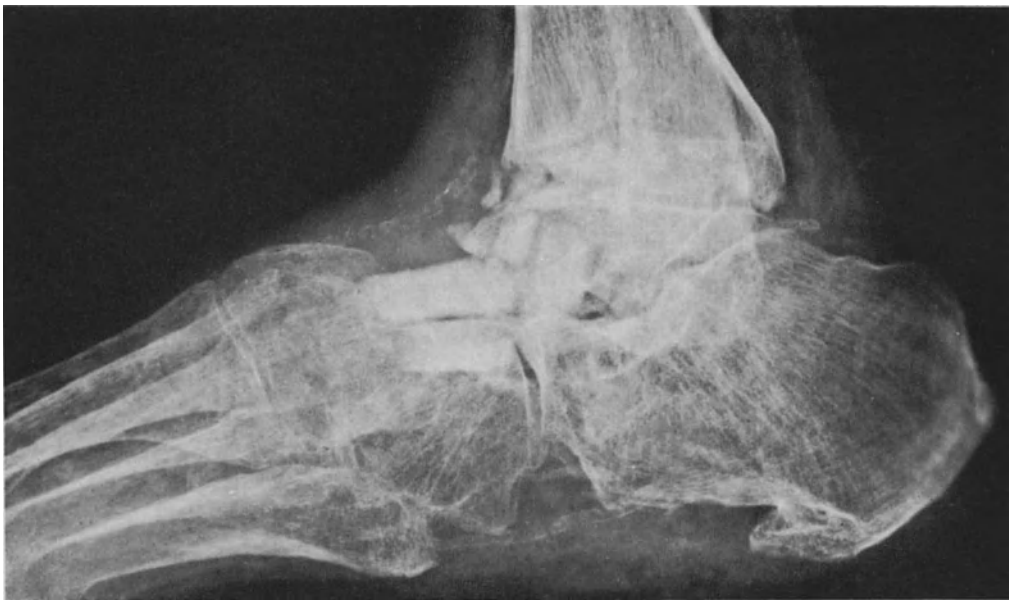
b





c

Fig. 36c. One month later, slight regression in the affected bones, with demarcation and sclerosis developing. No significant alterations in the soft tissue

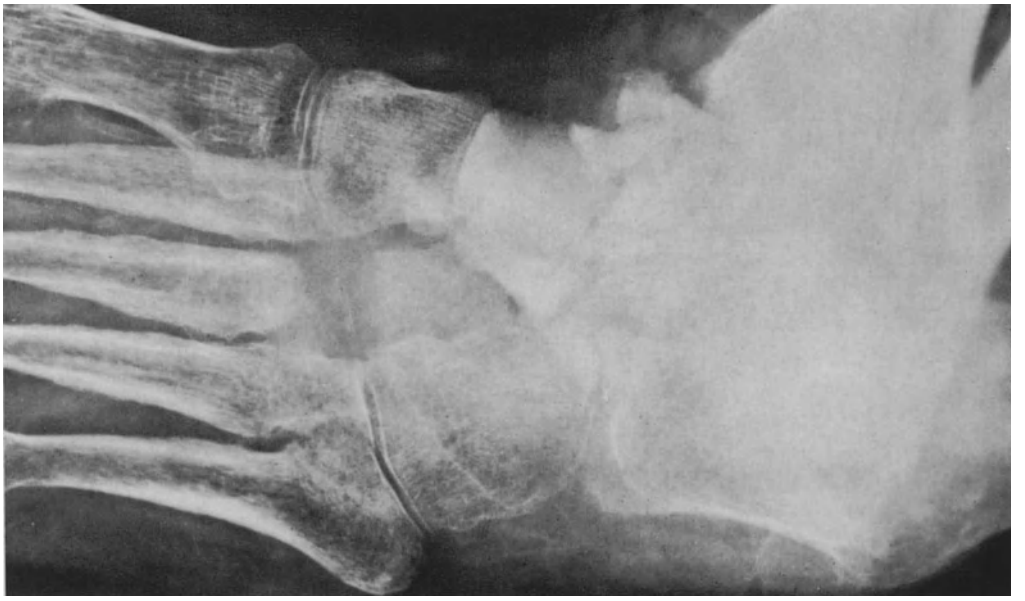


d

Fig. 36**d.** Three weeks following operation, the destroyed parts of the tarsus were removed and bone grafts implanted. The latter appear as intensive shadows between the porotic bones of the foot

Fig. 36**e.** Six weeks later, marked erosion of the cuneiform bone. Osteolysis in the corresponding metatarsals with severe damage of the tarsometatarsal joint

Fig. 36**f.** Six months later, significant regression. Deformed bones of the 3rd metatarsal joint with traces of osteolysis. The patient is capable of resuming work using a working splint



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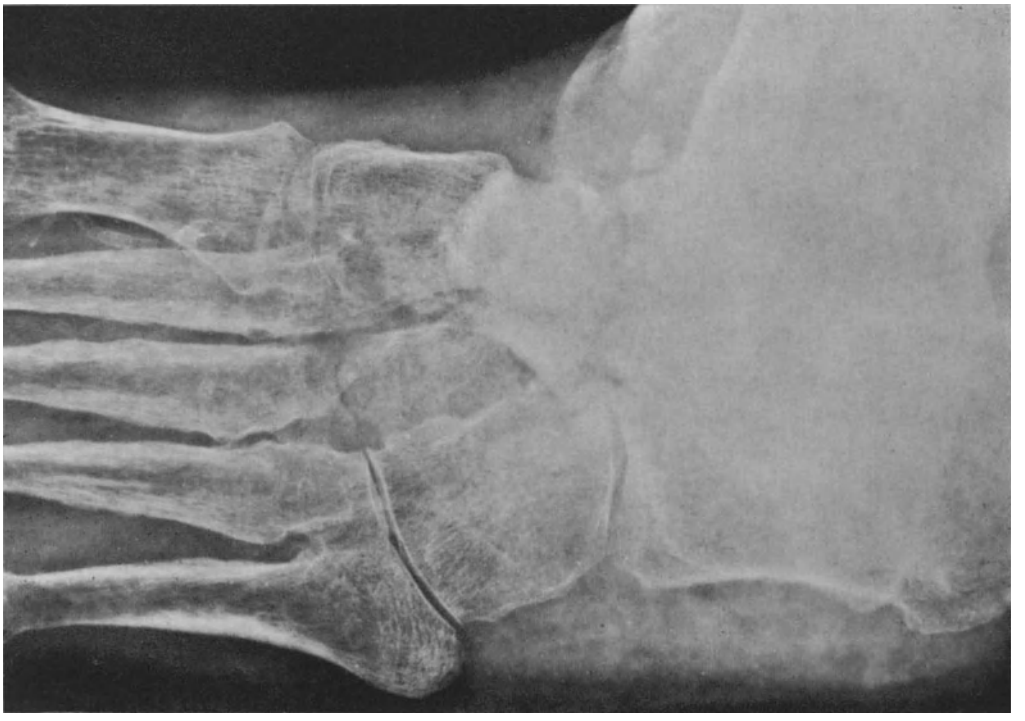


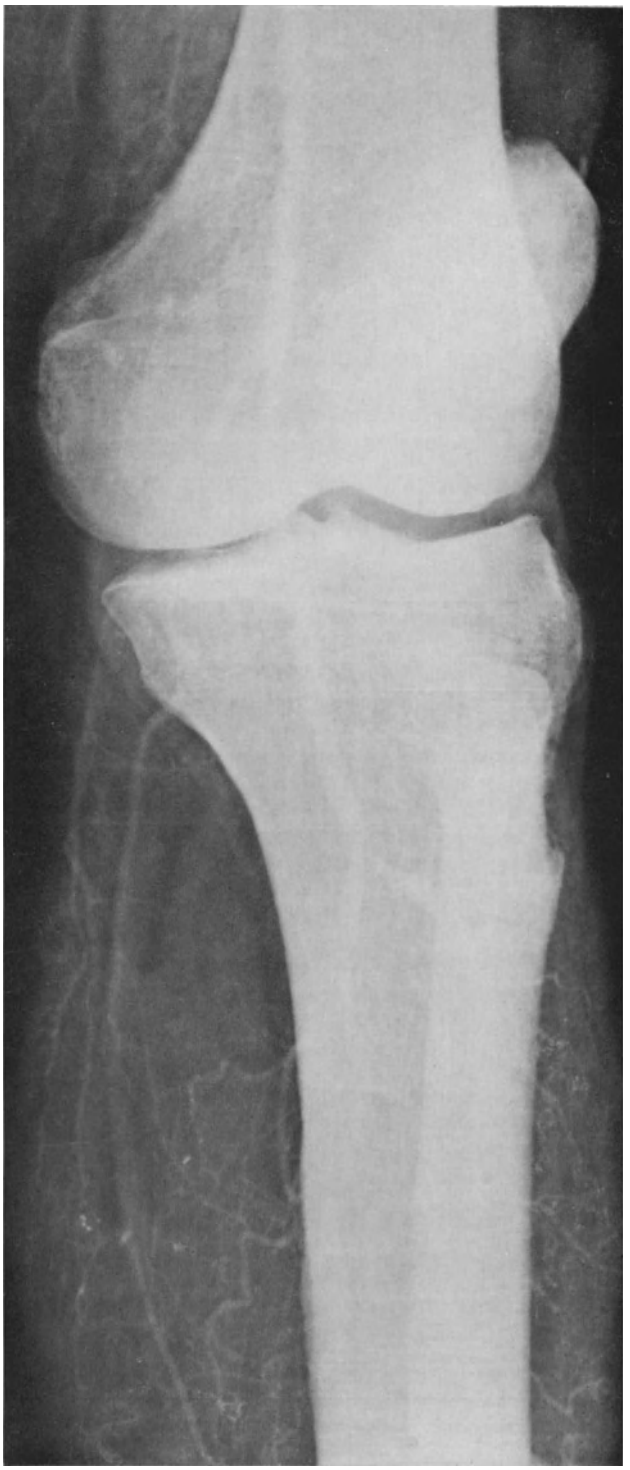
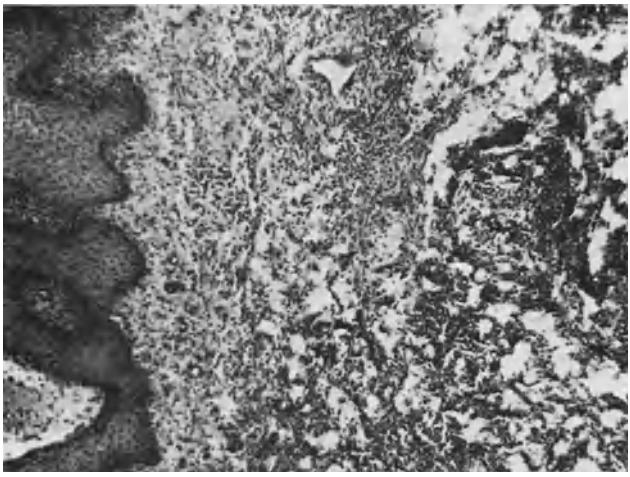


Fig. 36g. Femoral arteriography. The contour of the superficial femoral and popliteal artery is uneven due to severe diabetic macroangiopathy (arteriosclerosis). Narrowed anterior tibial artery. Occluded posterior tibial and peroneal arteries

g

Fig. 36**h**. Histological sample: abscess in the subcutaneous connective tissue separated from the bone



h

Fig. 36**i**. Part of the removed bone. Abnormal bone structure. The trabecules are fragmented and vascularized, and fibrous connective tissue, in some parts cystic areas are visible between the trabecules. No signs of inflammation

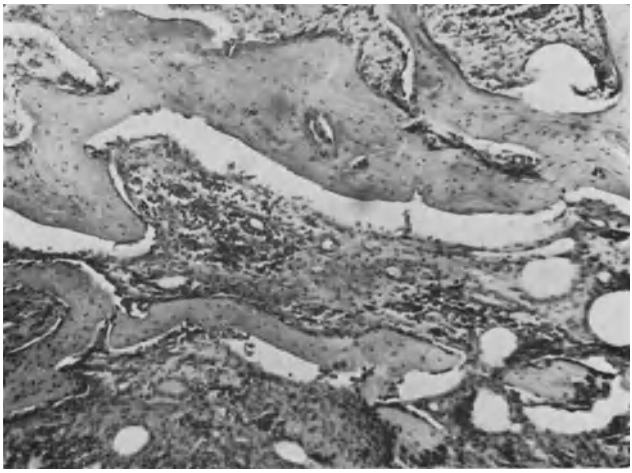


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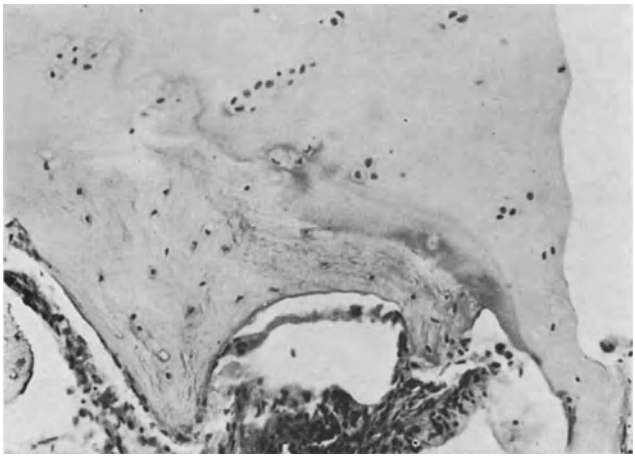
Fig. 36**j**. Degenerated cartilage from the surgical specimen. Swollen, aggregated chondrocytes (haematoxylin and eosin, magnification × 60)



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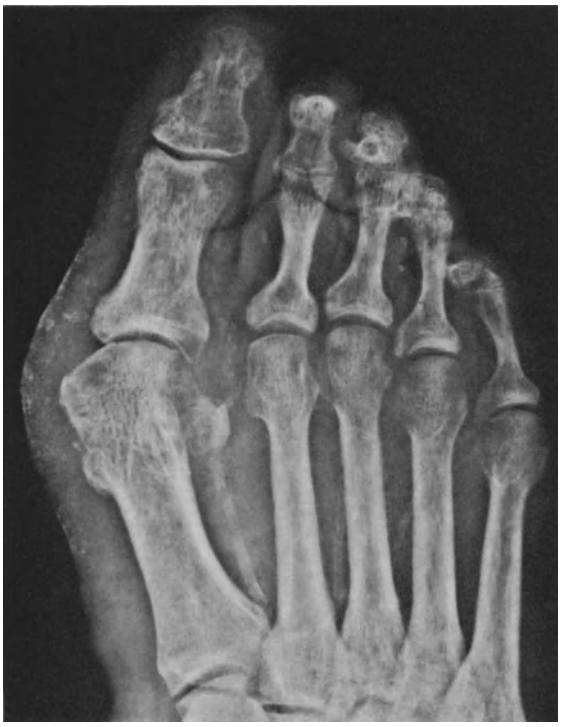

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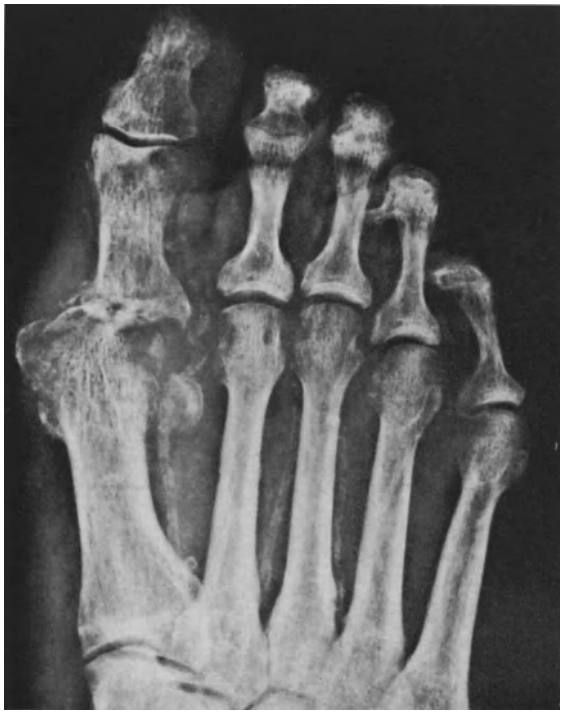
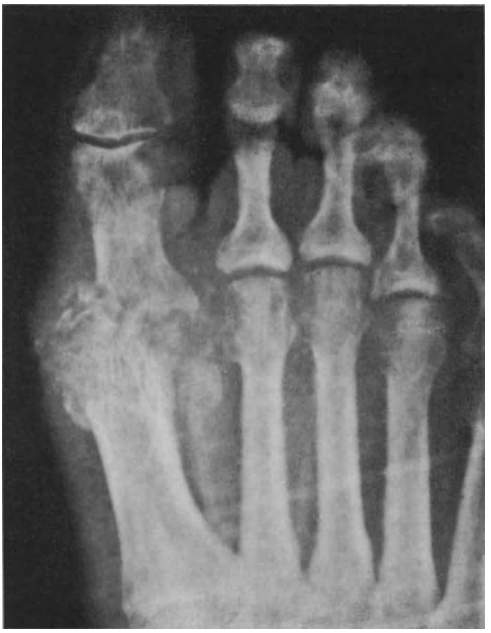


b

Fig. 37. Case 4. An inadequately treated diabetic. Before admission to our department, oral antidiabetic treatment proved to be unsuccessful. The patient's feet were swollen adjacent to the head of the 1st metatarsus, and he complained of mild pain

Fig. 37**a.** Demineralization of the lentil-sized area in the medial part of the 1st metatarsal head. The cortical area in the external part of the head is indistinct, its zone is porotic. In the lateral marginal corner of the proximal phalanx, rarefaction has started. Calcified arteries of the foot

Fig. 37**b.** Four weeks later, significant progression. Subluxation of the 1st toe in the metatarsophalangeal joint. The articular space can barely be seen. Extensive demineralization in the medial part of the head, disrupted cortex in some places and fragmentation of the head above. Rarefaction extended also to the lateral side, and a triangular bone fragment has been separated. Osteolysis extended to the basis of the proximal phalanx as well



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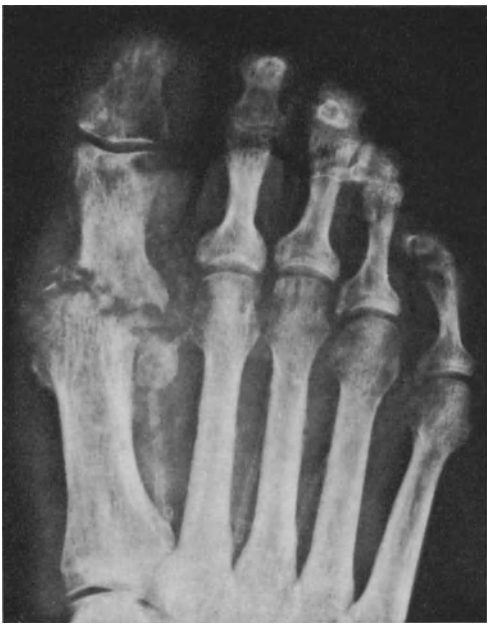

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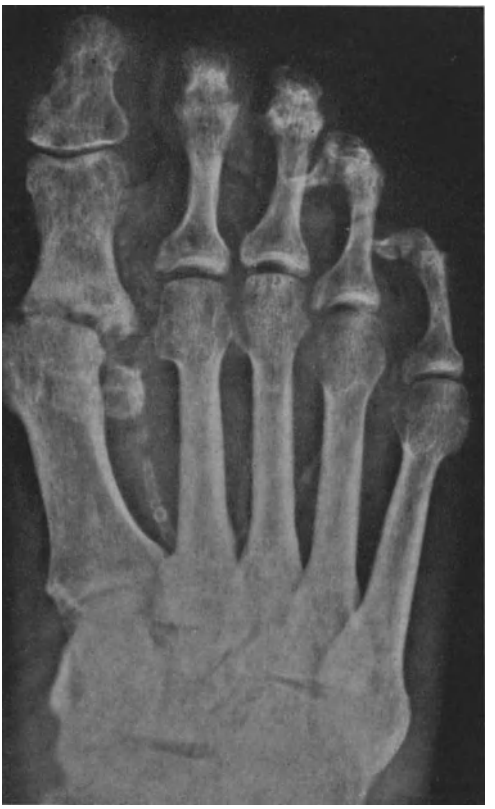


Fig. 37**c.** Two weeks later, complete destruction of the first metatarsophalangeal joint. Fragmented articular surfaces

Fig. 37**d.** Two weeks later, certain signs of regression. Smaller fragments with sharper contours

Fig. 37**e.** Continued healing, with the resorption of fragments and sclerotic margins on the articular surfaces. No ankylosis. Moderate subluxation

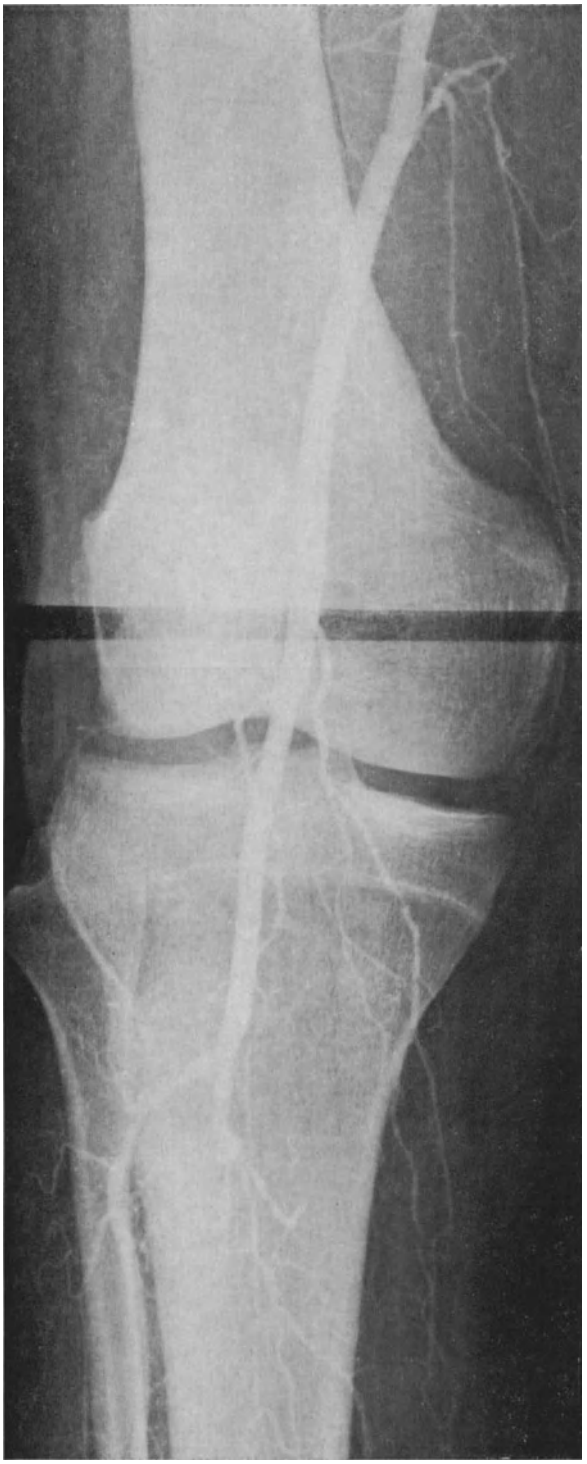
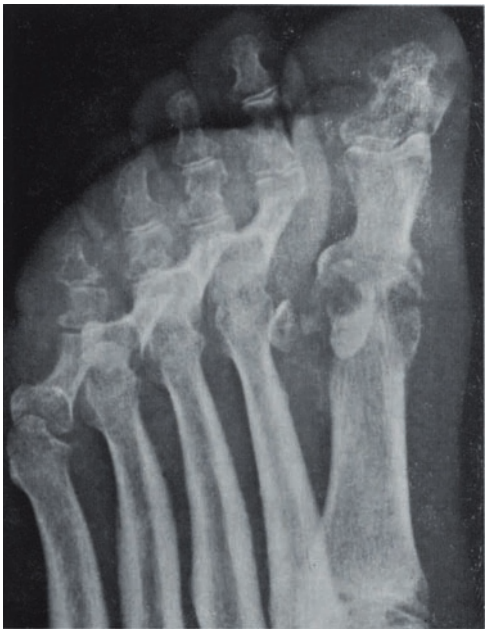


Fig. 37**f.** Arteriography. Severe degenerative changes. Uneven contour of the superficial femoral artery at the level of Hunter' canal due to arteriosclerotic plaques. Well-filled popliteal artery and anterior tibial artery, but the latter is deformed and narrowed. Occluded posterior tibial and peroneal arteries



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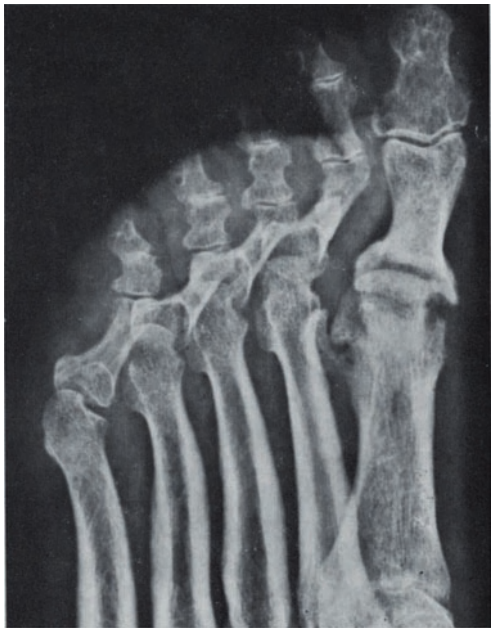

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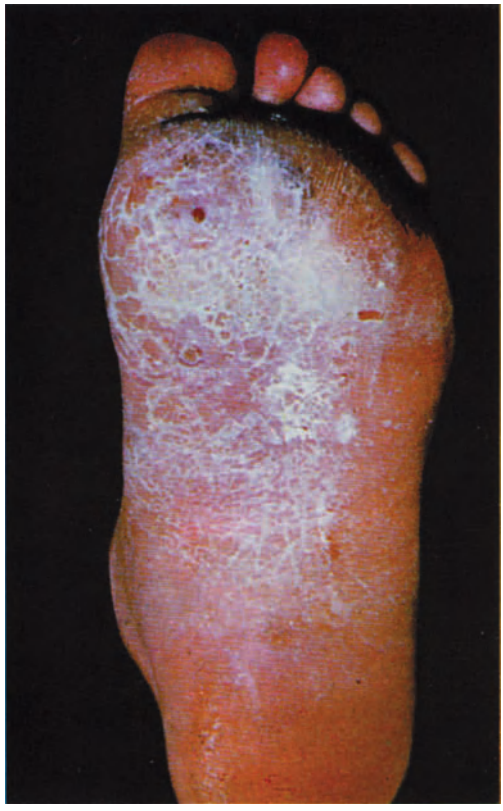


Fig. 38. Case 5. On the foot of the patient treated with combined oral antidiabetic drugs a deep plantar ulcer with sharp margins developed below the head of the 1st metatarsus

Fig. 38**a.** Lateral view of the foot near the articular surface of the head of the 1st metatarsus. Bone defects with sharp margins on both sides, resembling gout

Fig. 38**b.** The patient was started on insulin. The plantar ulcer healed as a result of conservative management. Eight weeks later, improvement of the bone process is visible. The cortical defects have become smaller and have refilled

Fig. 38**c.** Plantar ulcer in the stage of recovery

Stage II—Progression

Osteolysis

This is the most important symptom of DOAP, which includes two basic types: destructive and mutilating forms. According to Fochem (1971), these are only radiological terms; others assume blood circulation of the leg or weight-bearing to play a role in the development of the various forms.

At this stage, the area around the involved joint becomes swollen and sometimes even painful (see Group II clinical symptoms). Often the first radiogram is prepared at this stage and this explains why many authors consider osteolysis the first sign of DOAP.

The x-ray picture of osteolysis is variable, depending on the localization of the lesion. The articular surfaces are soon destroyed. A marked *fragmentation* (Fig. 35c) is characteristic, the area around the destroyed bone becoming irregularly sclerotic. The destroyed bones collapse into one another, or the adjacent intact bone sinks into the destroyed spongiosa (Figs. 35g and h). An enormous deformity may develop. The resorption of the fragments (Fig. 35d) indicates the onset of recovery.

Figure 36 demonstrates an entirely different form. The spongiosa of the navicular bone has almost disappeared, and only the cortical border has remained intact. In this case bone fragments are discharged through a fistula. This presents a differential diagnostic problem, all the more as signs of inflammation occur also in the soft tissues. Postoperative histological examination proved the inflammation to be independent from the bone process (Fig. 36h).

Figure 37 demonstrates destructive osteolysis of the short tubular bones. The gradual fragmentation of the first metatarsal head is visible. Further, dislocation of the toe and extension of the fragmentation to the basis of the phalanx can be observed. The articular space disappeared, having been filled with bone fragments, and the joint has been disrupted (Figs. 37c–e).

Fragmentation is an important process of destruction (Figs. 35c, 37c, 39a,b, 43a,b,f, 47, and 49). The epiphyses are fragmented and the joint space is filled with tiny fragments with obscure contours. The joint appears to be destroyed. Even in these cases recovery may take place.

In typical cases of the *atrophic form*, the process progresses from the periphery to the bone marrow. The controversial hypotheses concerning this mechanism will be discussed in detail later.

Principally, the metatarsal bones and the phalanges are affected. The distal part of the bone is destroyed, and the rest of the diaphysis tapers off. Broadening of the concave member of the joint is visible. The convex member becomes pointed, and a characteristic irregular sclerosis develops (Figs. 39f, 43d,e, 44, and 48). The latter x-ray signs indicate healing.

The atrophic form occurs more often in relatively young people with intact blood circulation. Changes affecting the distal phalanges are infrequent in diabetes; atrophic processes were only rarely encountered in these bones (Figs. 41 and 43). Acroosteolysis typical of scleroderma never develops in diabetics. Often the form of osteolysis cannot be exactly determined.

Fractures

Due to the relative insensitivity to pain, the so-called "spontaneous" fractures are relatively frequent in DOAP, particularly in the circumscribed porotic areas. In our patients, fractures were always associated with osteolysis. We observed fractures on the bases of the 1st metatarsal (Fig. 47), on the 2nd metatarsal (Fig. 39f), on the 3rd and 4th metatarsal bones (Fig. 41), and on the medial ankle (Fig. 35c). The latter two were transient forms between fracture and fragmentation, termed "microfracture" in the literature.

Opinions often differ concerning these fractures. Johnson (1967) found that neuropathic fractures play a major role in initiating or increasing joint disease. Osteolysis has been reported to follow fractures localized in the proximal part of the foot (Sinha et al. 1972). Several cases have been described when severe neurotrophic fractures developed in diabetic neuropathy, which were not followed by osteolysis. However, these are not considered to be DOAP cases. Muggia (1965) observed this type of fracture on the crural bones, and De Leeuw et al. (1974, 1975), Coventry and Rothacker (1979) reported bimalleolar and calcaneous fractures. Recently, El-Khourg and Kathol (1980) described neuropathic fractures in six diabetic patients, four of them had unusual avulsion fractures in the posterior tubercle of the calcaneus.

Giesecke et al. (1978) reported seven cases of 2nd tarsometatarsal joint fracture dislocation. Only one of these was secondary to trauma. Traumatic fracture dislocation of this joint is uncommon, due to the stability of the tarsometatarsal joints. The other six patients had diabetic peripheral neuropathy. This type of fracture may be one of the manifestations of peripheral neuropathy.

Periosteal reaction

Pogonowska et al. (1967) have rarely observed periosteal reaction and in their opinion this is not a symptom of DOAP. According to others (Clouse et al. 1974, Epiney and Medenica 1970, Sinha et al. 1972, etc.) and in our own opinion, this is a frequent and significant symptom. Velickov and Djanov (1971) grade the periosteal reaction as layered, multilayered, and irregular forms.

Periosteal reaction may appear simultaneously with extensive osteolysis on the crural bones (Fig. 35c), on the metatarsal (Figs. 39a,b, and 43c), and phalanges (Figs. 39c,f, 41b, 42, and 47c). In the advanced stage of DOAP, the periosteal reaction transforms into a thick periosteal calcification, resulting in an almost even thickening of the affected metatarsus (Figs. 40b and c). In other cases, a thick, irregular periosteal and parosseal calcification develops leading to joint deformity and eventually to hypertrophic arthropathy (Figs. 35e, g, and h).

According to some observations, a periosteal reaction may develop without bone destruction in the diabetic foot (Medenica 1970, Velickov and Djanov 1971). In our opinion, these are not true periosteal reactions, but periosteal appositions due to the predisposition to diffuse hyperostosis, as has already been discussed in the previous chapter. The manifestations of these two different forms of periosteal processes are very similar. For example, in Fig. 39a, periosteal reaction is visible on the 3rd metatarsus, but periosteal appositions are observable on the other metatarsal bones. The latter are of no practical importance, and are not considered as symptoms of DOAP.

Changes in the soft tissues

Soft tissues adjacent to the osteolysis should always be carefully examined, in the first place, for the demonstration of collection of gas. Nonclostridial gas-forming infections may occur in diabetic and nondiabetic patients, but are significantly more frequent in the former group. Gas-forming infections are particularly frequent on the feet of diabetics (Kahn 1974). In vitro, aerobic and anaerobic bacteria form carbon dioxide, lactic acid, and hydrogen from glucose. Obviously, the same process may take place in the tissues, leading to gas formation.

On the x-ray picture gas bubbles appear as negative shadows. Such a negative shadow is always a certain sign of infection. In these cases, the bone lesion is accompanied by a gangrenous soft tissue process, and amputation is generally inevitable (Fig. 46).

Stage III—Healing

Adequate treatment or spontaneous remission terminates progression and recovery begins. Stages II and III are not sharply separated; generally the beginning of recovery may be noticed by careful analysis of the radiograms. Due to the "silent" clinical picture, sometimes only x-ray examination reveals the healed bone process.

The radiographically observable forms of healing are the following:

Type a. The sharply bordered cortical defect is gradually refilled (Fig. 38b). Figures 35m and n demonstrate a healed knee joint of this type. Finally, a picture resembling arthrosis deformans develops. According to Reinhardt (1973*c*), painless monarthrosis in the lower extremity is always suspicious for underlying diabetes.

Type b. In forms associated with fragmentation, first the number of fragments is reduced; the contours become distinct and finally they are resorbed (Fig. 35). Recovery may occur even in cases of extensive destruction. Figure 37 demonstrates such a case: the fragments have been resorbed, the subluxation of the fingers has decreased, and irregular sclerotic margins are visible on the healed articular surfaces.

Type c. Total recovery after an apparently total destruction of the metatarsus or the phalanx occurs only in diabetics. Several authors have reported such cases (Jacobs 1958, Lithner 1976*c*, Pogonowska et al. 1967, Steinberg 1971). Nevertheless, these patients often undergo amputation because the x-ray signs are so alarming. The explanation for this type of recovery seems to be that the bone is not totally destroyed, only the calcium salts are dissolved, while functionally intact osteoblasts remain, eventually restoring the bone structure.

A nearly total destruction of the 4th metatarsus and toe is visible in Figs. 43a–c, that recovered with only a slight defect of the metatarsus and a tapering off in the proximal phalanx (Fig. 43d). Figure 39 demonstrates a similar process on the 3rd metatarsus. In our case, the reconstruction of tarsometatarsal process also belongs to this group (Figs. 36e and f).

Type d. The destruction of the distal parts of metatarsal and phalangeal bones often results in "pointed bones." Gondos (1972), who studied the pathomechanism of this process, rejects the concept of concentric atrophy, and instead proposes callus calcification in the site of the destroyed bone. Figures 39 and 43 seem to support this concept. Figures 43e, 44, and 48 demonstrate the pointed shape of metatarsal and phalangeal bones. This leads

to their dislocation and slipping onto one another. A characteristic picture ("pencil in the cup", "mortar and pestle" and "balancing pagoda") develops.

Type e. Ankylosis of the joints is not characteristic of DOAP. However, for cases in which the radiograph reveals ankylosis, as for example in Fig. 43e in the 2nd metatarsophalangeal joint, an associated infection is assumable. Figure 35e shows partial ankylosis between the detached fragments of the internal ankle and the distal articular surfaces of the crural bones. The deformity visible is due to the dislocation of the bones (clinical symptoms, group IV) (Fig. 44).

Vascular lesions in the lower extremities

The susceptibility of diabetics to arteriosclerosis is well known. Arterial disease was observed in 42% of the diabetics over 50 years old (Semple 1953). The difference between arteriosclerosis of diabetics and nondiabetics is merely quantitative. In diabetics, sclerosis starts on the small arterial vessels, and extends centripetally, usually involving blood vessels of the leg (Table 20). The incidence of sclerosis increases parallel to the duration of diabetes.

Table 20

Radiological signs of arteriosclerosis in nondiabetics and in diabetics

	Nondiabetics	Diabetics
Intima sclerosis	+++	+++
Media sclerosis (Möckenberg's type)	++	++++
Occlusion of the deep femoral artery	+	++
Occlusion of the crural arteries	++	++++
Extensive sclerosis, multiple occlusion	++	++++
Progression	Centrifugal	Centripetal

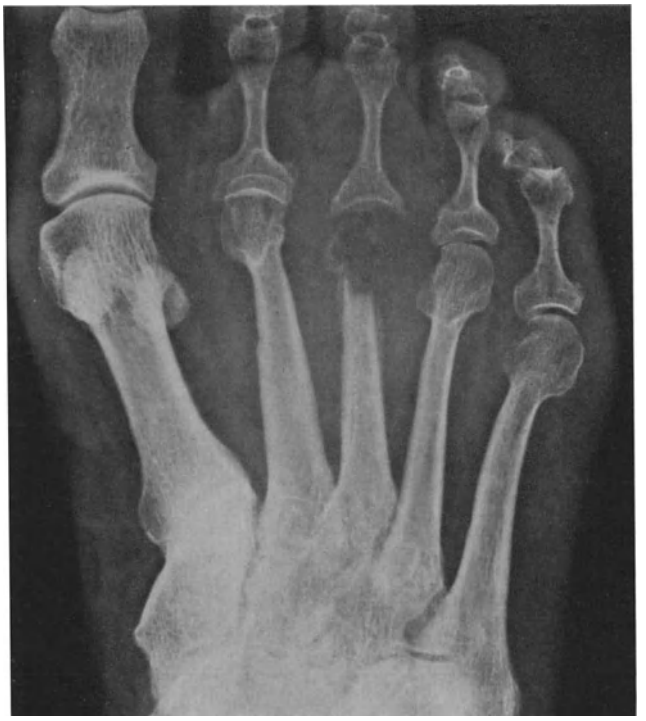
Vasosclerosis was found in 53% of diabetics who had been ill for over 10 years (Christensen 1972), and in 94% of those affected for over 25 years (White 1971).

We examined the radiograms of the legs of 418 nonselected diabetic subjects over the age of 40 (Table 21). Vasosclerosis was detected in 122 (29.3%) of the 418 patients.

Table 21

Occurrence of vasosclerosis in the arteries of the leg

Age (years)	Control group		Diabetics not requiring insulin therapy		Diabetics requiring insulin therapy	
	No. of cases	Arteriosclerosis	No. of cases	Arteriosclerosis	No. of cases	Arteriosclerosis
40–49	95	0 (0%)	31	6 (19.4%)	35	7 (20%)
50–59	91	6 (6.6%)	38	10 (26.3%)	70	17 (24%)
60–69	74	8 (10.8%)	63	22 (34.9%)	98	21 (21%)
<70	52	18 (34.6%)	27	17 (63%)	56	22 (39.5%)
Total	312	32 (10.3%)	159	55 (34.6%)	259	67 (25.9%)



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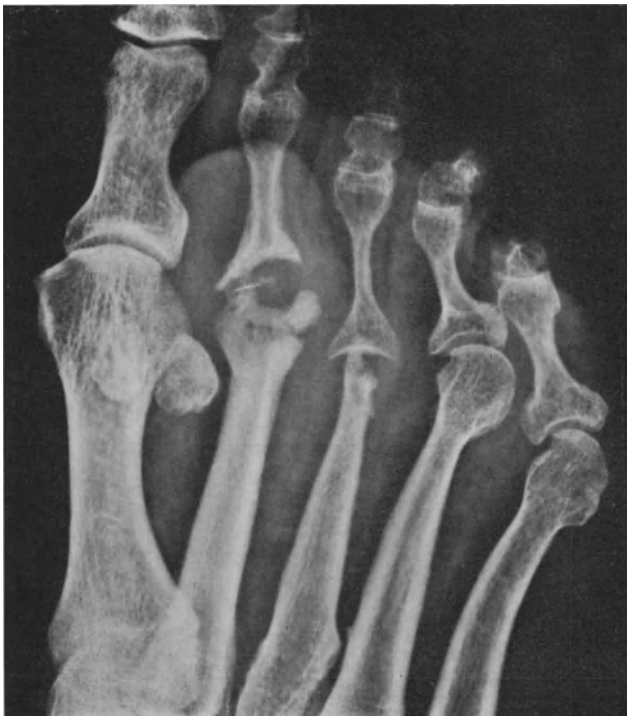
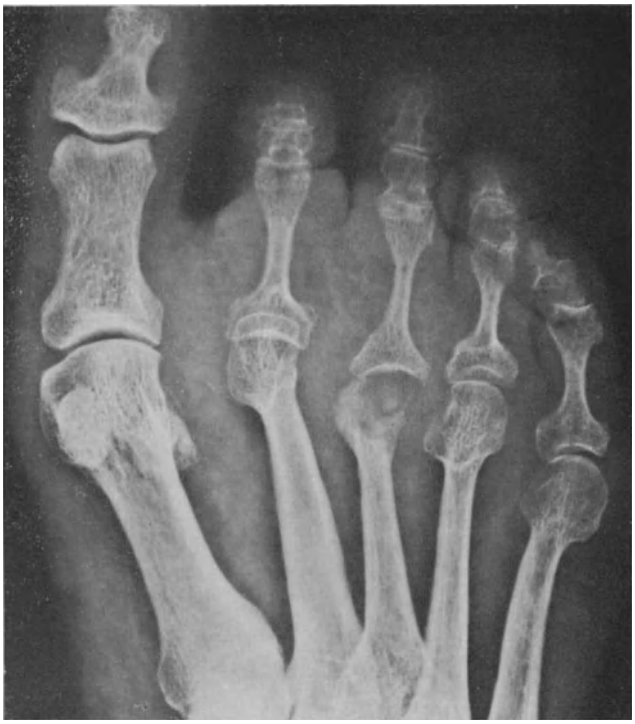


b

Fig. 39. Case 8. An undisciplined patient who did not keep to the dietetic and therapeutic prescriptions. Glucose excretion and blood glucose levels were extremely varied. The patient was admitted to our department due to plantar ulcer and bone destruction

Figs. 39**a** and **b.** Anteroposterior and lateral views of the foot. Dislocation in the 2nd metatarsophalangeal joint. The 3rd metatarsal head is almost totally destroyed, with a few irregular fragments only. The lysis extends towards the diaphysis, with adjacent periosteal reaction. Subluxation of the 3rd toe, lysis extends to the plantar marginal corner of the base of the proximal phalanx

Figs. 39**c** and **d.** As a result of bed rest and adequate insulin therapy the plantar ulcer healed, the bone process also improved. Anteroposterior and lateral views, eight weeks later: signs of bone regeneration with a smaller lytic area, part of the head, however, is still missing. Traces of lysis only on the base of the proximal phalanx



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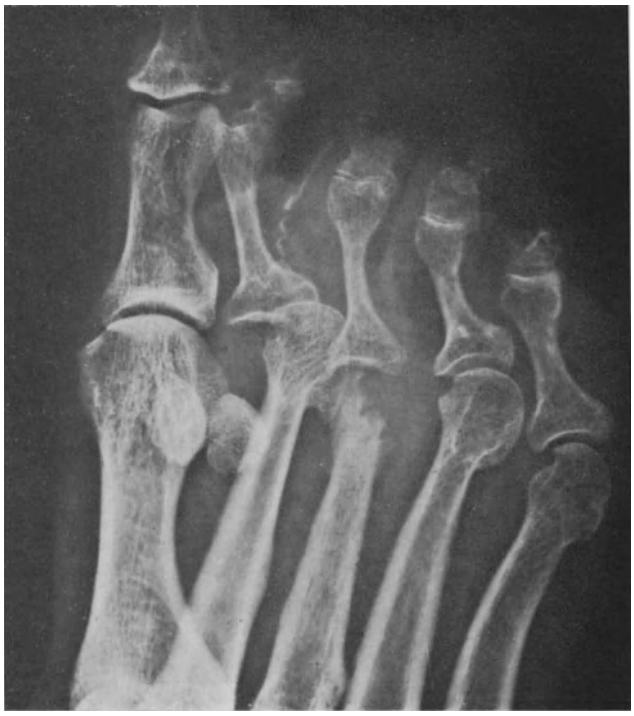

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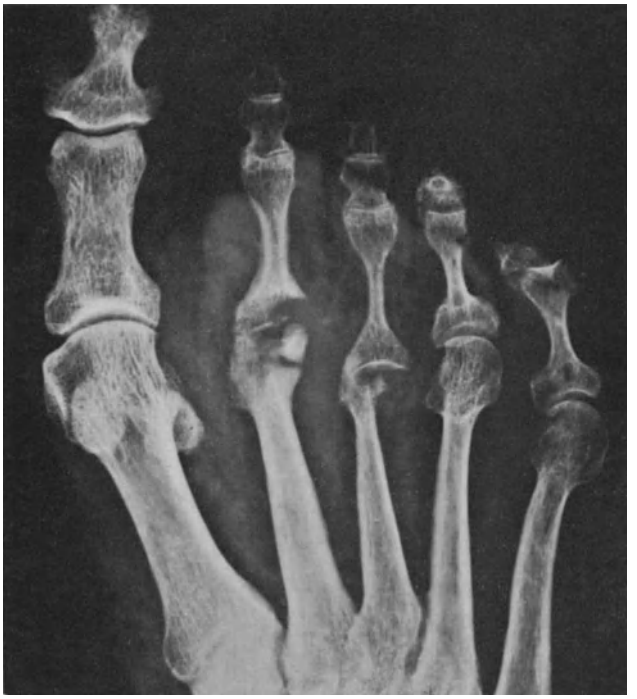

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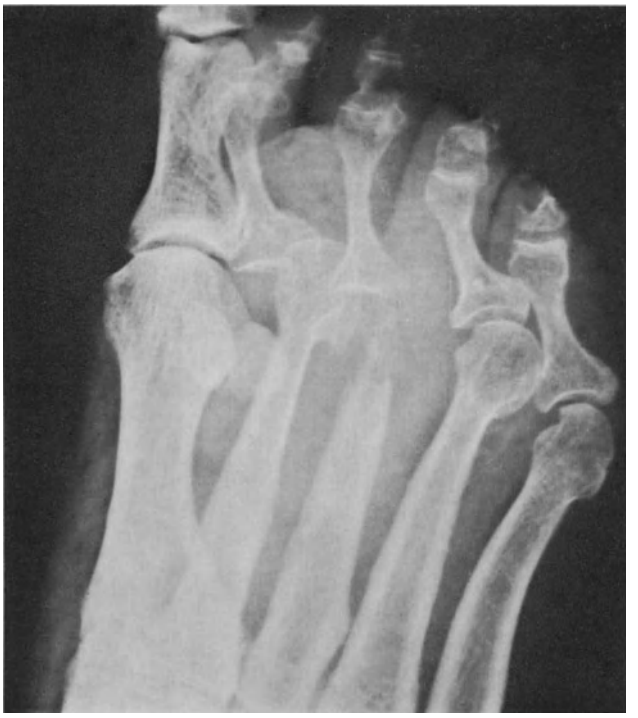
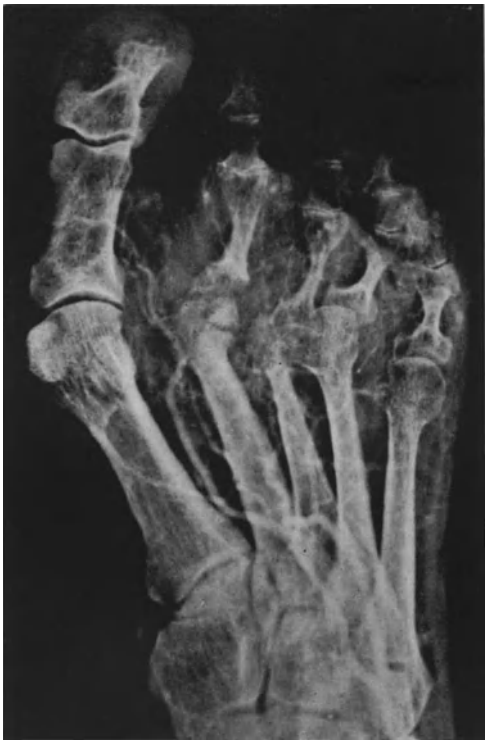
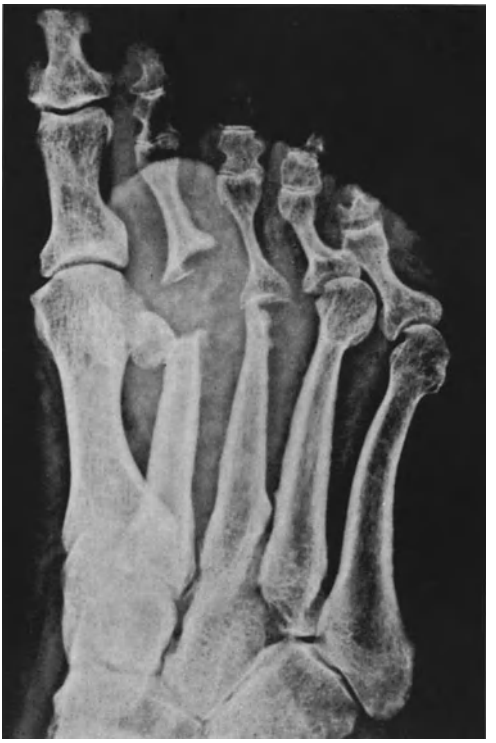


f

Figs. 39e and **f.** The patient returned to our department 8 months later because of recurrence of plantar ulcer. The distal part of the 3rd metatarsus is narrowed. No fragments, intact articular surface of the proximal phalanx. Partly recovered bone structure. The lesion is healed with a deformation of the metatarsal head. However, in the 2nd metatarsophalangeal joint, where up till now only dislocation had been observable, a severe destruction developed. The metatarsal head and a large part of the base of the proximal phalanx were destroyed with a few fragments. Periosteal reaction on the diaphysis of the proximal phalanx and on the metatarsals near to the lysis. The decalcified line of the head above the lytic area indicates a pathologic fracture





g **h**

Fig. 39**g**. Angiography. Intact circulation of the foot. Slight hypervascularization of the small arteries near the osteolysis

Fig. 39**h**. The metatarsal head was resected. Thereafter, the plantar ulcer healed

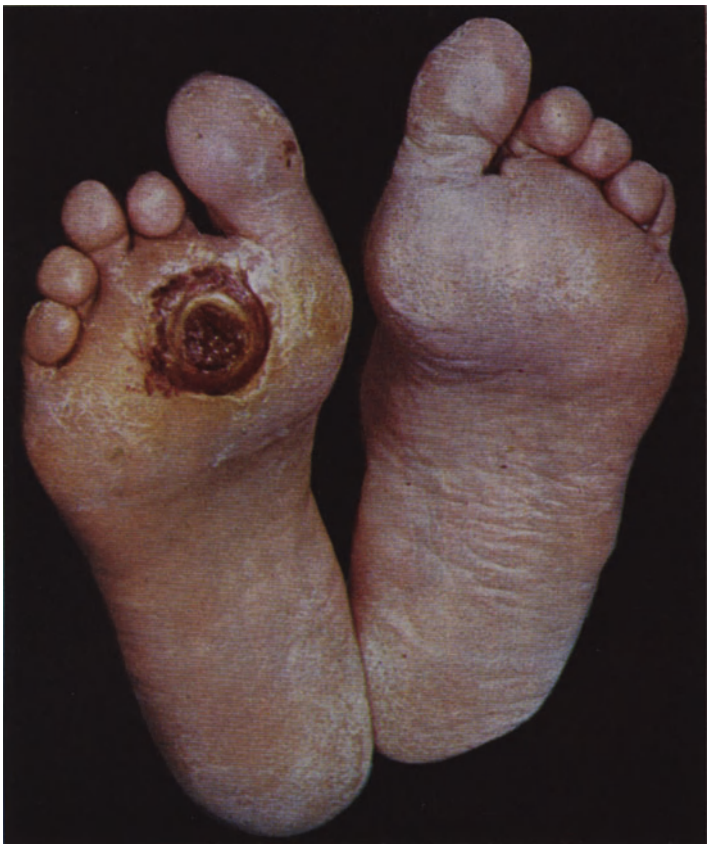
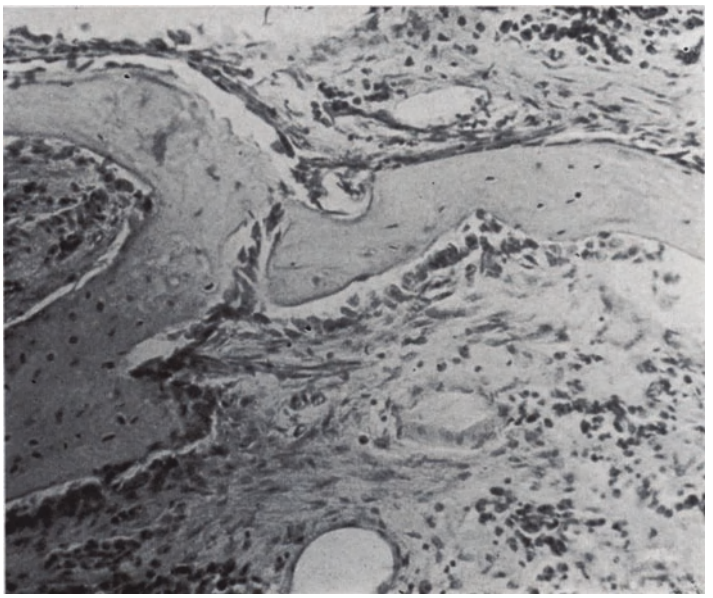


Fig. 39i. Neuropathic plantar ulcer in the area of the 2nd metatarsal bone with a simultaneous bone process

i



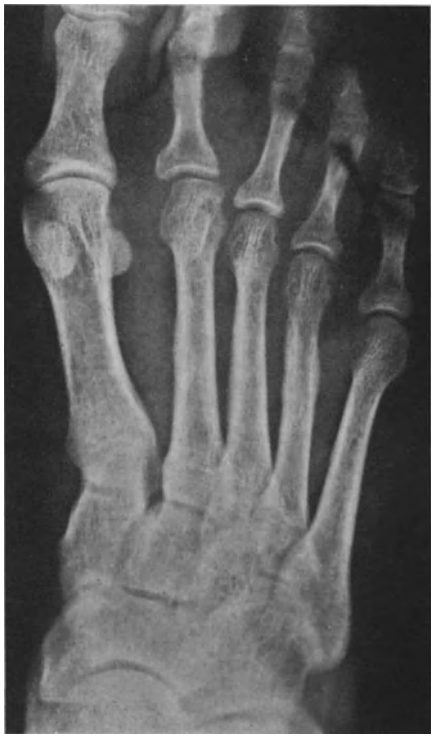
j

Fig. 39j. Histological picture of the removed bone. No signs of inflammation or abnormal bone structure. The area between the trabecules is filled with fibrous, vascularized connective tissue, with hemosiderophages and fibroblast proliferation

Fig. 40. Case 10. The patient was treated at the diabetic outpatient clinic and had well-controlled diabetes

Fig. 40**a**. The patient complained of numbness of the foot, she had no other complaints. Minimal subluxation of the second metatarsophalangeal joint, no pathological signs otherwise

Figs. 40**b** and **c**. The patient returned one year later, on account of progressive retinopathy causing almost complete blindness. The leg of the patient was periodically numb, she had no other complaints. Anteroposterior and lateral views of the foot. The 2nd and 3rd phalanges are dislocated. The 3rd metatarsus is thickened due to periosteal reaction, with a sharply demarcated bone defect in its head. Cystic rarefaction at the base of the proximal phalanx of the 3rd toe



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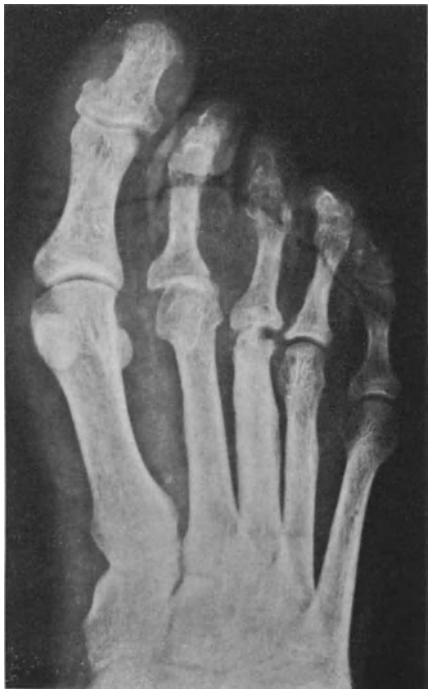

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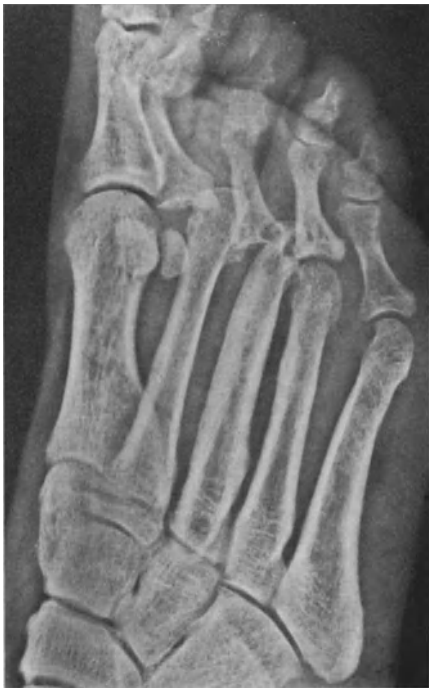

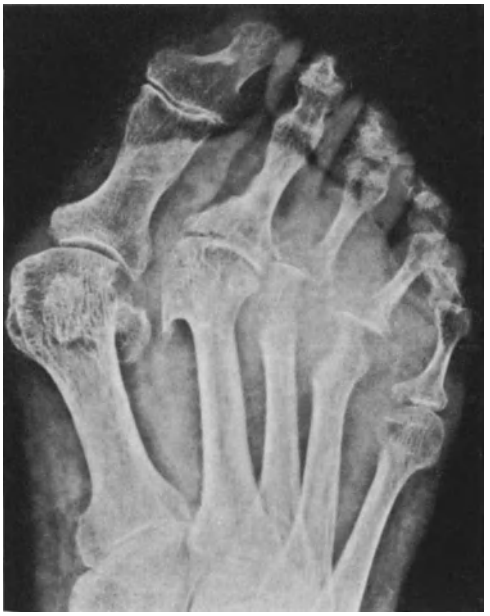

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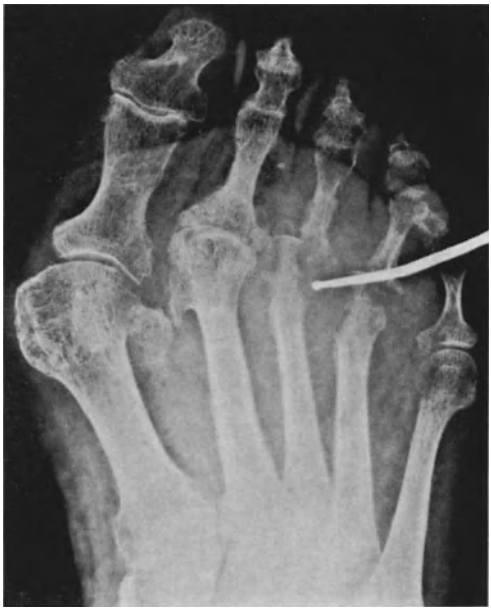

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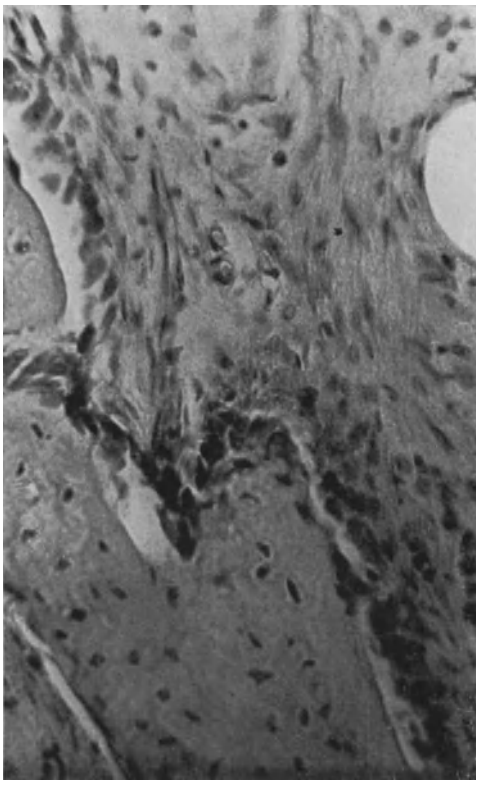


c

Fig. 41. Case 11. The elderly female patient was hospitalized because of plantar ulcer that was followed by the development of inflammation.

Fig. 41**a.** The articular surfaces of the 2nd metatarsophalangeal joint are deformed and widened, the articular space is hardly observable. The medial part of the metatarsal head is elongated assuming an exostosis-like appearance. Presumably these changes are attributable to healed osteoarthropathy. The lacking unguicular process of the 2nd toe also supports this fact. The 3rd and 4th toes are subluxated. Bone defects and circumscribed porosis in the heads of the 3rd and 4th metatarsi. The base of the proximal phalanges of the 3rd and 4th toes are fragmented. A tiny lytic area on the base of the proximal phalanx of the 5th toe

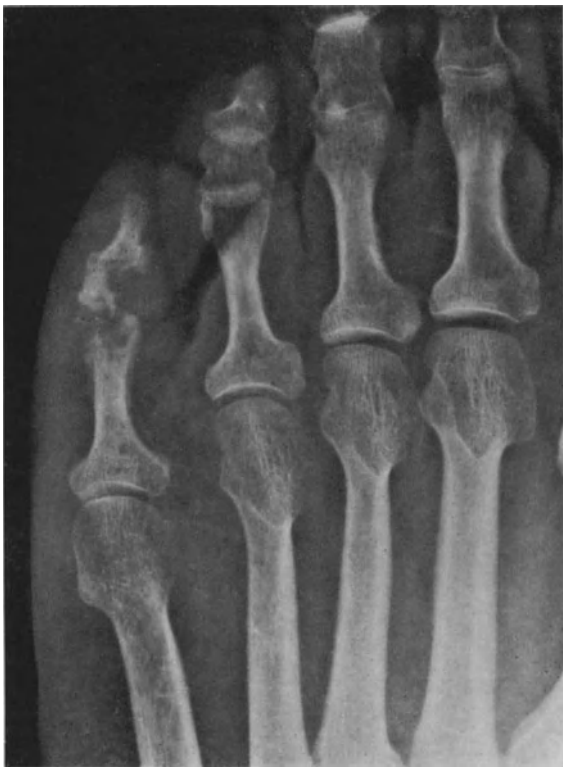
Fig. 41**b.** Three weeks later, further progression. Lysis extends to the diaphysis of the metatarsal bones, and only remnants of the articular surfaces are left. Both proximal phalanges of the 3rd and 4th toes are practically destroyed, the 3rd phalanx is dislocated upward. Marked periosteal reaction on the phalanges. The probe introduced through the ulcer can be followed almost up to the bone

Fig. 41**c.** Amputation. Histological picture of the removed bone. No signs of inflammation. Osteoclastic activity on the surface of the trabecules. Fibrous connective tissue between the trabecules

Fig. 42. Case 12. A poorly controlled diabetic because of his lack of discipline in keeping a diet. His foot was mildly swollen, and the little toe discolored with initial signs of gangrene. Hospitalization was necessitated by increased glucose excretion

Fig. 42**a**. Large bone defects of the phalanges of the 5th toe. Periosteal reaction on the proximal phalanx

Fig. 42**b**. Six months later, improvement of the osseous process. Smaller defects with sharp margins. The patient had no complaints, and no soft tissue changes on the foot



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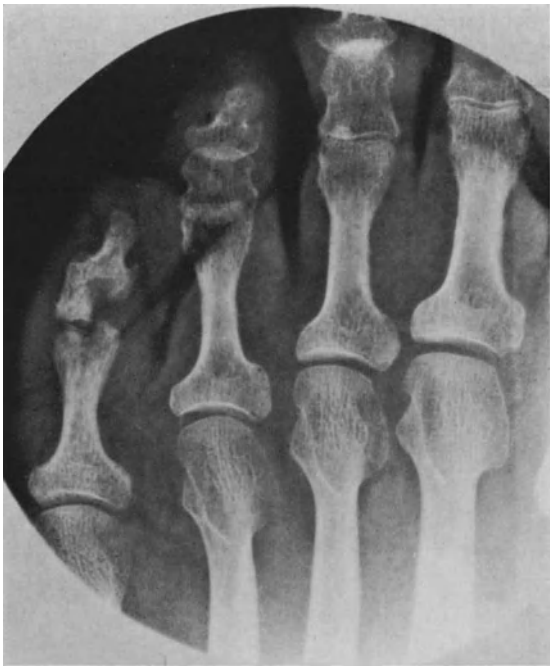

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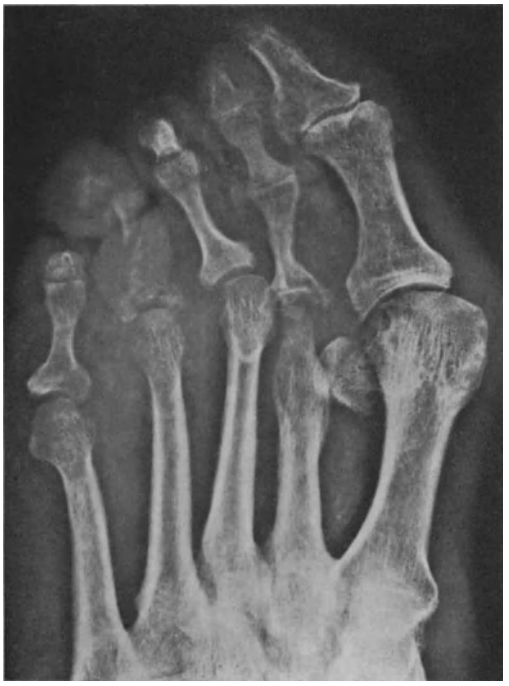
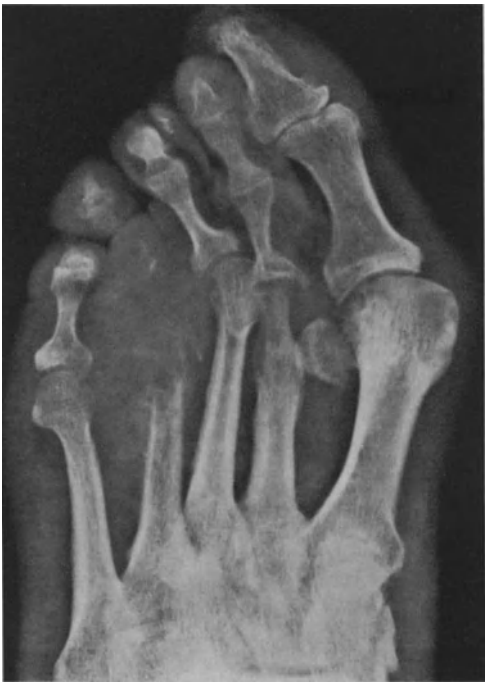


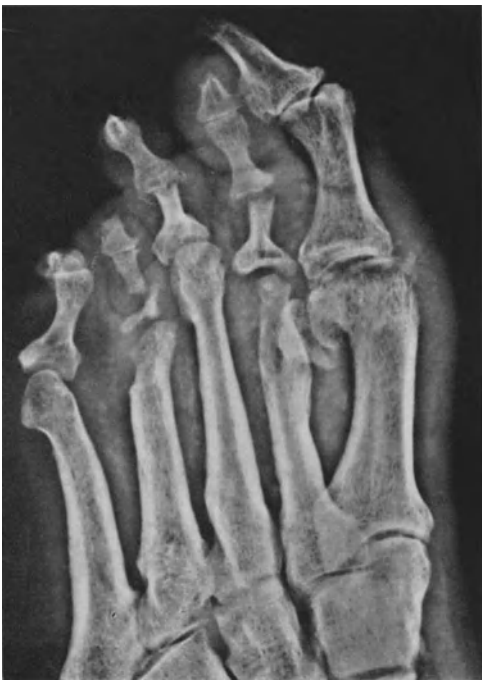
a

b

Fig. 43. Case 15. An irregularly treated, undisciplined patient with severe diabetes. His medical history revealed several recurrences of plantar ulcer and "foot suppuration." The patient was several times hospitalized, where incision was performed. He was admitted to our department because of recurrence of plantar ulcer

Figs. 43**a** and **b**. Lateral and anteroposterior views of the left foot. Both earlier and newer bone processes. Sharply demarcated cortical defect on the dorsolateral part of the 1st metatarsal head. Residual changes of the previous destructive processes of the bones of the 2nd metatarsophalangeal joint. The patient could not remember trauma. The unguicular process of the 2nd toe is narrowed and partly missing. The 4th metatarsal head is porotic, and the bone structure is obscure near the plantar surface. Severe bone destruction in the 4th toe, with dislocated fragments only

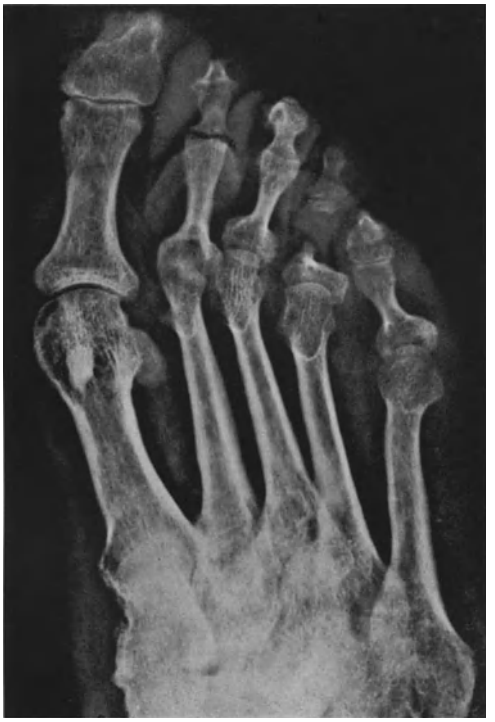


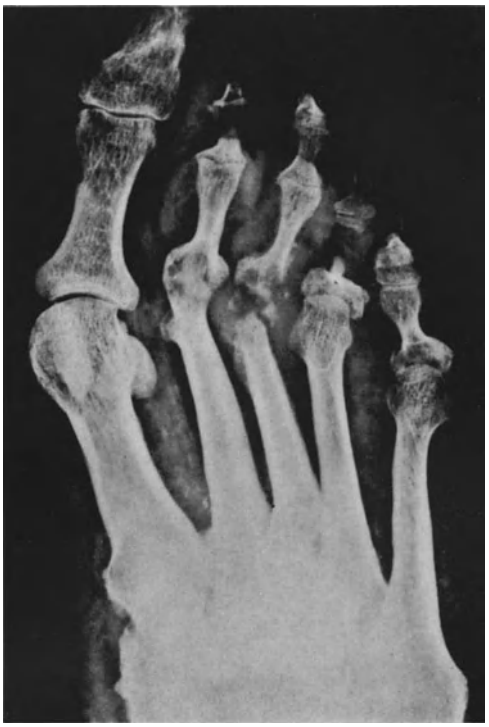


c **d**

Fig. 43**c.** As a result of conservative treatment the soft tissue improved rapidly, and the ulcers healed. The bone process, however, progressed. Six weeks later, no change in the 1st and 2nd metatarsi and phalanges. Entirely destroyed head of the 4th metatarsus; osteolysis extending toward the diaphysis, and periosteal reaction. Virtually complete destruction of the proximal phalanx of the 4th toe, with a narrowed unguicular process

Fig. 43**d.** Five months later plantar ulcer recurred. Nevertheless, the radiogram displays remodeling with return to normal density and almost normal trabecular pattern leaving a moderate deformation and periosteal new bone formation on the 4th metatarsus. The proximal phalanx is pointed, the contours are sharp; the process is healed. On the head of the proximal phalanx of the 2nd toe, initial signs of osteolysis



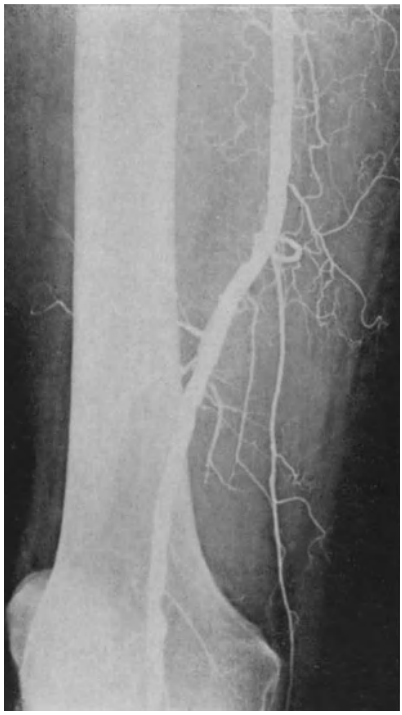


e f

Fig. 43e. Comparative radiographs were made each time of the other foot. The picture did not change. Osseous ankylosis of the 2nd metatarsophalangeal joint. On the proximal phalanx of the 4th toe the distal part of the diaphysis is destroyed; the diaphysis is narrowed and pointed. Part of the proximal phalanx head, however, still remains. The unguicular process of the 2nd toe is missing. These changes are characteristic of healed DOAP. No demonstrable active process

Fig. 43f. One year later, "active" disease has recurred with fragmentation of the 3rd metatarsal head

Figs. 43g and **h.** Left femoral arteriogram. Marked plaque formation in the superficial femoral artery, being multiple stenoses at the level of the abductor canal. The anterior tibial artery and peroneal artery are filled via a marked collateral branch. The anterior tibial artery can be followed up to the distal middle third of the cruris, the peroneal artery can be followed almost until the ankle. The posterior tibial artery is occluded. The plantar arteries are supplied by collateral branches (the examination was performed by Dr. L. Szlávy)



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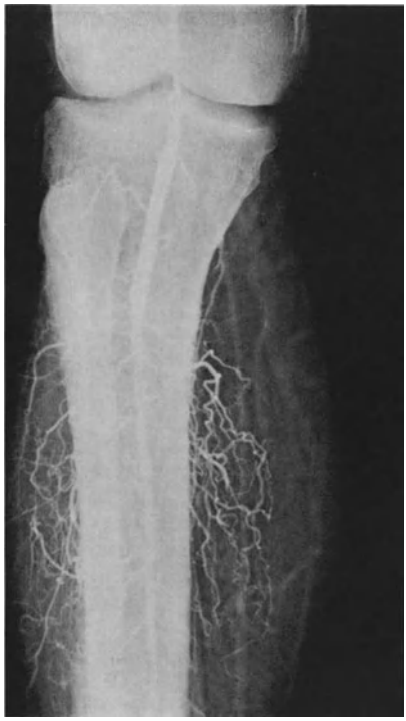

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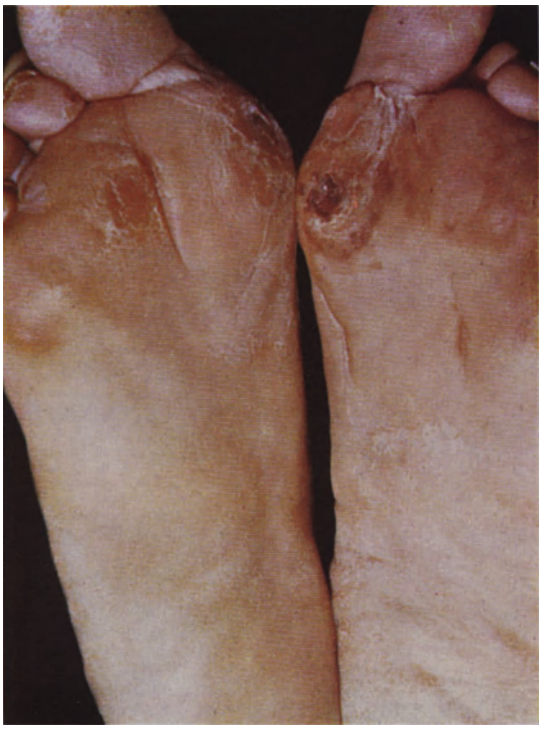

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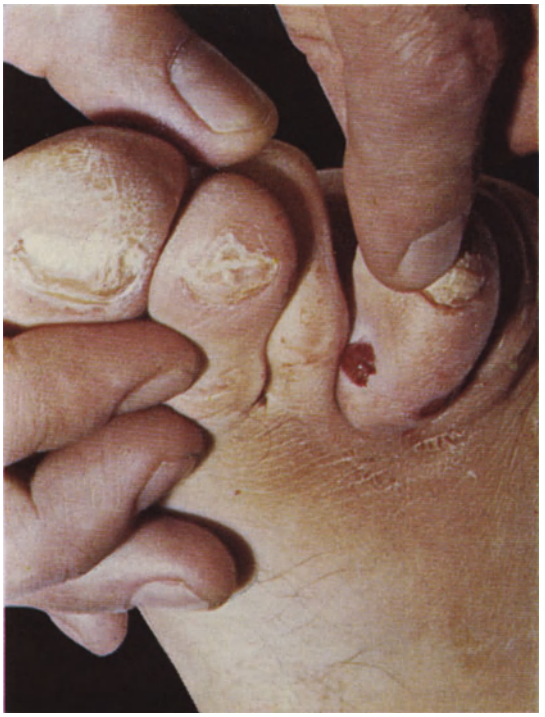


j

Figs. 43i and j. After hospitalization: signs of earlier and new plantar ulcers, callus formations, and incisions on both soles. Fresh, soft tissue ulcer on the medial surface of the 4th toe

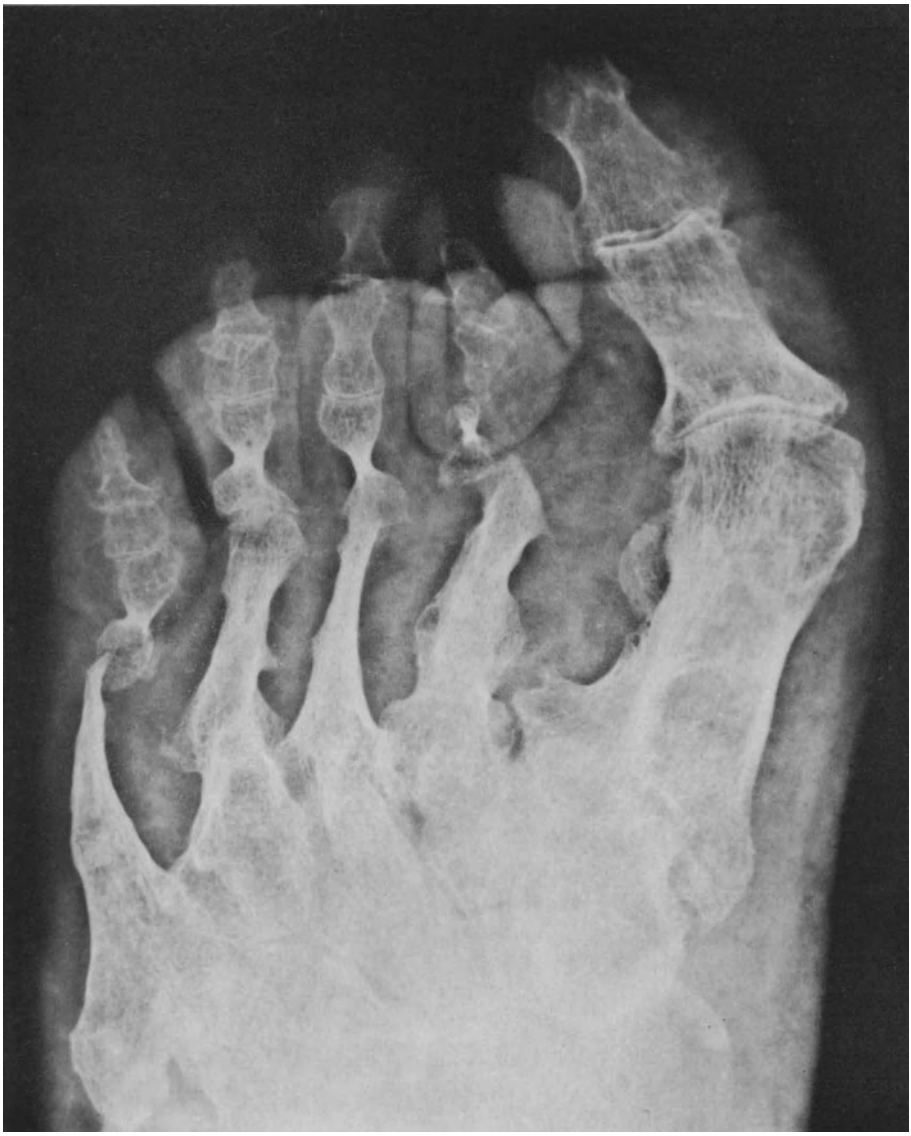


Fig. 44. Deformed and widened foot. Marked periosteal new bone formation and fusion of the tarsometatarsal joints. Penciling of the 2nd and 3rd and especially the 5th metatarsal heads; there is a similar process in the interphalangeal joint of the 2nd toe. The 2nd and 5th toes are shortened due to metatarsophalangeal dislocations. Severe mutilating type of arthropathy

In 312 traumatic patients, vasosclerosis was present in only 32 cases (10.3%). Interestingly, in the control group no such changes were found in the 40- to 49-year age group, while of 66 diabetics of the same age, 13 had vasosclerosis. This means that in patients under 50, calcification of the small arterial vessels occurred only in diabetics.

Two types of vasosclerosis, intima and media sclerosis, are distinguishable by radiography. In the first type, calcification manifests itself in irregularly shaped patches; in the latter (Möckenberg's sclerosis), calcification shows a regular ring shape. The latter is characteristic of diabetes. Christensen (1972) found media sclerosis on the x-ray pictures of the knees and legs in 22 (31%) of 71 diabetics, and in only one of the 25 controls. Ferrieri (1967) examined 250 patients. In 20% of these, he found media sclerosis, in contrast to the 8% incidence in the controls. Neubauer's semiquantitative assay of extension and incidence of media calcification (1971) displayed a significant increase in diabetics when compared to the control group. The incidence of intima calcification was also higher in diabetics, but a significant difference was not established.

There is a general agreement, and data unequivocally prove, that media calcification is frequent in diabetes. However, opinions differ on the importance of this phenomenon. The majority of authors do not attach clinical or prognostic significance to media sclerosis. In such cases, Christensen (1972), by means of the radioactive xenon technique, demonstrated deficiency of the circulation in the involved extremity. Extensively calcified arterial vessels are often found in DOAP, sometimes outlining the whole arterial system of the leg. Sclerosis was detected in half of the patients reported by Gondos (1968) and in 90% of those reported by Sinha et al. (1972). Of our own patients, 21 displayed this phenomenon (Figs. 35–37, 41, 43, 47, and 48).

In diabetics, femoral arteriography often revealed multiple obstruction, especially in the crural arterial vessels (Gensler et al. 1965, Guggenheim et al. 1969, Neubauer 1979). Data regarding arteriographic examinations in DOAP are scarce. Bossi et al. (1961) were the only group to report examinations performed in 5 patients. Extensive degenerative changes were found in most of them. A few negative cases have been detected, which is natural as DOAP may develop even when the blood circulation is intact.

In the early stage Seignon et al. (1974*b*) reported hypervascularization adjacent to advanced bone process. Angiography was performed in 11 of our patients. A normal picture was observed in 2 patients, and a moderately severe arteriosclerosis was observed in 2 others. In one of our cases, adjacent to osteolysis the small arteries displayed caliber changes and a moderate hypervascularization (Fig. 39g). In the other patients, extensive severe vasosclerosis, segmental obstruction was found, particularly in the area of the posterior tibial artery (Figs. 35o,p, 36g, 37f, and 43g,h).

Other radiographic findings

In several case reports hyperostosis of the skeletal system (Gottlob 1957, Rouillard et al. 1961) is mentioned as an accessory finding in DOAP. We made spinal radiograms in 19 of our patients: in 11, hyperostotic spondylosis was confirmed. We also found the type of hyperostosis described in the previous chapter on the calcaneus (Figs. 35 and 36), on the metatarsal bones (Figs. 36, 38–40, and 48), and on the phalangeal bones (Figs. 39 and 42).

Several authors reported signs indicating visceral neuropathy in DOAP. Sexual impo-

tence, diabetic diarrhea, and vesical atony are the most frequent symptoms. Diabetic visceral neuropathy can be revealed by radiography. The lesion is due to the damaged vagal nerve, and the picture resembles postvagotomy conditions. The most important symptoms are disturbances of gastrointestinal motility, and vesical dysfunction.

Are peripheral and visceral neuropathy related? To answer this question, we performed detailed gastroenterologic studies in 12 of our patients. None of them had signs of visceral neuropathy. In our opinion peripheral and visceral neuropathy occur independently. In Case 1, vesical atony developed two years after the healing of the bone process.

Histological findings in diabetic osteoarthropathy

During the early stages of the process the synovial membrane reveals bits of bone and cartilage detritus that have been ground into it (Buchman 1976). This early lesion is of high diagnostic value in differentiating between arthritides and neuroarthropathy. Marked thickening of the synovium and capsule follow. In advanced DOAP cases there are no pathognomonic histological signs. The aim of the histological examination is to exclude an inflammatory or tumorous origin. Reports presenting histological findings are rare. We performed histological studies in 7 of our cases (Juhász et al. 1975). The samples were obtained in one case from excochleation, in 2 cases from capitulum resection, and in 4 cases from the amputation of the phalanx. Biopsy was not performed, as in the other cases the diagnosis could be confirmed on the basis of the characteristic clinical and radiological pictures and the course of the disease.

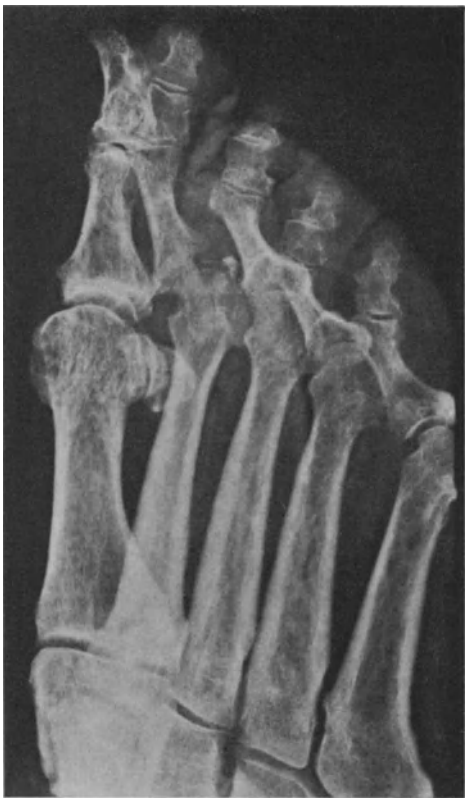
The most important histological findings (Figs. 36h–j, 39j, 41c, and 47d) resembling the picture found in syringomyelia, tabetic arthropathy, were as follows:

Degeneration was detected in all components of the joint. Fibroblast proliferation, edema, and round-cell infiltration were observed on the ligaments and capsule. The elastic fibers were fragmented and destroyed. The synovia displayed similar changes and, in addition, hemorrhages, and hemosiderin with pigment appositions, were visible. The cartilage was necrosed, and degeneration varying in degree was detectable (among others, this latter justifies the designation osteoarthropathy instead of osteopathy). The normal bone structure disappeared. Various stages of resorption were visible, with minimal tendency toward regression. Only the periosteum displayed new bone formation. The intertrabecular space was filled with fibrotic tissue, bone fragments, diffuse fibroblast proliferation, focal plasma lymphocyte, and histiocyte infiltration. An osteoblastic margin was visible on the surface of some bone trabecules, but marked osteoclastic activity and lacunal resorption were also detectable.

The osseous process was accompanied by angiopathic changes of the adjacent blood vessels of the skin and muscles.

Sinha and Kozak (1979) examined the amputated foot of a diabetic with tarsal neuroarthropathy. The tarsal bones and intratarsal joints were grossly disorganized with obliteration of the longitudinal arch by downward collapse of the cuneiforms. This resulted in the formation of a "rocker sole" (see p. 92). The tibiotalar and intratarsal joints were totally ankylosed. Microscopy showed severe degenerative arthritis with destruction of the articular cartilage in the tibiotalar joints.

Evaluating the histological findings one should take into account that alterations of diabetic origin may occur in the synovia even if bone defects are not present. These may be



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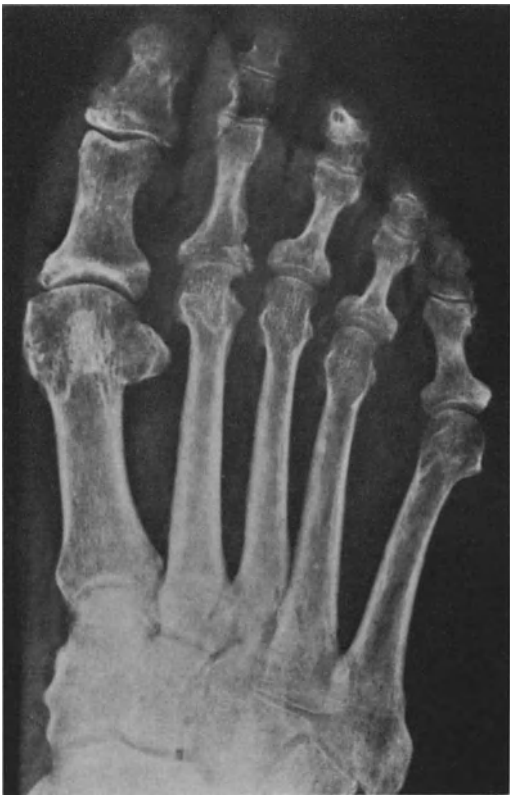
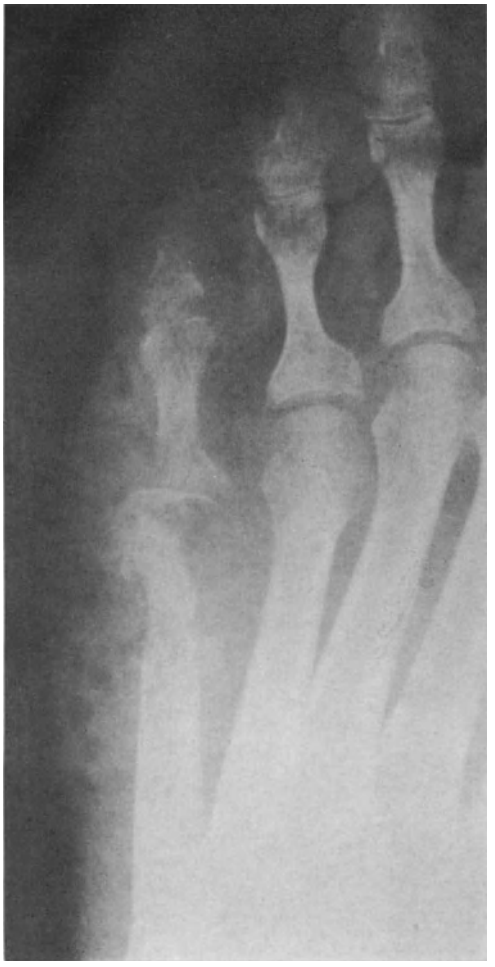


b

Figs. 45a and b. Subluxation of the 2nd phalanx in a patient with plantar ulcer. Sharply demarcated cortical defect. A similar change is visible on the plantar surface of the base of the proximal phalanx



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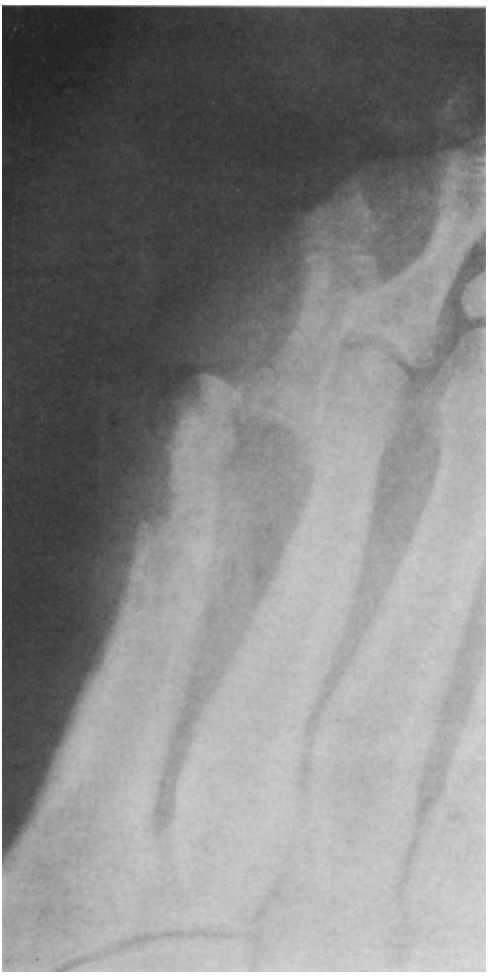
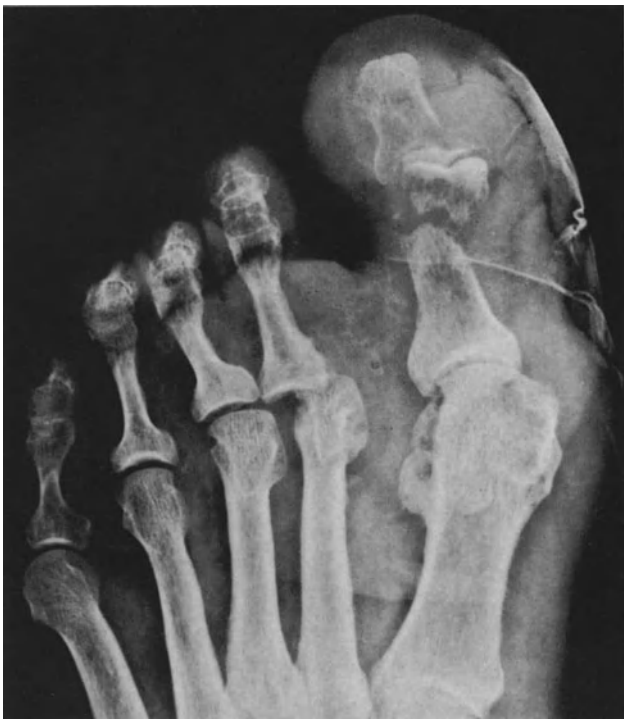


b

Figs. 46a and b. This case is not listed in the table. A–P and lateral views of the foot. The 5th toe is dislocated. Bone destruction on the 5th metatarsal head extending towards the diaphysis. Gas bubbles as signs of infection around the metatarsus in the soft tissue. Gangrene developed, the foot had to be amputated



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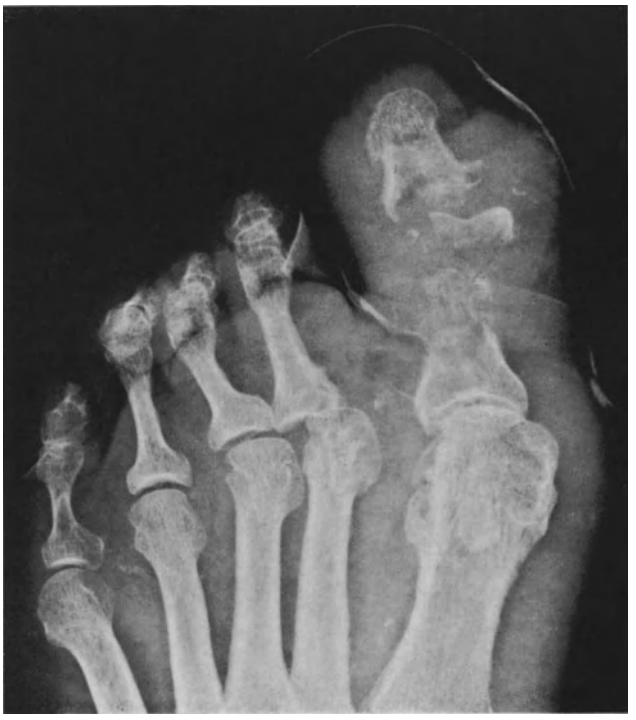

b

Fig. 47. An inadequately treated patient, maintained on oral antidiabetics. The 1st toe was swollen. Ulceration on the plantar surface

Fig. 47**a.** A medially dislocated pathologic fracture on the distal part of the diaphysis of the 1st proximal phalanx. Atrophic area with indistinct contour in the diaphysis, and marked osteolysis in the broken-off head. The surface of the head is relatively intact, even though lysis progressed into the unguicular process, where porosis is visible at the base. Cortical defect in the 2nd metatarsal head, dislocated 2nd toe

Fig. 47**b.** Ten days later, increased osteolysis on the proximal phalanx, with disintegrated structure on its diaphysis, initial signs of fragmentation. A large part of the head resorbed. The distal phalanx is dislocated, with extensive osteolysis at the base

Fig. 47c. One month later, simultaneous progression and regression. Fragmentation of the medial anterior margin of the head. Osteolysis of the diaphysis stopped; the bone is refilled and thickened due to periosteal apposition. The fragmented articular surface of the terminal phalanx resorbed. Sharp borders of the lytic areas

c

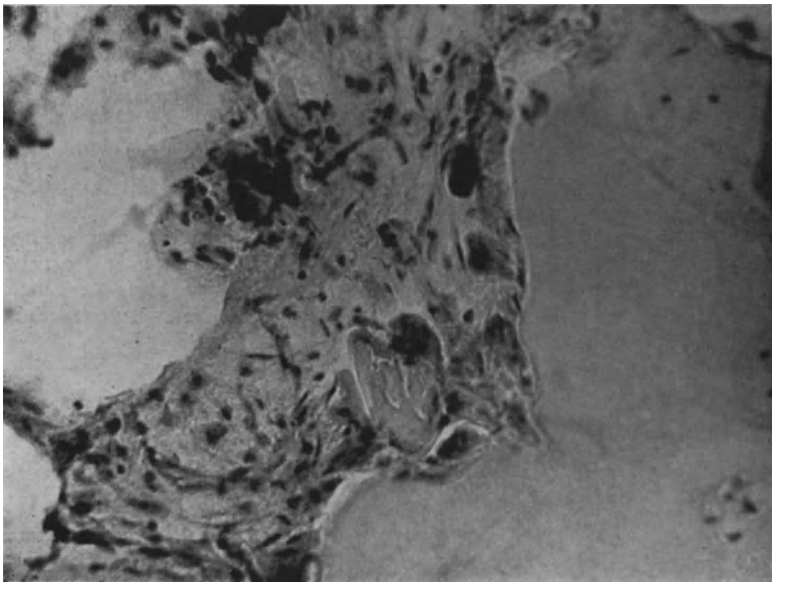

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Fig. 47d. The toe was amputated. Histological picture of the removed bone. No signs of inflammation. Marked osteoclastic activity at the border of the cartilage and bone. Aggregated, degenerative chondrocytes

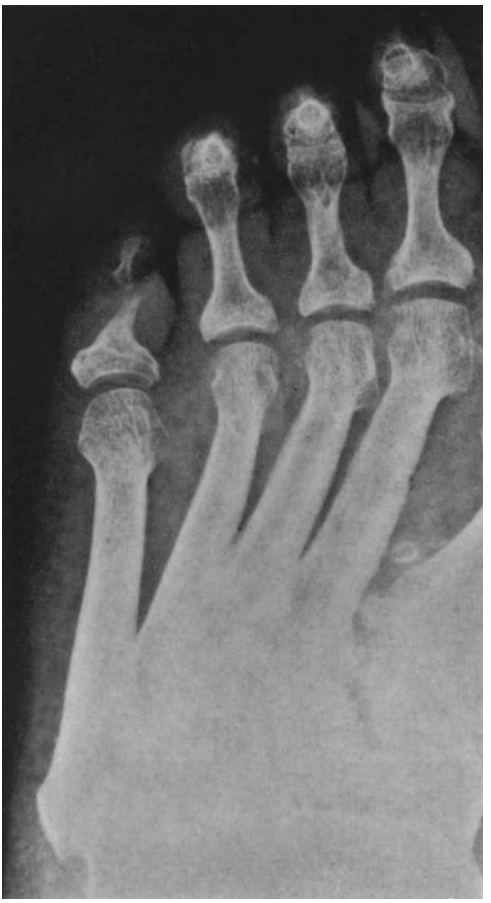


Fig. 48. The head of the proximal phalanx of the 5th toe is destroyed, and the diaphysis is narrowed, pointed. The process extended onto the base of the distal phalanx

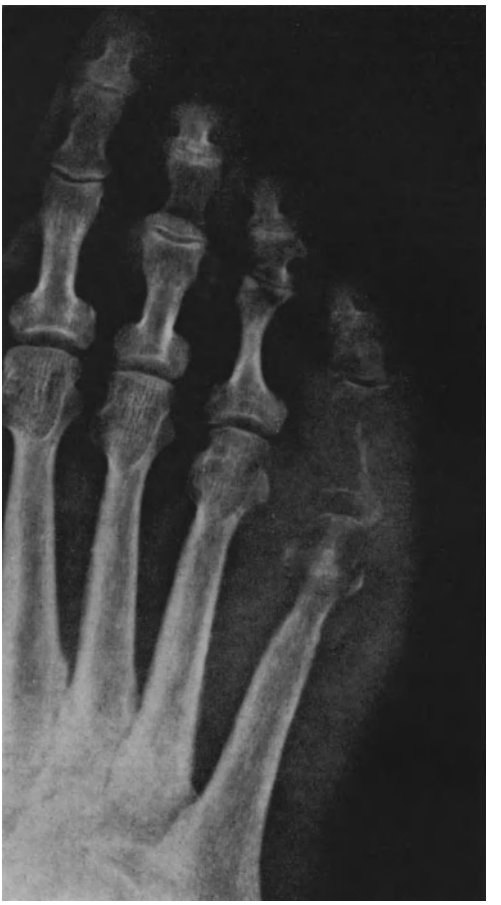
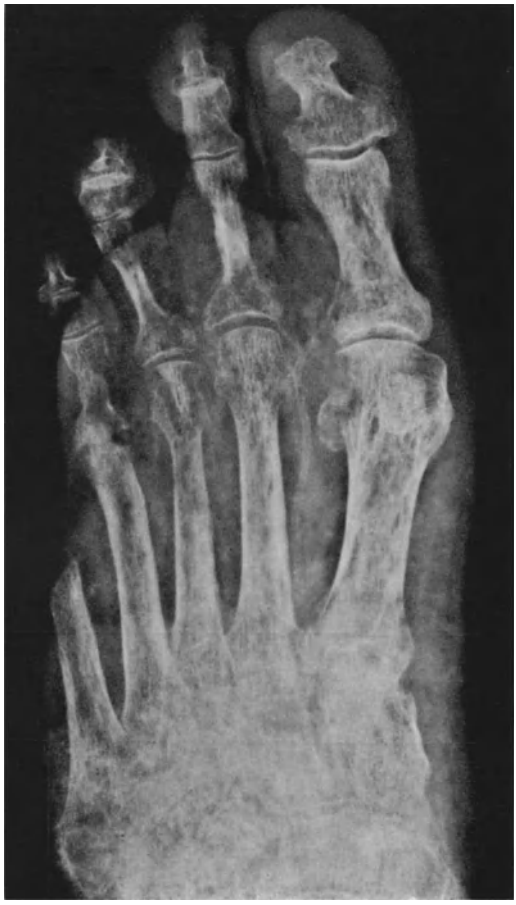


Fig. 49. The process started with a cortical defect in the head of the 5th metatarsus, of which only traces have remained due to fragmentation and osteolysis. The proximal phalanx of the 5th toe is almost entirely destroyed, and only irregular bone fragments have remained

Fig. 50. This case is not listed in the table. The 5th toe was amputated earlier. Clinical signs of arterial circulatory disorder and, in consequence, a marked, spotty Sudeck-type osteoporosis. Circumscribed defect on the 4th metatarsal head; part of the articular surface of the proximal phalanx is destroyed



(*i*) increased formation of synovial villi without proliferation of synoviocytes and without inflammation reaction and (*ii*) increased hyalinosis and fibrosis of the synovial villi as well as fibrosis of the flat synovial membrane (Huth and Weller-Boothe 1979). The alterations were far developed in more than 50% of all cases with diabetes.

Rare localizations of diabetic osteoarthropathy

In the previous chapters, we proved that the incidence of DOAP is not at all as low as generally reported. The ankle joint is affected in 10% of the cases, and the tarsometatarsal and phalangeal bones are affected in the rest. Other localizations of DOAP are actually rarities. The most important literary data are shown in Table 22. In 24 cases reported by 14 authors, distribution of the involved joints was as follows:

Shoulder,	7 cases	Wrist,	3 cases	Hip,	2 cases
Elbow,	3 cases	Hand,	1 case	Knee,	9 cases
				Spine,	3 cases

Table 22

Diabetic osteoarthropathies of rare localization according to literary data

Authors		Sex	Age (years)	Duration of diabetes (years)	Therapy	Localization
Takáts	1945	M	28	15	Insulin	Knee
Shore	1947	F				Knee
Spear	1947	M	62	8	Insulin	Knee
Zucker and Marder	1952	F	61	20	Insulin	Spine
Petersen	1960	F	62	15	Insulin	Knee
Schwartz et al.	1969	F	82			Shoulder
		F	78			Elbow
		F	71			Elbow, hip
		M	86			Shoulder, elbow, wrist, hand, knee
		M	38			Elbow
Bossi et al.	1961	F	70	11	Insulin	Knee, MP
Berényi et al.	1968	F	64			Wrist
Rathery	1968	M	29	14	Insulin	Knee, tarsus
Feldman et al.	1969	M	63	14	Insulin	Knee, wrist, ankle, tarsus
Reinhardt	1973	F	70			Knee
Feldman et al.	1974	F	69			Spine
		F	80			Spine
Campbell and Feldman	1975	M	67	8	Oral	Shoulder
		F	79	19		Shoulder
		M	79	7		Shoulder
		M	63	14		Shoulder
		F	56	30		Shoulder
		F	59			Elbow
Borejko and Jaworski	1976	F	62			Hip

MP = metatarsophalangeal joint.

According to Ellenberg (1972), the incidence of diabetic neuropathy is high not only in the lower but also in the upper extremities. Based on this concept, it may be assumed that more cases localized on the upper extremities exist than have actually been diagnosed.

The radiographic picture is variable. Extensive bone destruction is characteristic. Campbell and Feldman (1975) state that, in DOAP of the shoulder joint, initially cystic and sclerotic changes are detectable in the head of the humerus, glenoid cavity, and in the acromion. Later, the subchondral sclerosis increases, the cysts become pronounced, and the head of the humerus is deformed. The interarticular space is extremely narrow and partial dislocation develops. Bone fragments may appear periarticularly.

Critical analysis of the tabulated data raises several questions. Cystic changes were observed in the shoulder joint, although neurogenic osteoarthropathy is characterized by the lack of subchondral cysts. The second problem is that patients suffered from rheumatoid arthritis. The severe form of this disease is very similar to DOAP. In our diabetic patients, signs of severe rheumatoid arthritis with few clinical symptoms were often observed. This is probably due to the impaired perception of pain caused by diabetic neuropathy. We observed a severe case of multiple diabetic osteoarthropathy including the shoulders, elbows, wrists, hands, hips, and feet (Fig. 51). She was a 40-year-old diabetic patient with clinical and laboratory evidence of long-standing diabetic peripheral neuropathy and severe rheumatoid arthritis. Thus, we concluded that it was a mixed form of the two diseases.

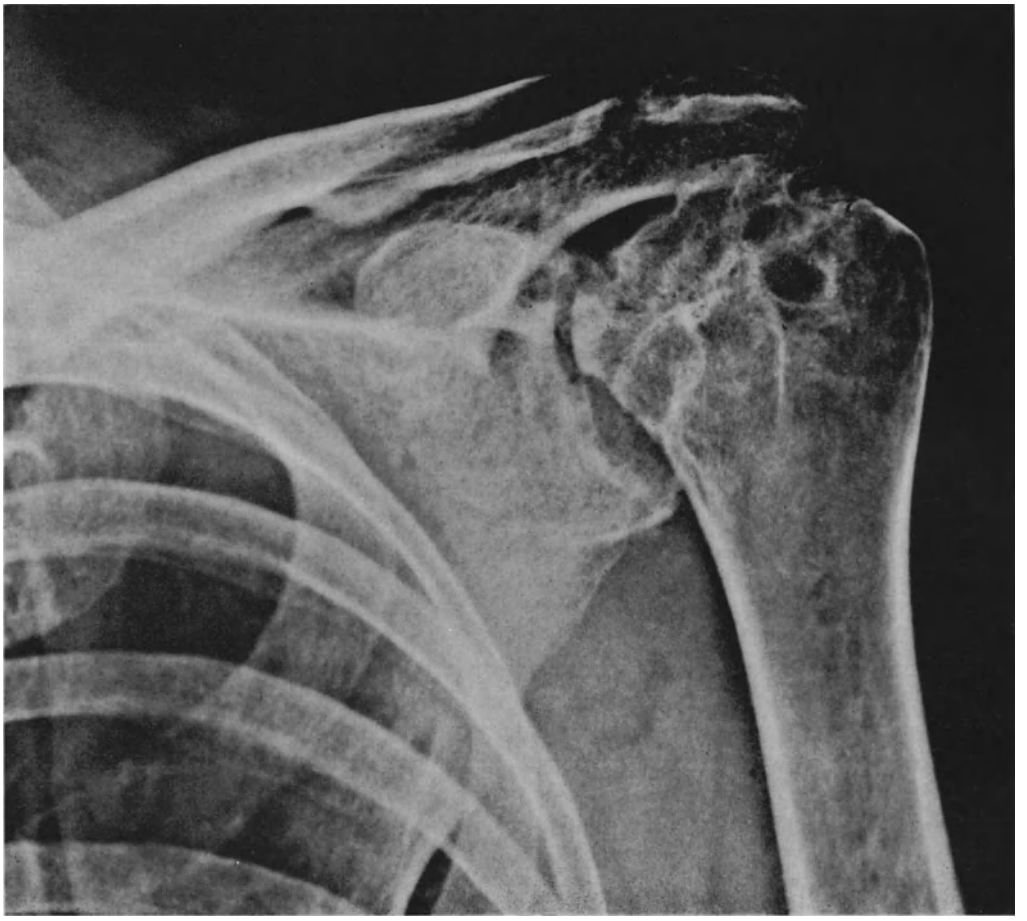
Among the DOAP cases not localized to the foot, the most frequent predilection site is the knee (9 such cases have been reported). Petersen (1960) demonstrated the fracture of the tibial articular surface. In other reports, however, radiographic documentation is lacking or the presented picture displays severe arthrosis deformans. Undoubtedly, this is the terminal phase of the process, but at this stage one cannot decide whether diabetes or some other disease is responsible for the anomaly. In our patient, we detected an irregularly shaped defect on the juxtaarticular surface of the tibial condyle (Figs. 35m and n), which healed in 6 months. Our case is of particular interest as DOAP manifested itself simultaneously in the ankle and knee.

One should always think of diabetes in cases of unusually localized arthrosis. Reinhardt (1973) reported a case of hip osteoarthropathy that manifested as malum coxae senile, but, we never encountered such a case among our own patients.

The diabetic hand

In analogy to the diabetic foot, some authors (Canavese et al. 1979, Cochet 1973, Fossati et al. 1975. Jung et al. 1971) have attempted to summarize the features of the diabetic hand. The symptoms are less severe, less known, and not characteristic. Campbell and Feldman (1975) found periarticular cortical erosions in the metacarpophalangeal and interphalangeal joints in 6% of their diabetic patients and in 2% of their control group. Subchondral cystic changes were twice as frequent in diabetics as in the control group.

The diabetic hand does not seem to have characteristic radiographic features. There is no osteoarthropathy. The occasional paresthesia and atrophy of the small hand muscles are due to peripheral neuropathy. Approximately 50% of the carpal tunnel syndromes are idiopathic occurring more often in acromegaly (O'Duffy et al. 1973, Oldberg 1971). Its relation to diabetes is worth attention. Yamaguchi et al. (1965), and Frymoyer and Bland (1973) found a 5%–8% incidence of diabetes in patients with carpal tunnel syndrome.

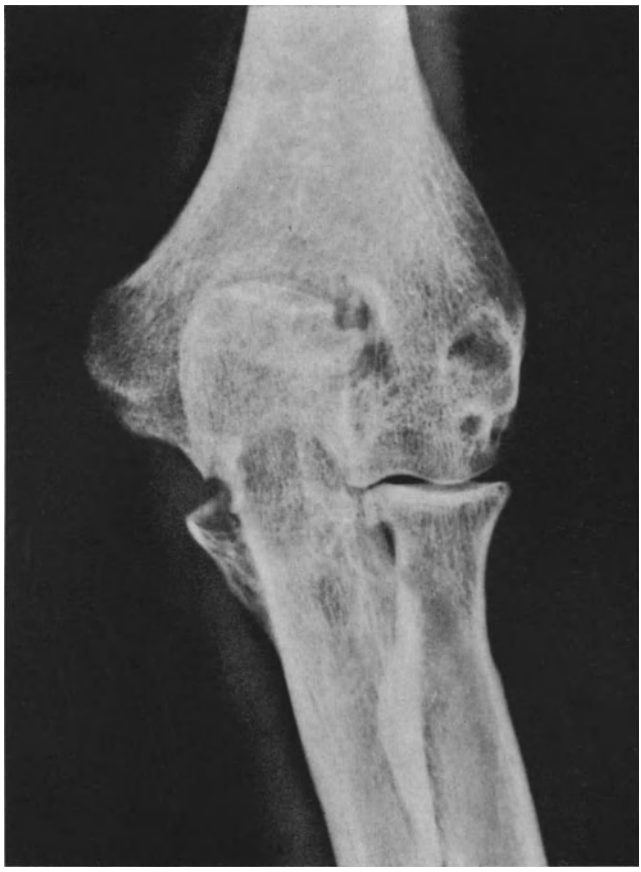


a

Fig. 51. A 40-year-old diabetic woman with long-standing juvenile-type diabetes. Clinical evidence of peripheral neuropathy and rheumatoid arthritis

Fig. 51a. Marked shoulder osteoarthropathy. Narrowed glenohumeral joint space. Deformed humeral head with evidence of bone resorption, cystic changes, cortical defects, and subluxation

Figs. 51b and c. Cystic lesions in the bones of the elbow joint. Severe bone resorption in the olecranon



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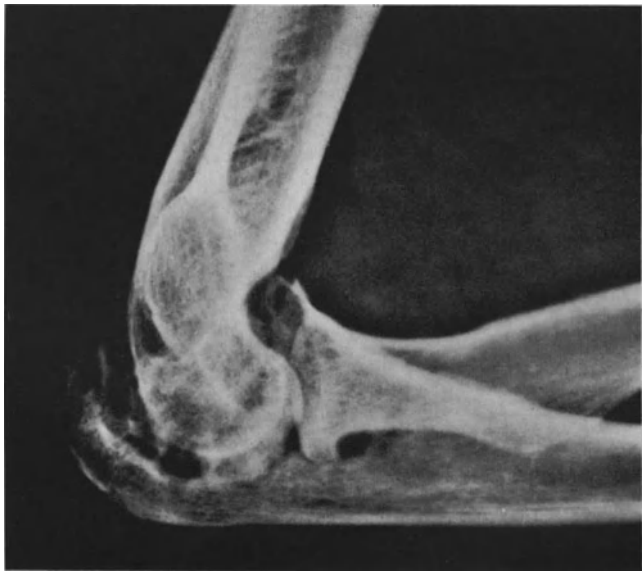

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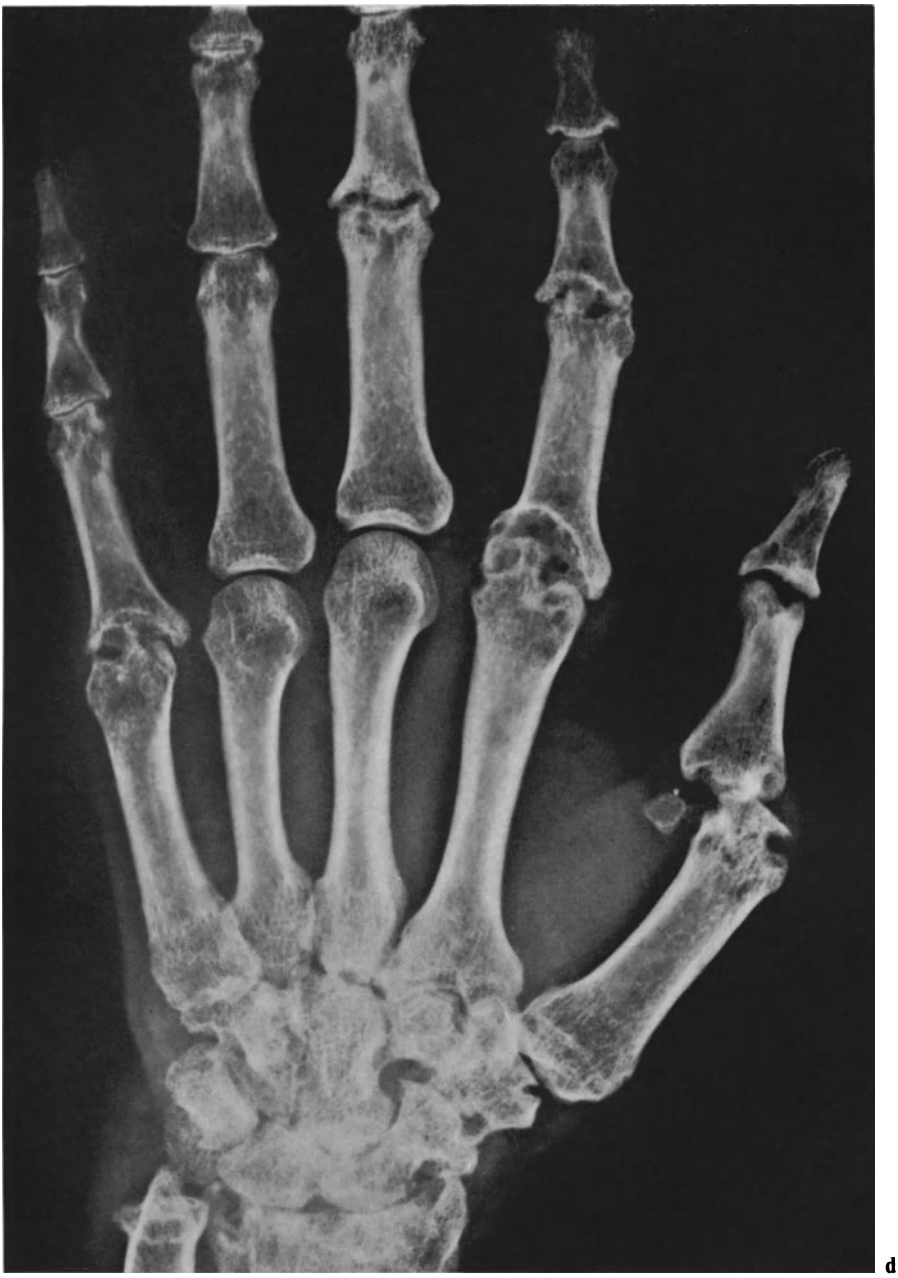
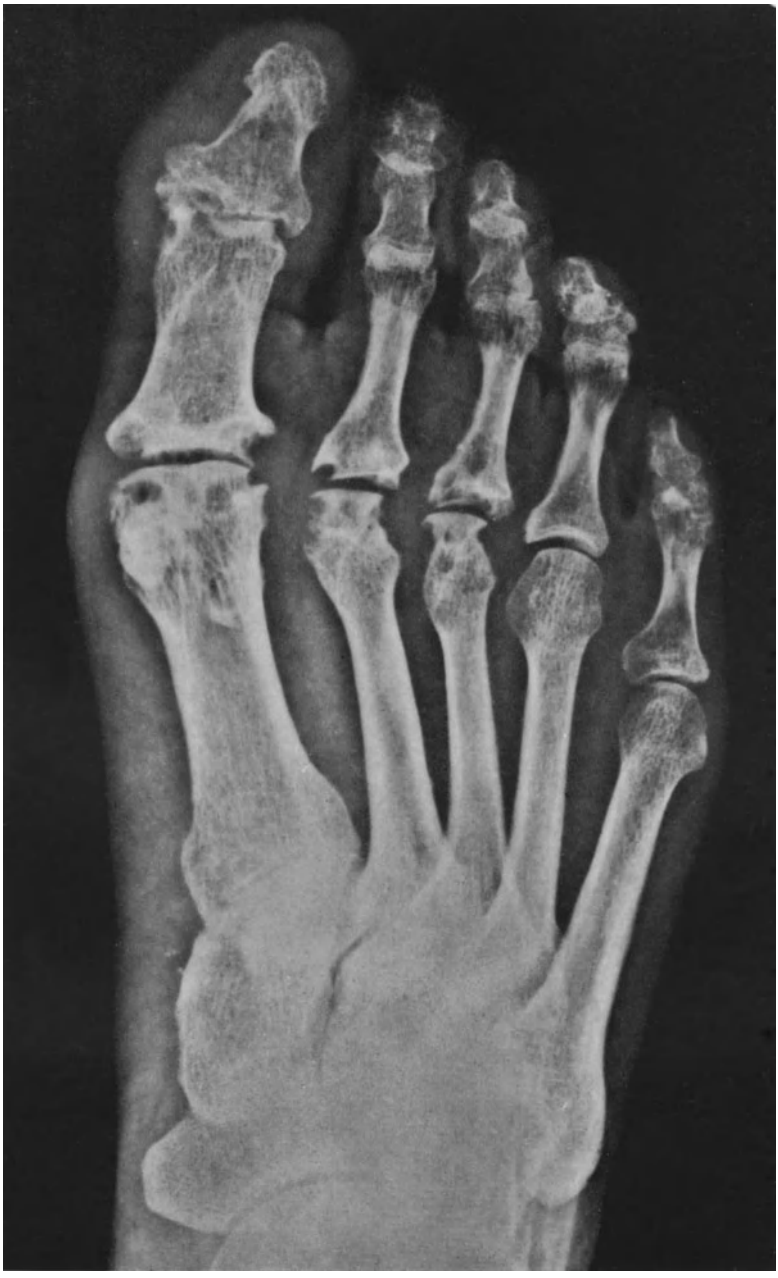


d

Figs. 51**d** and **e.** Mutilating type of rheumatoid arthritis and diabetic osteoarthropathy in the bones of the wrists, hands, and feet



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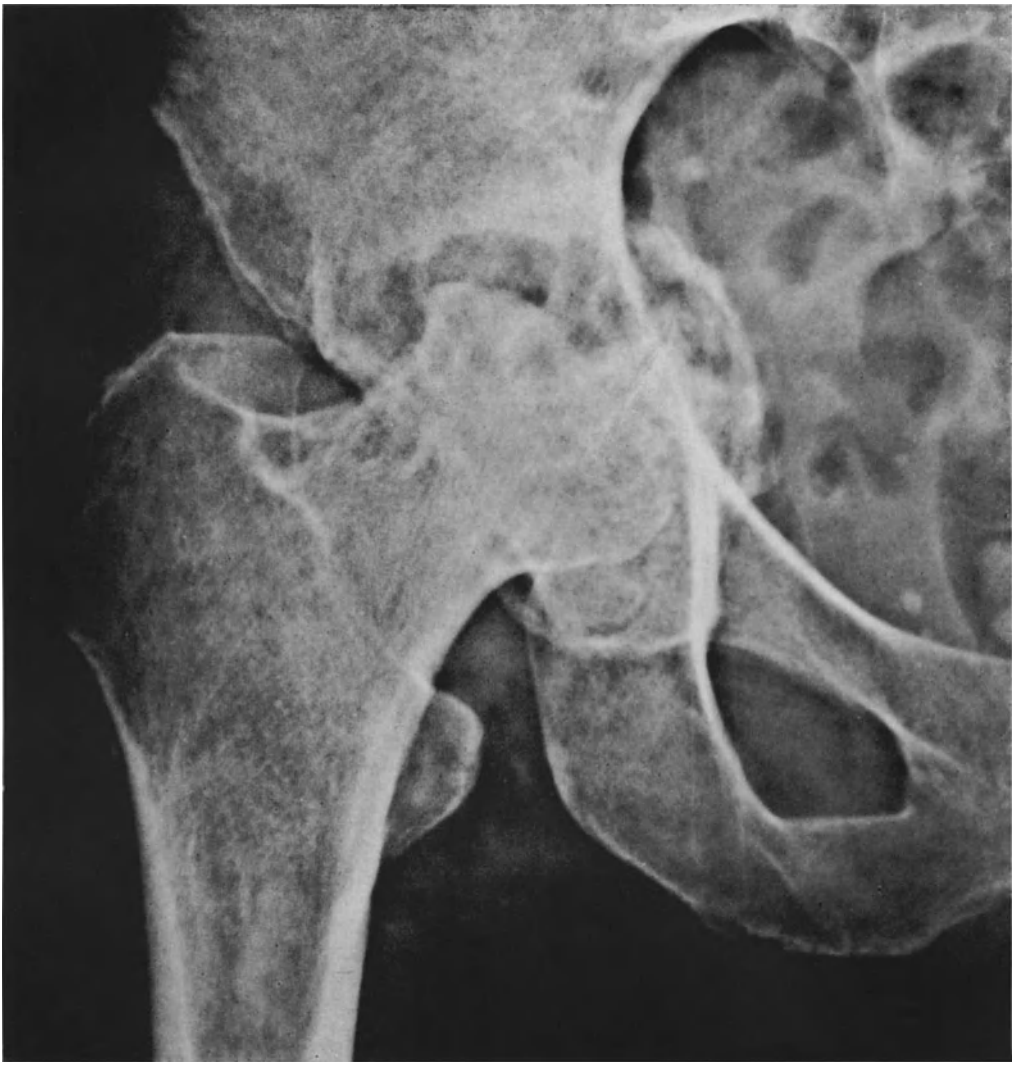


f

Fig. 51f. Severe joint destruction in the hip joint. Roughened cortical contours; varying degrees of subchondral sclerosis and cystic lesions

In Phalen's opinion (1970), diabetes is the most frequent systemic disease leading to the manifestation of this syndrome: diabetes was found in 63 (16.6%) of his 379 patients, and a family history of diabetes was detected in further 40 cases. The carpal tunnel syndrome of diabetics may be related to the diabetic lesion of the median nerve (Jung et al. 1971).

Mackenzie (1975) reported 11 diabetics in a series of 36 patients with multiple, bilateral flexor tendosynovitis (stenosing tendovaginitis, trigger finger).

The cardinal symptom of the diabetic hand is flexion contracture. Dorwart and Schumacher (1975) found bilateral changes in the metacarpophalangeal and interphalangeal joints. No pathological changes are visible on the radiogram. The flexion contracture is often of Dupuytren's type. According to the literary compilation of Spring et al. (1970), Dupuytren's contracture occurs in 3%–32% of the diabetics, and diabetes is established in 1%–20% of the patients with contractures. Spring and Cohen (1966) found Dupuytren's contracture in 48 (20.6%) of 233 diabetics. Günther and Misoga (1972) reported an incidence of 9.6% in 1000 patients with diabetes, in contrast to 2.7% in the control group. Rhonberg (1967) found normal glucose tolerance in only 19 of 100 cases with contractures. Whether contracture is linked to severity and duration of diabetes has not yet been decided. Klunker (1964), and Ziliotte (1967) failed to find a significant correlation. Out of 320 diabetics Vitry et al. (1979) found 38.1% with contractures. According to them the histological and histochemical results did not clarify the relation between diabetes and Dupuytren's disease.

Mackenzie (1975) suggested that a microangiopathy of the tendon sheaths leads to the frequent association between diabetes and flexor tenosynovitis, concluding that diabetes should be looked for in patients with flexor tenosynovitis. The literature suggests that 10% of patients with trigger finger are diabetics (Clark et al. 1973, Wealby 1970).

Interestingly, flexion contracture also occurs in diabetic children. Grgic et al. (1976) found this derangement in 65 of the 229 children with diabetes. The radiographic examination only revealed enlargement of the soft tissues. Benedetti et al. (1975) reported contracture associated with retarded growth, "poorly controlled" diabetes and Mauriac's syndrome. The authors designated this picture "juvenile diabetic cheiroarthropathy."

In our own patients the simultaneous manifestation of Dupuytren's contracture and diabetes was often associated with hyperostotic changes, and ligamentous calcifications. Thus, the possibility arises that the factor responsible for contracture is also related to that causing diffuse ligamentous calcification.

Besides vasosclerosis of the foot, sclerosis of the small arterial vessels of the hand is also frequent. Campbell and Feldman (1975) reported 8% in comparison to 1% in the age-matched healthy controls.

Differential diagnosis

Based on the literature and our observations, we have compiled the abnormalities that should be considered in the differential diagnostics of DOAP (Table 23).

Table 23

Differential diagnostics of diabetic osteoarthropathy

1. Inflammations	
Osteomyelitis	Arthritis psoriatica
Septic arthritis	Arthritis urica
Rheumatoid arthritis	Bone tuberculosis
Arthritis mutilans	Fungal infections (coccidiomycosis)
2. Malignant bone tumors	
Primary tumors	
Metastases	
3. Bone changes accompanying arteriosclerosis obliterans	
4. Neurogenic osteoarthropathies of other origin	
Tabes dorsalis	Traumatic lesion of the ischiatic nerve
Syringomyelia	Spina bifida
Leprosy	Alcoholic neuritis
Poliomyelitis	Neurogen osteoarthropathies of unknown origin
5. Other changes	
Osteoarthrosis, posttraumatic deformity, aseptic necrosis	

Inflammatory changes

Osteomyelitis

It is the most frequent differential diagnostic problem. In cases of osteomyelitis occurring after burns, frostbite, trauma or operation, the history of the patient is unambiguous. Hematogenic osteomyelitis is relatively rare in the foot and is mostly localized in the calcaneum (Whitehouse and Smith 1970), which is rarely affected by itself in diabetes. Sometimes the infected soft tissues contaminate the bone. Many authors emphasize that in these cases the clinical picture is decisive, as in DOAP clinical and laboratory signs indicating inflammation are lacking.

In our opinion, the radiographic picture is also decisive in most cases. The distinct cortical defect, fragmentation, destruction of the epiphyses, and the forms developing during recovery are not characteristic of osteomyelitis. In cases where the anomaly is not only localized on the epiphysis but extends toward the diaphysis, diagnosis is somewhat more difficult. This is characteristic of inflammation, and periosteal reaction accompanies both diseases (Figs. 39a,b, 43c, and 49). Even bone fragments appearing through fistulas do not confirm osteomyelitis (Fig. 36). In these cases the clinical picture, the course and sometimes histological examination are decisive. In 10% of the cases (Kahn 1974), gas bubbles develop which are detectable on the x-ray picture.

Septic arthritis

It is but a rare differential diagnostic problem. When the illness starts with a local inflammation, observation of the clinical course is decisive.

Rheumatoid arthritis

The severe form of rheumatoid arthritis is similar to DOAP. However, rheumatoid arthritis affects many small joints of the hand and foot; destruction of the cartilage is primary. In cases of simultaneous occurrence, the characteristic clinical appearance of rheumatoid arthritis may be overshadowed by the symptoms caused by diabetic neuropathy.

Mutilating arthritis

In many respects it is similar to DOAP. Some authors consider it a mutilating form of rheumatoid arthritis (Crasselt 1960/1962, Eisenstadt and Eggers 1955), while others assume a neurogenic origin.

Psoriatic arthritis

The picture of psoriatic arthritis resembles the severe forms of rheumatoid and mutilating arthritis and it is dfficult to differentiate from these on the x-ray picture (Avila et al. 1960, Killebrew et al. 1973).

Gouty arthritis

A characteristic sign of the first stage of DOAP is the sharply demarcated juxtaarticular bone defect, which may also be a sign of gouty arthritis, however, in DOAP, gouty pains, and soft tissue tophi are missing.

Tuberculosis of the bones

Bone tuberculosis displays all signs of inflammation. Slowly, evenly progressing osteolysis and striking porosis are visible. Recovery (bone ankylosis) also differs from DOAP. Dactylitis tuberculosa or spina ventosa affects the hand more frequently, but a similar form may also occur in the foot.

Coccidiomycosis

The disease may affect the bones of the foot. In young patients, lytic lesions accompanied by periosteal reaction are visible (Whitehouse and Smith 1970).

Bone tumors

Primary bone tumors rarely originate in the foot (Lénárt and Csató 1974, Norman 1970). Lénárt and Csató reported on 33 tumors of the foot among 690 patients with musculoskeletal tumors, and found the calcaneus to be most frequently affected. The histological type of these tumors varied: chondroblastoma, giant-cell tumor, chondrosarcoma, reticulum cell sarcoma, Ewing's sarcoma. The latter two are difficult to distinguish from each other (Papolczy and Molnár 1972). The incidence of osteosarcoma is even smaller. Malignant tumors of the phalanges are extremely rare (Paoli et al. 1958, Seyss 1975).

The above-listed tumors seldom present differential diagnostic problems. However, *synovial sarcoma* of soft tissues of the foot may cause serious diagnostic problems.

Metastases are even more rare than primary bone tumors. Bronchial carcinoma may rarely form metastases in the phalanges. Metastases of breast (Pirschel et al. 1978, Szakolczai and Gottwald 1976), cervical (Grumbeckl and Tager 1972), prostata (Pirschel et al. 1978), and colonic cancer (Seife 1973) have been reported in the foot.

Osseous changes associated with obliterating arteriosclerosis

Histological examinations in obliterating arteriosclerosis have revealed bone necrosis (Sherman and Selakovich 1957). It is rarely visible, however, by radiography. Spotty atrophy is observable (Naide and Schnall 1961, Scott 1959), the degree of which, according to Betoulières et al. (1955), depends on the circulatory deficit.

Based on our examinations the bone defects do not indicate the degree of arterial occlusion. If soft tissue necrosis is extensive or there is gangrene, especially if this develops rapidly, structural changes in the bone are hardly visible (Fig. 52). Severe atrophy occurs in cases of chronic circulatory disorders, but in these cases inactivity plays a role in its development (Fig. 53).

Bone necrosis, due to gangrene, is unusual; if it develops, however, the distal phalanges are affected, causing severe pain (Fig. 50).

Nondiabetic neurogenic osteoarthropathies

The radiographic and histological pictures of neurogenic osteoarthropathies due to various causes, including DOAP, are very similar. Several features, however, should be mentioned.

1. In DOAP, soft tissue calcification adjacent to the joints is unusual. This is frequent, however, in syringomyelia and tabes.
2. The favorable healing tendency is characteristic exclusively of DOAP, where total or nearly total recovery takes place.
3. DOAP with rare exceptions involves the feet. Neurogenic osteoarthropathies of other origin generally affect the upper extremities. Rittmeyer and Poppe (1974), among 56 cases of neurogenic arthropathy, reported only 5 cases localized to the lower extremities.

Tabes

Arthropathy was confirmed in 10% of the tabetic patients. Earlier, this was the most frequent form of neurogenic bone derangement. The knee is a typical predilection site, this is the classic "Charcot joint." Also the bones of the ankle and metatarsus are often involved. Szántó (1969), in a series of 22 patients, reported 7 cases involving the foot. Reinhardt (1973*a*) summarized the radiographic features. The lack of synovial effusion in DOAP cases is a differential diagnostic sign, according to Fochem (1971). In DOAP, tabes must be exluded; therefore, lumbar puncture is indicated, particularly when the proximal part of the foot is affected.

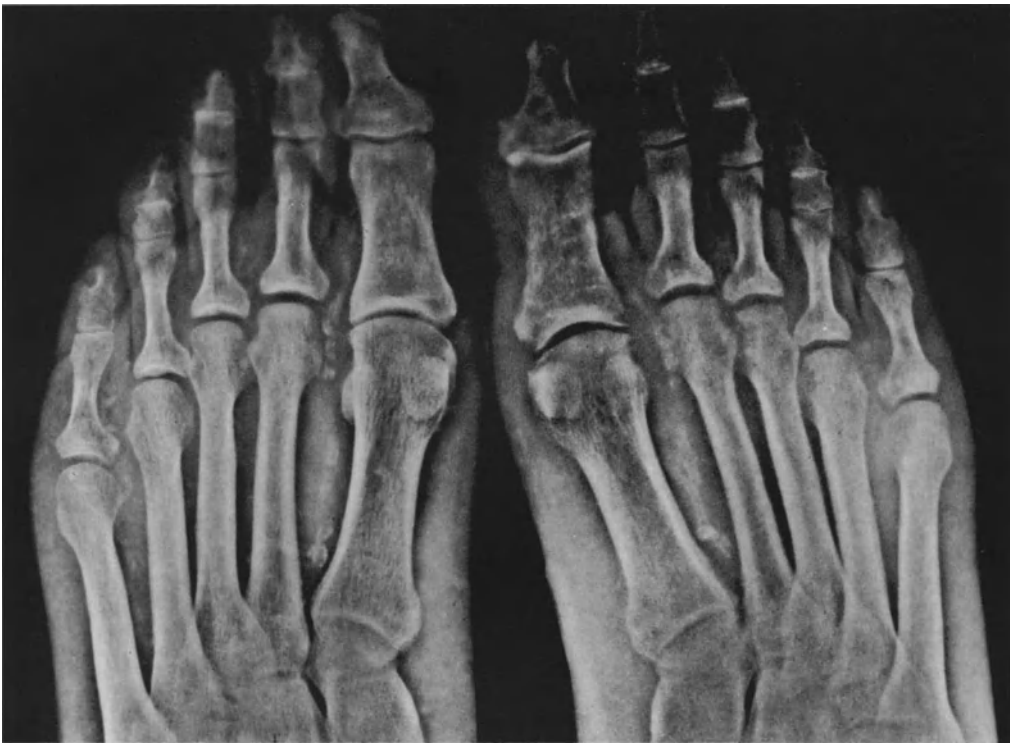
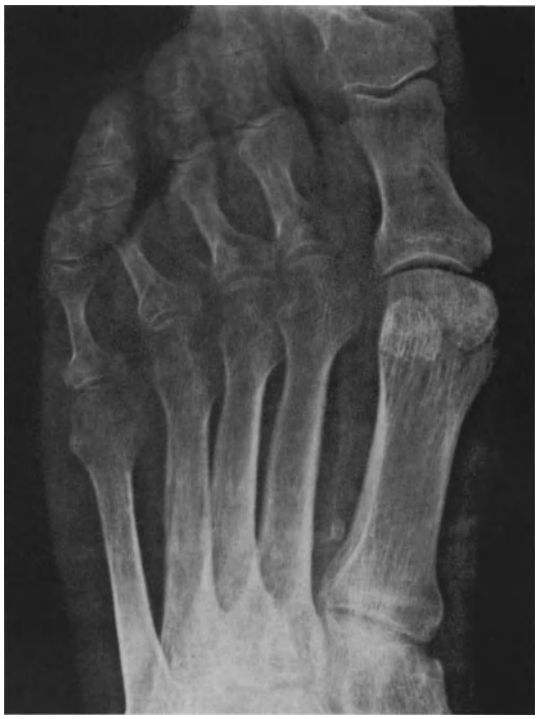
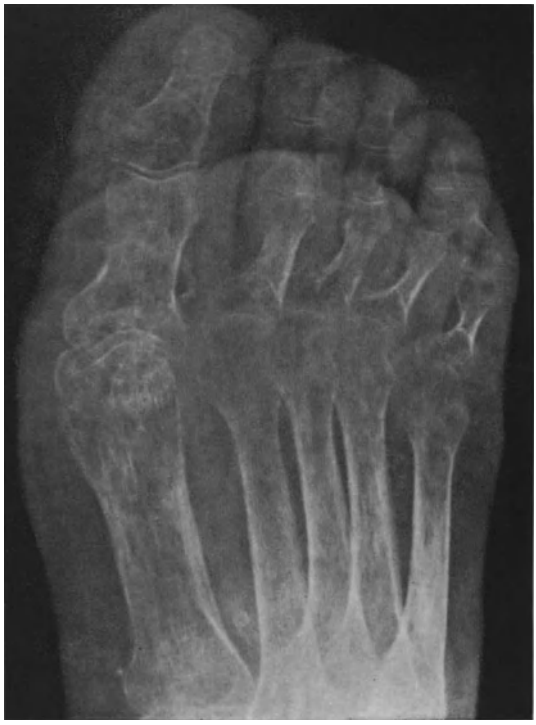


Fig. 52. Comparative pictures of gangrenous feet. Severe gangrenous change on the right foot, indicated on the radiograph by the lack of soft tissue shadow around the distal phalanx of the 1st toe. Bone lesions, however, are hardly visible. Fine porosis on the affected foot, particularly in the 1st toe and in the metatarsal head. Calcified arteries on both sides. The right foot needed amputation

Figs. 53**a** and **b.** Comparative foot radiography. Clinical signs of chronic arterial circulatory disorder, particularly on the right foot (**b**) where oscillation values were extremely reduced. Gangrene did not develop. Calcified small arteries. Extremely porotic and transparent bones of the right foot



a



b

Syringomyelia

Syringomyelia is a rare disease. It is characterized by the dilatation of the central canal of the spinal cord, where fluid accumulates, resulting in injury of the grey substance. Most often the cervical part of the spine is affected. Accordingly, the joints of the upper extremities are involved. Schlesinger (cit. by Zsebők) reported 8 cases localized in the lower extremities in a series of 150 cases, while other authors dispute localization on the lower extremities.

Leprosy

Osteoarthritis associated with *leprosy* (Basu 1970, Bureau et al. 1965, Enna et al. 1971, Merklen et al. 1960) and other *tropical* diseases (Ennis et al. 1972, White 1971) displays more severe bone destruction than that seen in DOAP. Some authors for example reported breakdown of the calcaneus (Harris and Brand 1966).

Lesion of the sciatic nerve

Atrophic arthropathy may accompany the *traumatic lesion of the sciatic nerve* (Crasselt 1960/1962, Klümper et al. 1968*a*, Reinhardt 1953, Zsebők 1952). Lumbosacral tumors, even benign ones, may cause this nerve lesion (Zsebők 1952).

Intraarticular hydrocortisone-induced arthropathy

Intraarticular hydrocortisone administration may lead to Charcot joint in the knee (Steinberg 1971) and in the hip joint (Chandler et al. 1959, Schwob et al. 1962). Such changes have not been observed in the foot.

Alcoholic neuropathy

Bone disorders due to alcoholism have been reported by Barrière et al. (1975), and by Thornhill et al. (1973). The most severe cases were those in which diabetes was associated with alcoholic neuritis. According to the aforementioned authors, these two diseases differ only in the type of nerve conduction: in diabetes segmental demyelinization occurs, while in alcoholic neuritis the nerve axon is affected.

It is yet undecided whether joint disorders associated with *hemiplegia* should be listed in this group. In the opinion of Palmia and Volterrani (1974), paraarticular ossification is a dominant symptom. Mizushima and Yamaura (1969) have described cases resembling rheumatoid arthritis.

Neurogenic arthropathies of unknown etiology

Among the patients of Eichenholz (1966) the exact origin of neurogenic bone lesions could not be determined in 8 cases. There is a considerable degree of confusion regarding the classification and designation of these cases. Many forms are covered by the same terminology and, in other cases, changes of known and unknown origin are similarly named. Therefore, in our opinion the correct denotation is *neurogenic osteoarthropathies of unknown etiology*.

"*Acropathies ulcero mutilantes*" is subdivided into two forms: familial (sec. Thevenard) and sporadic (sec. Bureau). Initially, lumbosacral syringomyelia was suspected, but pathological examinations did not confirm this hypothesis, because changes were found in the posterior roots and in the peripheral ganglions.

"*Acrodystrophic neuropathy*" (Banna and Foster 1972), "*hereditary sensory radicular neuropathy*" (Pallis and Schneeweis 1962, Reimann et al. 1958), *essential neurogenic acroosteolysis* (Chiappa and Pagano 1955, Fiumicelli 1971), and "*pseudosyringomyelic ulceromutilating arthropathy*" (Badanoui and Bucur 1973) are the terms for abnormalities of similar type. Konrád et al. (1975) observed such a derangement associated with ankylosing spondylitis. Bone defects occurring in "*idiopathic multicentric osteolysis*" are also similar, sometimes accompanied by nephropathy (Tyler and Rosenbaum 1976) or by the early loss of teeth (Hermann and Zubige 1973).

The interpretation of "*acroosteolysis*" is not uniform either. The classic form of acroosteolysis occurring in scleroderma (Fogel et al. 1960) does not occur in diabetes, nor is it characteristic of other neurogenic osteoarthropathies. Several authors consider acroosteolysis a syndrome under which they list all neurogenic osteoarthropathies with epiphysis destruction, including DOAP (Bloch-Michel and Brizard 1960, Crasselt 1960/1962, Gougeon et al. 1969, Phelip and Pras 1975). Undoubtedly, these changes have many common radiomorphological signs, but we believe that pathologic processes of known and unknown origin should be separated.

The clinical and radiological picture of the above-listed diseases is similar to that of DOAP. The only difference reported by Seignon et al. (1974*a*) was that while the sex distribution was identical in diabetic osteoarthropathy, there is a mainly male preponderance in ulceromutilating acropathy. The triad described by Banna and Foster (1972), namely, sensory neuropathy, trophic ulceration, and bone erosions, are also valid for diabetes. An intact sensation to vibration is reported and this may be a differentiating sign since this disappears early in diabetic neuropathy. In many cases of "unknown etiology," an underlying diabetes may be suspected which often escapes detection because no examinations are performed in this direction.

Literature discusses bone abnormalities due to *congenital insensitivity to pain* as an entirely separate disease. Analyzing the reports of rare cases (Abell and Hayes 1964, Baxter and Olszevszki 1960, Franklyn 1972, van der Hoeven 1961, Lièvre et al. 1969, Mooney and Mankin 1966, Silverman and Gilden 1959), it appears that there is only a quantitative difference from the aforementioned disorder. Severe bone destruction with consequent deformities develop early.

Miscellaneous

In osteoarthropathies associated with *poliomyelitis* large periosteal appositions were encountered (Fried 1969, Zsebők 1952).

Neurogenic osteoarthropathy has been described in *multiple sclerosis* (Norman et al. 1968), *pernicious anemia* (Eichenholz 1966), *Waldenström's macroglobulinemia* (Scott et al. 1973), and in a rare familial disease, *Riley-Day*'s syndrome (Brunt 1967). Changes due to *spina bifida* appear already in childhood (Zsebők 1952).

Degenerative changes, aseptic necroses

Regarding the radiographic signs of DOAP, a form of recovery was described which sometimes cannot be differentiated from osteoarthritis. In cases of neurogenic bone defects the lack of arthrogenic cysts may be a differentiating sign.

The advanced stage of certain *posttraumatic deformities*, *aseptic necroses* (first of all Köhler I and II), can hardly be distinguished from the final stage of certain types of DOAP.

Pathogenesis of diabetic osteoarthropathy

No uniform concept exists as yet regarding the pathogenesis of DOAP. Generally, the role of diabetic neuropathy is accepted; however, as far as the role of other factors is concerned, views differ to a great extent. Apart from the theoretical interest in this problem, detailed discussion is justified since knowledge on the role of single factors determines the management of the patient.

Role of diabetic peripheral neuropathy

Undoubtedly, this factor plays the greatest role in the development of DOAP. According to *Charcot*'s classic concept the disease is the result of the disorder of the central nervous system, namely the lack of trophic effect upon bones and joints. Lately, authors tend to accept that an impaired sense of pain as well as motor instability and the lack of proprioceptive impulses lead to the loss of defense mechanisms in the case of trauma. Evidence supporting the role of neuropathy is summarized as follows:

1. The clinical signs of diabetic neuropathy are detectable in all DOAP cases. The few instances in which neuropathy is not confirmed, should be accepted with reservation as the neuropathic symptoms are often very mild and therefore may escape notice if no detailed neurological examination is performed.

2. Increased protein level in the cerebrospinal fluid is a frequent symptom of diabetic neuropathy. Bailey and Root (1947) reported this laboratory finding in 11 of 14, and Sinha et al. (1972) in 30 of 39, cases. Our own experience also supports this observation, since in 10 of 14 cases, when lumbar puncture was performed in order to exclude tabes dorsalis, there was an elevated protein level.

3. DOAP is often accompanied by neurotrophic plantar ulcer.

4. The clinical, radiographic, and histological manifestations of DOAP display many similarities, moreover, they are often identical with other bone abnormalities of positively neurogenic origin.

5. Histological findings of nerve biopsies performed in DOAP (Martin 1954, Miller and Lichtman 1955) displayed similar changes to those observed in the crural nerve of patients with diabetic neuropathy (Chopra et al. 1969, Vital et al. 1973). Nerve lesions were detected in extremities amputated due to DOAP (Foster and Basset 1947).

Two main concepts exist concerning the relationship between neuropathy and metabolic disorder. Both are based on studies performed on a large number of patients.

In Pirart's (1970) opinion, the incidence and severity of diabetic neuropathy are related to the duration and severity of diabetes and in general depend on the balance of the metab-

olism. This concept explains the development of bone defects in severe, long-standing, inadequately treated diabetes.

Lately, however, Ellenberg's (1963, 1972) opinion is gaining acceptance. According to this, neuropathy is not a complication but a concomitant disease, which may occur in the early stage of mild diabetes, provided that the metabolic balance is adequate. Moreover, it may appear before the manifestation of metabolic disorder. This concept explains those few cases of DOAP which were found in association with fresh or latent diabetes.

The problem is further complicated by the fact that no direct relationship has been found between the severity of neuropathy and DOAP. For example, at the Diabetic Outpatient Clinic many patients were observed with severe polyneuritis without any bone defects. In the majority of DOAP cases the complaints connected with peripheral neuropathy were either lacking or were very mild, and only neurological examination could reveal them. These neurological deficits, for example, diminished vibration sense, are frequent in diabetics, while DOAP is a rare disease. Thus, it seems logical to assume the contribution of several other factors in the development of the bone process.

The role of diabetic angiopathy

In the case reported by Ochsenschläger (1958) the angiographic picture of the foot displayed the most severe lesions at the site of the bone process. Other authors, however, did not confirm this relationship between the angiographic and the bone involvement picture (Bossi et al. 1961, Cécile et al. 1973), but the role of the small and large blood vessels in the foot lesions was proposed by some studies (Faris 1975).

The angiographic picture was discussed in the previous chapter. Naturally, these severe changes result in reduced oscillometric values, as we have also observed it in 18 of our patients.

Retinopathy, being a manifestation of microangiopathy, is frequent in patients with DOAP. Diabetic microangiopathy is detectable in the blood vessels of the foot (Moore and Frew 1965, Pedersen and Olsen 1962). Walsh et al. (1975) observed retinopathy in 417 newly detected cases of diabetes; in 47 of these patients, foot lesions were also present. This simultaneous manifestation indicated bad prognosis. The bone process developed at the same time as the rapid and severe progression of retinopathy (see Fig. 40).

Thus, the role of diabetic angiopathy is assumable in the development of DOAP. The problem is even more complicated considering the relationship between neuro- and angiopathy. Combined occurrence is frequent (Faris 1975). Neuropathy is also involved in the development of gangrene. Supporting evidence for this was provided by Holt (1928) and recently by Williams et al. (1974).

The old, appealing concept attributing neuropathy to diabetic microangiopathy of the vasa nervorum is a matter of increasing dispute. Clinical and histological examinations have indicated that the vascular changes are not severe enough to explain the severe lesions of the ganglion cells and nerve fibers (Reske-Nielsen and Lundbaek 1968, Somló et al. 1962). According to recent studies, metabolic disorders are responsible for nerve lesions. In experimental animals and also in humans (Tackmann et al. 1975) the rate of nerve conduction is decelerated. This can be attributed to the morphological changes of the nerve fibers (decreased diameter, Jakobsen 1975), and to the metabolic disorder of the myelin lipids (Ellenberg 1972).

Vascular changes may also be attributed to neuropathy due to the primary metabolic disorder of the nerve elements (Budzilovich 1970). Sympathic dysregulation leads to "autosympathectomy." This leads to the phenomenon we have also observed: surgical sympathectomy in diabetics yielded worse results than the same intervention in nondiabetic subjects, as in diabetics the sympathic function has been previously impaired.

One of the results of "autosympathectomy" is the warming of the foot, which has been confirmed by thermographic measurements in the initial stage of DOAP (Sandrow et al. 1972). According to Diankov et al. (1978), bone scanning studies indicate an increased blood flow in most cases of diabetic osteoarthropathy. Klümper et al. (1968*b*) found that osteolysis develops in the following way: in the epiphysis, which is a well-vascularized part of the bone, blood vessels are capable only of dilatation if they are given space by active cell function of the osteoclasts. Thus, osteoclasis is increased; at the same time osteoblastic activity is reduced due to metabolic lesion. The role of hyperemia in osteolysis is also emphasized by other authors (Friedman and Rakow 1971).

Two opposing vascular factors (ischemia and hyperemia) seem to determine the type of osteolysis. Atrophic osteolysis develops in cases of hyperemia.

Infection

Authors emphasizing the role of infection refer to the paper by Hodgson et al. (1949), who reported 61 cases of "neurotrophic" bone lesions (19 of these were diabetics). In their opinion the bone is always infected through the plantar ulcer or the microlesions of the foot, and that is why the term "neurotrophic" was put in quotation marks. This concept is easily contradicted. The presented radiographs demonstrate characteristic DOAP cases; the plantar ulcer may be localized far away from the bone abnormalities, and the soft tissue and bone process may change independently. The articular fluid is sterile (the cited paper also mentioned this), and antibiotic therapy remains ineffective.

Copland (1954) ventured to support the concept of infection by stating that destruction may stop at any stage, but this statement just supports the neurogenic origin where spontaneous remissions often occur. Naturally, the histological picture is decisive. Nevertheless, in some cases infection may play a role, as in the cases of Aubertin et al. (1974), Fiorio (1969), and Róna and Kóczé (1970) and Whitehouse and Wechstein (1978). Infection is always secondary and interestingly, considering the susceptibility of diabetics to infection and that the osteoarthropathic bone serves as "locus minoris resistentiae", it is relatively rare. The symptoms of infection, and differential diagnostics, have been discussed in the relevant chapters.

According to Siegelmann and Jacobson (1970), infection by dramatically increasing the rate of osteolysis worsens the prognosis. In some cases this seems to hold true, yet we rather support the opinion of Sinha et al. (1972), who caution against the overestimation of radiographs made during the stage of infection. The exact size of the inflamed area on the foot is difficult to assess, since the disturbed circulation also makes it difficult to determine the focus of the destructive process. Gas formation, characteristic of inflammation, has been previously discussed. Bacteriological examinations have shown that these are not due to clostridial but staphylo- and streptococcal infections.

Mechanical and traumatic factors

In Eloesser's classic experiments (1917), cutting of the posterior roots in cats only resulted in Charcot joint if it at the same time injured the extremity. Authors attributing a significant role to trauma refer to this experiment.

Our own experience, however, did not provide supporting evidence. Fractures never occurred at the onset of the disease, but always as a symptom accompanying osteolysis. It is true, however, that trauma is thought to play a role mainly in the development of ankle and foot abnormalities.

Nevertheless, the contribution of mechanical factors is not negligible. The foot, besides being a frequently injured part, also bears the weight of the body. Due to neuropathy the patient is not careful with his painless foot; thus the role of frequent microtraumas in the development of DOAP is assumable. Bone abnormalities occur most frequently at the sites of greatest weight-bearing, as Seewald's exact mathematical calculations (1969) have proved.

The fact that DOAP occurs only rarely in the knee or spine, which are also mechanically strained parts of the bony system, proves that mechanical factors are only partly responsible or the pathogenesis.

Metabolic and hormonal factors

Since the metabolic disorder of diabetes also involves the proteins, the concept attributing a role to the direct *metabolic effect* on the bone matrix proteins is justified (Azérad et al. 1963, Buia and Lensi 1966).

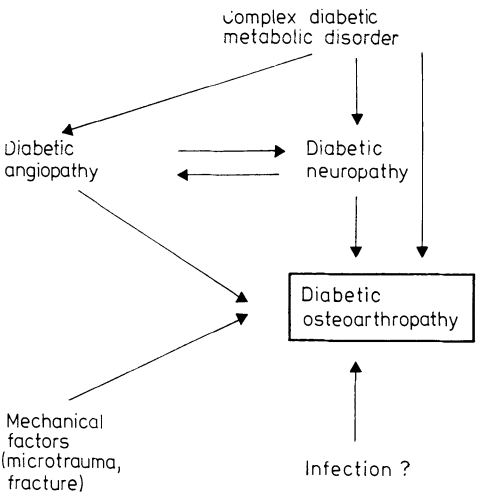
The possibility of *hormonal effects* must be added to the above hypotheses. Describing the radiographic picture of DOAP, we mentioned the high incidence of hyperostotic changes. As discussed in the previous chapter these are linked to the overproduction of somatotrophic hormone and are frequent in mild cases of diabetes mellitus. DOAP is generally a complication of insulin-dependent, severe cases. Therefore, a contradiction arises that is difficult to explain. Yet, if the disposition to hyperostosis is associated with labile, insulin-dependent diabetes, the conclusion must be drawn that a complex hormonal and metabolic disorder is present that may lead to severe complications.

The pathways of the development of DOAP are demonstrated in Fig. 54. The figure shows that complex metabolic disorders in diabetes lead to DOAP either indirectly via neuropathy or angiopathy or directly. These may also be associated with mechanical, traumatic factors and sometimes even with infection. In our opinion, besides the basic neuropathy, the joint effect of many factors is necessary for the development of the disease, and this explains the relatively rare incidence of DOAP.

Prognosis of diabetic osteoarthropathy

Bailey and Root (1947), the first to report a large number of cases, emphasized that in DOAP there is no tendency for recovery, and destruction advances slowly. Today this concept is not accepted; we feel that our patients also provide evidence supporting good prognosis. Moreover, gangrene of the soft tissues has a better prognosis if osteolysis accompanies it. Naide and Schnall (1961) drew attention to this apparently controversial phenomenon.

Fig. 54. Pathogenesis of diabetic osteoarthropathy



The explanation is that in these cases the neurogenic factors for a better prognosis are dominant in the pathogenesis of the soft tissue process. The sometimes striking recovery of soft tissue necrosis in diabetes was recognized long ago (Holt 1928).

Another apparently controversial phenomenon in our experience was that prognosis was better and recovery was more rapid in patients with inadequately managed carbohydrate metabolism, for example, their metabolism was poorly controlled because of inadequate treatment with oral antidiabetic drugs. In these cases, introduction of adequate insulin treatment resulted in recovery from the bone process. Bone processes rarely develop in adequately managed diabetes, but they are extremely difficult to control if they do. Lund and Holstein (1979) found that the prognosis for limbs with diabetic neuropathic ulcer is good under conservative treatment. Life expectancy is reduced.

Treatment and prevention of diabetic osteoarthropathy

It is not the aim of this book to give a detailed description of treatment. Nevertheless, reviewing the basic therapeutic principles is important. There are advocates of both surgical intervention and conservative management. We wish to emphasize the importance of conservative treatment in this introductory part.

Spontaneous recovery

If the disease is not treated or insufficiently treated, the osteolytic course will stop at a certain stage and recovery will start. This finding is supported by those cases in which radiography revealed only the end stage of the process. This is linked with the tendency to spontaneous recovery of diabetic neuropathy.

Conservative management

Conservative treatment is of utmost importance. Two main factors are involved:

1. The most important task is to ensure good diabetic control, which often means changing from oral antidiabetic drugs to insulin therapy.

2. Protection of the foot from weight-bearing; bed rest. The length of this must be longer than in cases of traumatic fractures. Calcium and large doses of vitamin B are recommended (Belser 1969, Reinhardt 1974*a,b*). We have also applied these measures. The evaluation of the therapeutic effect is difficult because the process also recovers without these drugs. A few other drugs are recommended in treating the painful peripheral neuropathy associated with diabetes (Davis et al. 1977).

Orthopedic shoes and walking splints also aid conservative management; with these the progression of deformities may be halted, and static functions and walking are ensured. Orthopedic literature discusses these in detail (Mau 1971). Other conservative procedures, for example to raise the limb (Bourne 1977), and decompression with the aid of insoles (Holstein et al. 1976), are also recommended.

According to Larsen (1958), neuropathic ulcers do not need any specific treatment. Others recommend local application of insulin solutions. We have tried the latter with good results. However, the exact evaluation of the therapeutic effect cannot be judged in these cases either. Graber et al. (1972) observed rapid recovery of the ulcer after incision and suturing. But this already leads to the question of surgical intervention.

Surgical treatment

In cases of nonhealing plantar ulcers, and especially for the maintenance of remission after recovery, several authors have performed resection of the destroyed capitulum and/or the base of the phalanx (Classen 1964, Kelly and Coventry 1958, McCullogh 1961, Singer 1976). We demonstrate such a case in Fig. 39h. It is worth waiting in these cases, too, as the process may recover without intervention.

Even extensive bone destruction is not an indication for surgical treatment, and caution is especially necessary before deciding on amputation. In cases of neurogenic bone changes, surgery is recommended only in young patients whose condition has not been sufficiently improved by conservative measures (Cauchoix and Darcy 1960). In Mau's opinion, the advance in surgical techniques has extended the list of indications. He recommended the resection of destroyed bone extending as far as the vascularized spongious area. Removal of necrosed bone fragments, and arthrodesis have been performed and recommended by several authors (Bruni et al. 1971, Heiple and Cammarn 1966, Takáts 1945).

In certain destructive bone changes of the tarsals, when the circulation and neurologic conditions are sufficient, plombage may be necessary in spite of secondary or concomitant infections. After removal of the necrotic bone fragments the cavity is filled with a preserved spongious block (Fig. 36d). Treatment with antibiotics will halt the infection. The reorganization of the preserved, transplanted bone may follow after several months of sufficient control of diabetes. During the process of total reorganization the foot must be protected from all weight-bearing stress.

Juhász et al. (1977) have demonstrated with tetracycline labeling techniques that the course of reorganization is similar in diabetics and nondiabetics, the only difference being in the rate: the process takes much longer in diabetes.

"Minor amputation" is recommended in infected cases. A few days of careful monitoring, however, is also justified for determining the severity and the extension of infection. A delay in the time of operation until maximum improvement of the local infection should improve the operative success rate (Goodman et al. 1976). Antibiotics should be administered in these cases.

"Major amputation" is only indicated if the process is accompanied by gangrene, unresponsive to conservative therapy. Gangrene has been reported to be 50 times more frequent in diabetics over 40 years of age than in nondiabetics of the same age. The results of the major amputations have not been uniformly good (Robson and Edstrom 1977).

Thus, DOAP "per se" is not an indication for amputation; the classic indications of obliterating arteriosclerosis will always be decisive in determining whether amputation should be performed. Recently, the importance of interdisciplinary teamwork is emphasized (Faerman et al. 1979).

Other therapeutic possibilities

Parsons and Norton (1951) reported 2 cases of DOAP in which progression stopped after lumbal sympathectomy. Others (Martin 1954, Sheppe 1953) did not report good results after this intervention. According to Cauchoix and Darcy (1960), sympathectomy can help only at the onset of the process, and its effect is uncertain. Considering the previously discussed role of vascular factors in the pathogenesis, we do not recommend the use of sympathectomy.

Grönberg and Saarme (1969) attained surprisingly good results by intraarterial injection of antibiotics. Kardos and Varró (1958), injecting antibiotics into the joint, reported worsening of the patients' condition.

Koluchenko and Kudryaisev (1964) observed good results with the local use of hydrocortisone. We do not apply these therapeutic methods and do not recommend their use.

In the therapy of DOAP conservative methods should be applied. In spite of extended bone destruction, the prognosis is good if neuropathic factors dominate the picture; the process may recover spontaneously and conservative management is definitely justified. Many unnecessary amputations are performed in these cases!

The prognosis is bad in cases where ischemia is the dominating factor, even if bone destruction is slight. Only in these cases is major amputation justified. In cases of infection, incision, drainage, and minor amputation may be applied.

This is how practice and theory (knowledge of pathogenetic factors) are related.

Prevention

It is a recognized fact that the foot of the diabetic patient requires close and special care (Ellenberg 1973, Scarlet et al. 1976). Larsen (1979) found that 62 of 100 diabetics had wrong positions or deformities in the feet. Both the patient and the physician have an important role. To ensure good diabetic control is the most important factor in prevention, as DOAP develops mostly in patients who are inadequately treated.

The patient suffering from diabetic neuropathy must be instructed to spare his feet as far as possible. He should not wear tight-fitting shoes, and if he notices any change on his foot, even if painless, he should consult his doctor immediately. In our experience, mild diabetic neuropathy causing many complaints is far less dangerous from the point of view of

DOAP, than those cases in which long-standing diabetes is associated with discrete neurological symptoms. In diabetics, examination of the feet must become a routine procedure; the initial disorders of sensation, and the stretching of ligaments must be revealed. The careful examination of the sole is important with special attention to callus formation. In diabetic neuropathy, radiographic examination belongs to prevention, especially in cases with clinical symptoms on the foot.

Summary

The term diabetic osteoarthropathy has been used to describe destructive lytic bone changes, which are late severe complications of diabetes mellitus affecting primarily the pedal bones and only exceptionally others.

The incidence of DOAP in diabetics is 0.2%–0.5%. Considering the high number of diabetics, this ratio is significant. A further rise is to be expected.

The changes occur more frequently among the 50- to 69-year-old patients. Sex distribution shows no significant difference. Bone abnormalities develop after a long duration of diabetes; in 70% of the cases 10 years after the onset. Other diabetic complications also occur.

DOAP develops more frequently in patients with labile metabolism, or in inadequately treated patients with chronic unbalanced metabolism.

The clinical symptoms and accompanying soft tissue changes are subdivided into four groups: There are neurological symptoms (Group I), which can be found in each stage of the disease. Sometimes only these symptoms are revealed by clinical examinations and, yet, bone destruction appears. Often the loose joints and articular swelling (Group II) draw attention to bone abnormalities. Bone changes often accompany plantar ulcers (Group III) and certain skin lesions. The deformities of the foot (Group IV) often indicate the terminal stage of the process.

The course of the disease is subdivided into three stages with characteristic radiographic features. I. Initial symptoms (osteoporosis, dislocation, cortical defect). II. Progression (osteolysis, fragmentation, pathological fractures, periosteal reaction). III. Healing, which has several radiologically distinguishable types. Severe degeneration of the vessels and frequent hyperostosis in other bones are found.

The process has no characteristic histological features and the destruction of all articular components can be found.

The ankle is affected in 10% of the cases; the tarsus, metatarsal, and phalanges are affected in the others. DOAP localized elsewhere is a rarity in the literature.

In differential diagnostics DOAP has to be distinguished from inflammatory, tumorous, degenerative processes, and neurogenic osteoarthropathies of other origin.

The changes are the results of a complex process. Apart from the basic diabetic peripheral neuropathy, vascular, mechanical, metabolic, hormonal, and sometimes infective factors play a role. Furthermore, the combined effect of these factors can also be involved in the pathogenesis.

Prognosis is generally good. Conservative therapy should be applied whenever possible; even in cases of extensive bone destruction recovery may be expected. Amputation should be considered only in cases where other complications are also present.

Good diabetic control is a decisive factor in the outcome of therapy and prevention. Education of the diabetic patient is also of utmost importance for the prevention of lesion.

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Chapter 5

Metabolic joint diseases and diabetes mellitus

Gout and diabetes mellitus

Uric acid is a compound chemically related to alloxan. Alloxan destroys the pancreatic beta cells and thus induces diabetes. According to Griffiths' studies (1950) uric acid has the same effect. Presumably in patients with gout, uric acid crystals are precipitated in the pancreas and as a consequence the islet cells are destroyed. According to this concept the concomitant manifestation of gout and diabetes would be expected. The relationship is not at all equivocal. According to the results of the Framingham study (Hall et al. 1967) and the Tecumseh study (Mikkelson et al. 1965) conducted on large populations, there is no such relationship between gout and diabetes.

In diabetes there is not a higher incidence of gout; on the contrary, it is lower than in the average population (Berkowitz 1966, Eyman 1969, Hasslacker et al. 1974, Shichikawa and Komotsubara 1964, Varjas and Bobkó 1972). Herzberg (1973) found one patient with gout among 314 diabetics. Herman et al. (1976), examining 10,000 subjects, found that in prediabetic conditions the uric acid level was lower as compared to the average population and, at the time when diabetes appeared, the level was further reduced and the lowest uric acid levels were detected in manifest diabetes. These findings were supported by the clinical observations of Bartels et al. (1960): after the manifestation of diabetes the number and severity of gouty attacks were reduced. Bruncsák and Faragó (1977) observed that in patients whose diabetes was well controlled the uric acid level hardly differed from normal, while in poorly controlled cases the uric acid levels were significantly reduced. These low levels are probably due to increased excretion.

At the same time, a disorder of the carbohydrate metabolism is frequent among patients with gout. According to the type of disorder in their patients and the criteria of glucose tolerance, various authors found latent or manifest carbohydrate disorders in 2%–61% of the patients with gout (Table 24). Apart from the tabulated data, Bernheim (1968), Gerfeldt (1973), and Mader (1972) demonstrated such a relationship. According to Boyle et al. (1968, 1969), in gout the values of the glucose tolerance test were significantly higher as compared to the values in patients without gout.

The link between hyperuricemia and hyperglycemia is manifold and complicated (Buttorini 1973). The concept assuming that hyperuricemia is not directly linked to the disorder of the carbohydrate metabolism, but to hyperlipidemia and obesity, is also justified (Berkowitz 1966, Bobkov 1968, Boyle et al. 1968, Fekete et al. 1976, Mader 1972, Weidemann et al. 1972). Thus, hyperuricemia, gouty arthritis, and diabetes mellitus are frequently found in association with hyperlipidemia, obesity, hypertension, and vascular disease, but a direct association between the two diseases has not been proven.

Two of our diabetic patients had manifest gout. In both cases, we observed the typical picture of hyperostotic spondylosis. This is not at all surprising, considering that both hyperostosis and hyperuricemia are part of a complex metabolic disorder. We found two data

Table 24

Incidence of disturbed carbohydrate metabolism in patients with gout according to literary data

Authors		Disturbed carbohydrate metabolism, incidence (%)
Gamp et al.	1965	2.5
Whitehouse and Clearly	1966	10
Knick et al.	1968	59
Baccarini and Porzio	1969	5.2
Denis and Launay	1969	7–55
Eyman	1969	4.7
Spring and Fleck	1970	4–5
Mertz and Babucke	1971	22.5
Varjas and Bobkó	1972	22.7
Klotz and Prohaska	1973	8.8
Babucke and Mertz	1973	30
Durward	1973	2
Diamond et al.	1974	42.9
Matkies et al.	1975	61

in the literature referring to the link between hyperostotic spondylosis and gout: Schilling et al. (1965) observed hyperuricemia in 48% of their patients with hyperostotic spondylosis and, in one third of these, they found manifest gout. Queiros et al. (1974) found an 18% incidence of gout among their patients with Forestier disease. Bogner and Tilscher (1976) often observed chronic recurring back pains in patients with gout.

Chondrocalcinosis and diabetes mellitus

Although various authors have found carbohydrate metabolic disorders in 9%–70% of patients with chondrocalcinosis (Table 25), the link between the two disorders is questionable. Control of hyperglycemia does not influence the number and severity of the acute attacks of symptomatic chondrocalcinosis. Most authors agree that there is no causal linkage between chondrocalcinosis and diabetes, and that the frequent simultaneous manifestation of the two disorders cannot be unequivocally proved (Bastin 1964, Berkowitz 1966, Gerster et al. 1975, Radi et al. 1970). Bossa et al. (1970) found two cases of chondrocalcinosis of the knee among 60 diabetics.

Berry and Miller (1973) observed the concomitant occurrence of chondrocalcinosis, diabetes mellitus, hereditary spherocytosis, and hemochromatosis.

Currently the combined occurrence of hyperlipidemia, hyperuricemia, and diabetes associated with the *aseptic bone necrosis* of the *femoral head* has been frequently observed (Reinhardt and Wagner 1980). In the case reported by Wilke et al. (1974), multiple aseptic necroses occurred bilaterally in the head of the femur and humerus and in the knee joints.

Yaretzky et al. (1976) reported the simultaneous occurrence of hyperlipidemia, diabetes, synthoma, and abnormal fractures.

Table 25

Incidence of disturbed carbohydrate metabolism in chondrocalcinosis

Authors		Disturbed carbohydrate metabolism, incidence (%)
Serre et al.	1965	12
Currey et al.	1966	9
Solnica et al.	1966	10.7
Moskowitz and Katz	1967	31.5
Skinner and Cohen	1969	70
Radi et al.	1970	9.7
Boussina et al.	1971	26.5

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Chapter 6

Congenital and hereditary bone disorders and diabetes mellitus

Fetal skeletal abnormality

There is a high incidence of fetal skeletal abnormalities in the children of diabetic mothers. Diabetic metabolic disorders presumably provoke and deteriorate hidden developmental anomalies. According to Navarette et al. (1967), a pathological material glucose tolerance test was found in 10% of various congenital malformations as compared to 3.3% in the control group. Passarge and Lenz (1966), and Blumel et al. (1959) found 14%–18% maternal diabetes in cases of *lumbosacral agenesis*. In 0.1%–1.0% of maternal diabetes, the tubular bones of the lower extremity, primarily the femur, are either entirely missing or hypoplastic. Diabetes in the father does not seem to increase the number of skeletal abnormalities, suggesting that maternal vascular insufficiency in the placenta is a major factor in the development of malformations. Another factor possibly causing fetal abnormalities is the control of carbohydrate metabolism during gestation.

Merimée et al. (1970), and Stimmler et al. (1970) found the occurrence of dwarfism, various developmental disorders, and diabetes.

Osteogenesis imperfecta and diabetes mellitus

Osteogenesis imperfecta has been described to be linked with several diseases, first of all with those of the hematopoietic system (Forgács 1970). As diabetes has not been listed among these diseases, our observation of osteogenesis imperfecta associated with diabetes in a 57-year-old woman and in her 75-year-old mother was worth attention. Blue sclera and bone fractures were found in five generations of this family, and several members suffered from diabetes.

We compiled some data in an attempt to correlate the two diseases.

1. Early arteriosclerosis has been observed in osteogenesis imperfecta (Langness and Behnke 1970).

2. Diabetes-linked biochemical changes have been found in osteogenesis imperfecta (Langness and Behnke 1970).

3. According to a modern concept, osteogenesis imperfecta is due to disturbed hydroxyproline metabolism, which has also been detected in diabetes (Lohmann et al. 1970).

Naturally, these data are very scarce and insufficient for determining a definite relationship. It seems more likely that in our cases the concomitant occurrence of familial diabetes and osteogenesis imperfecta was accidental.

Achondroplasia

Collip et al. (1972), Tempany (1961), and Wolcot and Rallison (1972) reported pathological blood sugar curves and diabetes in *achondroplasia.* Cotton et al. (1970) found disorders of the carbohydrate metabolism in *Cockayne's syndrome.*

Osteopoikilosis

Haddad et al. (1976) found familial osteopoikilosis in five siblings; one had diabetes and many members of the family were also diabetic. Presumably this was a chance coincidence. We also observed hypergammaglobulinemia, but apart from this no other metabolic disorder was detected (Forgács 1970).

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Chapter 7

Growth and bone development in diabetic children

Many contradictory data have been published on this topic, mainly because unambiguous, severely retarded bone development occurs only in *Mauriac*'s syndrome (diabetes mellitus with hepatomegaly and dwarfism). In other diabetic children, normal, retarded, or accelerated development may equally occur. Another reason for arguments is that the body height in most cases is abnormal when diabetes is first detected (Gegesi-Kiss and Barta 1966); the children are either shorter or taller (Drayer 1974) when compared to the average values. Even in the latter group, however, the final body height often lags behind the normal. According to Pond (1970), the retardation in growth is approximately 6%–10%, influenced by the duration, type, and control of the metabolic disorder. In the opinion of Jivani and Rayner (1973), only the duration of diabetes plays a role. According to Saccetti et al. (1978), better metabolic control exerts an evident influence on growth.

In certain cases small stature is associated with flexion contracture of the hand (Barta 1980; see also "Diabetic hand on p. 133).

Weil (1967), studying the bone development of diabetic children and their nondiabetic siblings, found no significant difference. According to Tattersall and Pyke (1973), growth retardation in twins was detectable if diabetes manifested itself before puberty.

Weil (1967), Birbeck (1972), and Evans and Lister (1970) found normal bone development in cases of adequately controlled diabetes. The final height of the children depends on genetic factors and not on diabetes. According to Craig (1970), normal bone development does not prove a balanced metabolism.

Roentgenologic studies of diabetic children (Jaffe 1972) revealed that the postnatal ossification centers are slightly ahead in development of the chronological age. In children with long-standing diabetes, however, the ossification centers are less developed than in nondiabetic controls of the same age. Transverse lines frequently occur in the metaphyses of the long tubular bones of these children. These dense, thin lines are not characteristic roentgenologic signs. They are present in several bone diseases, and eventually also in normal children. Hadzidekov et al. (1968), and Weber et al. (1969) also found disturbed ossification in diabetic children.

Summarizing the literary data, the following conclusions can be drawn: although a mild disorder in bone development is observable, in cases of well and regularly controlled diabetes substantial ossification disorder will not develop.

Similarly, Barta and Bókay (1976), examining the body height of diabetic children, found that even adequately treated diabetes has a negative effect on growth. However, in cases where body height is extremely low, other factors are also involved.

Adler et al. (1973), and Bohátka et al. (1972) studied the development of teeth in diabetic children. Acceleration or retardation was found, depending on the age of the patient at the onset of diabetes. A prolonged toothless period was observed.

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Chapter 8

Periarthritis of the shoulder and diabetes mellitus

Kaklamanis et al. (1975) studied the calcifications around the shoulder in diabetics and nondiabetics. These changes were often bilateral, and occurred in 22% of the diabetics as compared to 8% observed in the control group. The authors were unable to explain this phenomenon. Considering these calcifications as part of a disposition to generalized hyperostosis, it is easy to understand the frequent occurrence in diabetes. The disease is often associated with Dupuytren's contracture, and is less painful than in nondiabetic cases (Lequesne 1977). The presence of retraction caused by capsulitis was confirmed by arthrography.

There are other reports in the literature considering the relationship between periarthritis of the shoulder and diabetes mellitus (Bridgman 1972, Drouin et al. 1973, Laul 1967, Rodrigez et al. 1968). Bridgman (1972) found humeroscapular periarthritis in 86 (10.8%) out of 800 diabetics, particularly among the insulin-dependent patients. Laul (1967) observed elevated fasting glucose values in 90% of patients with periarthritis of the shoulder. Sullivan found bursitis in 22% of diabetics and in 4% of the control group.

Chaiton and Sullivan (1974) disputed whether a relationship could be established between the two diseases on the basis of the above studies. Lundberg (1969), examining 216 "frozen shoulders," found 12 cases of diabetes (6%) among them. Lequesne et al. (1977) found diabetes in 17 of the 60 patients with capsulitis of the shoulder versus 7 in 60 control subjects. The difference is statistically significant.

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Chapter 9

The connection between other disorders of the skeletal system and diabetes mellitus

Rheumatoid arthritis

Weigl (1970) found 3 manifest and 3 latent diabetes among 100 patients with rheumatoid arthritis.

In Sweden, 0.9% of the diabetic males and 2.4% of the diabetic females suffered from rheumatoid arthritis (Grönberg et al. 1967). Powel and Field (1964) found a higher incidence of retinopathy when the two diseases occurred jointly, as compared to other diabetic populations.

A difficulty in the evaluation of the two diseases when occurring jointly is caused by steroid therapy applied in rheumatoid arthritis (steroid diabetes). Some features of joint manifestation have been discussed in the chapter on diabetic osteoarthropathy.

Mehrota and Singh (1976) found a higher incidence of rheumatoid factor in insulin-treated diabetics as compared to diabetics treated with oral antidiabetic drugs, suggesting that in some individuals the presence of rheumatoid factor activity is associated with chronic antigenic stimulation by insulin.

Paget's disease

Frehner and Hohl (1961), studying 28 patients with Paget's disease, found pathological glucose tolerance test results in 14 cases; one patient had manifest diabetes. Epiney and Medenica (1970) found 8 cases of manifest diabetes among 75 patients with Paget's disease. These authors suspect the presence of a common genetic factor.

We examined the carbohydrate mechanism in 8 patients with Paget's disease. One patient had manifest diabetes, and in 4 cases pathological glucose tolerance was established, which indicates a disturbed carbohydrate metabolism. Early, severe atherosclerosis and hypertension are symptoms associated with both diabetes and Paget's disease, which may support the concept of a relationship between the two diseases.

Hyperparathyroidism

Hyperparathyroidism is associated with hypercalcemia and characteristic x-ray features. Yasuda et al. (1975) reported increased insulin production in this condition. Ziegler et al. (1972) also observed an increased insulin secretion related to hypercalcemia. However, there is no clinical evidence suggesting that increased insulin secretion leads to hypoglycemia in patients with hyperparathyroidism.

Moreover, Walsh et al. (1975) reported 8 cases in which hyperparathyroidism was associated with diabetes. Although the joint manifestation of hyperparathyroidism and dia-

betes may be accidental, there seems to be a link between hyperparathyroidism and pancreatitis that often appears in a subclinical form. On the other hand, hyperglucagonemia is frequently found in this disease, and this may also be due to the deranged carbohydrate metabolism.

Osteomyelitis

Earlier literature stressed the high incidence and severity of osteomyelitis in diabetics, with less marked signs of inflammation (Beck 1959). Following recovery, a marked sclerosis develops (Donner and McAffee 1960). According to Kubin and Sebek (1974), the joint incidence of chronic osteomyelitis and diabetes is 3.9%. Younger and Hadley (1971) observed osteomyelitis of rare localization in diabetics: in two cases the sternoclavicular joint, in one case the upper cervical vertebrae, were involved. Hirschmann et al. (1976) reported a case of vertebral osteomyelitis caused by *Candida albicans* in a 22-year-old diabetic woman.

Periodontal changes

The importance of oral hygiene and periodontal changes in diabetics has been recognized and emphasized for many years. Both the soft tissues and bones are affected. Bone atrophy, osteoporosis, and early loss of teeth are characteristic (Cheraskin and Ringsdorf 1970, Cohen et al. 1970, Finestone and Booruly 1967, Wysokinska 1970). Similar changes are observable in experimental diabetes (Borghelli et al. 1967, Cohen et al. 1970).

Miscellaneous

Gas in the joint and periarticular tissues may be an early manifestation of gram-negative septic arthritis in diabetics ("pneumoarthropathy") (Meredith and Rittenberg 1978).

Carbohydrate metabolism plays an important role in the development of *ankylosing spondylitis* (Stepan and Ott 1969). Carbohydrate metabolic disorders were revealed in one-third of these patients.

Islet cell carcinoma of the pancreas producing insulin and causing hypoglycemia sometimes leads to bone metastases. Cubilla and Hajdú (1975) detected bone metastases in 4 of 30 cases.

In a series of 40 cases of *synovial chondromatosis* (Schiano et al. 1976), 17 patients (42.5%) suffered from diabetes mellitus, and all of them were non-insulin-dependent. There are no other data of such a significant occurrence in the literature. Krause (1973) reported chondromatosis in the knee joint in association with diabetes in an elderly female patient.

Scleroderma results in characteristic radiographic changes on the terminal phalanges and is rarely accompanied by diabetes. Bhargava et al. (1973) encountered scleroderma accompanying extensive subcutaneous calcinosis and diabetes.

Thiers et al. (1967) reported the joint manifestation of polychondritis and diabetes mellitus.

Growth disturbances occur in *Turner*'s and *Klinefelter*'s syndrome, genetically linked to diabetes.

Smith (1976) followed the joint manifestation of hypophosphatemic osteomalacia, Fanconi's syndrome and diabetes in four generations of a family.

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Chapter 10

Bone changes in lipoatrophic diabetes

Lipoatrophic diabetes is an extremely rare disease. According to Griffiths and Rossini (1975), only 70 cases were reported in the literature until 1975.

Symptoms: insulin-deficient diabetes, hepatosplenomegaly, and entirely missing lipoid tissue. In some cases gigantism (Seip 1959), hirsutism (Fairney et al. 1969), and other congenital abnormalities accompany the disorder.

Radiographic changes were detectable in each case, although the x-ray signs were different in each case report. Advanced ossification has often been described in affected children (Arky and McCully 1974, Fairney et al. 1969, Gold and Steinbach 1967). The initial accelerated growth in children slows down later (Reed et al. 1965) and finally the body height remains low.

Osteosclerotic changes are characteristic. Diffuse increased density of the bones or localized sclerosis are observable. The density is highest in the diaphysis of the long tubular bones, where the red marrow is replaced by yellow marrow. Localized sclerosis resembles bone infarction (Lejeune and Tourniaire 1969) or osteopoikilosis (Griffiths and Rossini 1975). In the elongated epiphyses, especially in the head of the humerus, cystic changes occur besides sclerosis (Brunzell et al. 1968, Gülell-Gonzales et al. 1971, Wesenberg et al. 1968, Zöllner et al. 1975).

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Chapter 11

Bone fractures and diabetes mellitus

Before the insulin era, fractures due to generalized osteoporosis in diabetic patients caused much trouble.

According to a few reports, there is a high incidence of diabetes among the patients who have fractured the neck of the femur. Julkunen et al. (1971) found 16 diabetics among 166 such accidents. Menczel et al. (1972) compiled the data of 340 such cases and found a 22% incidence of diabetes. Diabetics with fractures of the neck of the femur were relatively young, and often the fracture was due to a very slight trauma.

Recenthy Heath et al. (1980) observed nearly 1,000 diabetics. Their data strongly affirm that diabetes mellitus is not a risk factor for skeletal fracture.

Fiandaca et al. (1975) studied the effect of bone fractures on the carbohydrate metabolism in diabetics and nondiabetics. They found that fractures may induce manifestation of latent diabetes. Well-controlled diabetes may become decompensated due to trauma; therefore, establishing the necessary diabetic regimen is an absolute precondition before a surgical intervention. In these cases, the fractures show a favorable healing tendency. In contrast, Cozen (1972) often observed prolonged healing of fractures in diabetics.

The susceptibility to gas-forming infection in diabetes has already been discussed (pp. 108). Deutsch (1975) reported a case of closed femur fracture associated with nonclostridial gas-forming infection.

Severe bone fractures occur rarely in hypoglycemic coma (Prillman and Thompson 1969, Wheelock and Root 1959).

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