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OSTEOMALACIA

PATHOGENESIS AND TREATMENT

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[WITH SPECIAL PLATE]

Two processes are to be distinguished in the formation of osseous tissue. First the matrix, a tissue rich in proteins, is formed by the osteoblasts. Then this matrix is calcified by precipitation of calcium phosphate. In osteomalacia the bone matrix is formed but its calcification is insufficient, and this gives rise to the development of osteoid zones—that is, non-calcified matrix—around the bone trabeculae.

The same abnormalities are found in rickets, which is only distinguished from osteomalacia in that it concerns young persons in whom the epiphyses have not yet closed, so that here also the deficient calcification becomes manifest. Owing to the insufficient calcification an adjoining osteoid zone is formed. Thus wide and irregular epiphyses develop. In adults the epiphyses are closed, so that the morbid process manifests itself only in the formation of new bone, which also regularly takes place in adults. Apart from the osteoid zones around the trabeculae on the flat and long bones, a more or less general decalcification of the skeleton is found, which is attributable to the inhibited regenerative calcification. Especially in osteomalacia, with which the present paper mainly deals, this is very characteristic.

The inadequate calcification may be the result of deficiency of calcium as compared with the inorganic phosphate level, or of a too low inorganic phosphate level with respect to the calcium content, necessary for a normal precipitation of calcium phosphate in the bone matrix. The causes of disturbed calcification may be various.

Vitamin-D Deficiency

The action of vitamin D has so far not been completely elucidated. It is, however, an established fact that under the influence of vitamin D calcium absorption from the intestine is stimulated, and, probably indirectly, also the absorption of inorganic phosphate. In the event of a deficiency a considerable quantity of the calcium and phosphate taken up with the food is therefore lost; calcium excretion in the stools increases markedly, while excretion of calcium in the urine is much decreased. The latter may be regarded as an early manifestation, as the blood calcium level may still be normal at this stage. The tubular reabsorption of inorganic phosphate is also disturbed, either as a direct result of vitamin-D deficiency or, as Albright *et al.* (1946, 1953) think, as a result of a secondary hyperparathyroidism.

In many cases the disturbed reabsorption of amino-acids, as sometimes observed in rickets, is favourably influenced by vitamin D (Jonxis, 1955a). It is further probable that vitamin D stimulates the deposition of calcium phosphate in the bone matrix.

Vitamin D is formed in the skin from 7-dehydrocholesterol under the influence of sunlight (ultraviolet rays). Lack of sunshine will therefore promote the development of osteomalacia. When the sun's rays pass through a deep layer of fog or through ordinary window glass, much of the ultraviolet radiation is lost, and thus also the power to synthesize vitamin D.

An important source of vitamin D for man is his food. It is present in large amounts in the liver oil of certain kinds of fish, and in much smaller quantities in milk, butter, cheese, eggs, and fat fish (herring, salmon, sardines). The fat of fish contains much vitamin D, that of other animals little or none, unless they feed on fish. The vitamin-D content of liver oil and of the foodstuffs mentioned shows wide variations, depending on a number of factors. The greatest differences depend on the season of the year. Thus milk and its products and eggs obtained in summer contain far more vitamin D than in winter.

Here a reminder should be given that nowadays margarine is often used as a butter substitute, and that this product does not contain vitamin D unless it has been specially added. It should also be pointed out that the regular internal use of liquid paraffin may lead to a disturbance of vitamin-D absorption, the vitamin being taken up by the paraffin.

Calcium Depletion

As vitamin-D deficiency is often due to a shortage of milk products, the nutrition is also deficient in calcium. Even so, this need not lead to the development of frank osteomalacia so long as the subject is exposed to a sufficiency of sunlight. Hence it is that the disease is most often seen in those who lead mainly an indoor life.

The risk of osteomalacia developing is greater when the vitamin-D deficiency is accompanied by some other condition—for example, pregnancy—promoting calcium depletion. In the last stages of pregnancy the mother loses 20–30 g. of calcium to the foetus, and during lactation there is a daily loss of 250–350 mg. of

calcium in the maternal milk. Moreover, during pregnancy the *p*H of the gastric juice is often high, and this exerts an unfavourable influence on calcium absorption from the intestine. Although "hunger osteomalacia" occurs only rarely, mild forms of the disease have been observed in pregnant women and, according to Meulengracht, also in the elderly.

Faulty Intestinal Absorption

An important cause of osteomalacia is a disturbance of absorption of vitamin D by the intestine, which is usually accompanied by a disturbed calcium absorption. Vitamin-D absorption takes place in the small intestine, the presence of bile being necessary even though there is an excess of the vitamin. Hence absorption is inadequate when there are biliary fistulae, and in cases of prolonged jaundice due to biliary congestion or liver disease. Sprue or chronic pancreatitis is more often the cause, in which vitamin D as well as vitamins A and K (the fat-soluble vitamins), but also calcium, are insufficiently absorbed. Lastly, in regional ileitis and after operations in which an intestinal shunt has been made the absorption of vitamin D may be inadequate.

Lack of calcium may be due to the formation in the bowel of insoluble calcium complexes (oxalate, and particularly phytate). The latter is found in large amounts in cereal grains.

Skeletal Abnormalities

It is worthy of note that in the clinical picture of osteomalacia as sometimes observed it is not so much the skeletal deformities caused by the calcium deficiency (thin, flexible cortex of long bones, deformed pelvis, and "fish vertebrae" due to pressure of the intervertebral disks) which dominate the picture, but rather more local abnormalities with more or less (and not rarely very little) decalcification. This is to be attributed to the shorter duration of the process (Dent and Hodson, 1954). It should be realized that radiologically visible general skeletal abnormalities do not arise until after the calcium reserve has decreased by about 30%. The abnormalities are then limited to slit-like or wider (band-shaped) clear areas in the skeletal shadow. Usually there are several at the same time, in most cases localized symmetrically. These gaps may be shallow, but they may also interrupt the whole continuity of the skeleton (pseudo-fissures or pseudo-fractures). They are especially to be found in the os pubis and ischii, collum femoris, the ribs, radii, ulnae, and metatarsals. Looser (1920), who extensively studied these abnormalities in patients suffering from osteomalacia and rickets, called them *Umbauzonen* (zones of transformation) because they are not real fractures. Histological examination proved them to consist of non-calcified cells, which was confirmed by Seeliger (1923) and Justin-Besançon, and Delarue.

In the literature these radiological abnormalities are sometimes referred to as the "Milkman syndrome." They occur, however, especially in osteomalacia due to vitamin-D deficiency or disturbed renal tubular function (renal tubular osteomalacia; see below). They are sometimes also observed in other skeletal diseases (Paget's disease, Cushing's disease, congenital syphilis, hyperparathyroidism), but in such cases they are not symmetrically localized, which is usually the case in osteomalacia (Albright). Moreover, these *Umbauzonen* develop at sites where osseous abnormalities were already present, or as a result of trauma (Steinbach *et al.*, 1954).

These skeletal abnormalities and the above-mentioned localization were initially attributed (Looser, 1920; Justin-Besançon, 1942; Debray *et al.*, 1943; Boquien and Bureau, 1943; Pompen *et al.*, 1946) to the association of decalcification with "mechanical stress" to which these parts of the skeleton were especially exposed. Recently, on the basis of anatomical (Le May and Blunt, 1949) and angiographic research (Steinbach *et al.*, 1954), it has been sought to establish a relationship with the locally close contact of pulsating blood vessels with these bones, and thus introduce the concept of "vascular stress."

It may here be of interest to present some examples of these skeletal abnormalities observed in patients with osteomalacia caused by deficient nutrition during the war years 1943–5. The patients were nuns living in convents, 15 of whom showed the same signs and symptoms. In these cases lack of solar radiation was probably an additional factor. The patients complained of pains in the loins and upper legs, with difficulty in rising from the sitting position. They had a tottering gait, and often were unable to lift their legs adequately during walking. It is important to remember that these patients are usually not emaciated, as it is the quality rather than the quantity of their food which is at fault. Both the inorganic phosphate and calcium levels of the serum may be decreased, though it is not unusual for normal values to be found, as in our patients; the alkaline phosphatase level is increased, however (Table I).

TABLE I.—*Laboratory Findings and Skeletal Lesions in Patients with Osteomalacia Due to Nutritional Deficiency*

Patient	Age (Years)	Serum			E.S.R. (mm. in 1 hr.)	Haemoglobin (%)	Achylia Gastrica	Pseudofractures
		Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (K.-A. units)				
M.	54	11	4·2	17·4	20	80	+	Os pubis
H.	38				14			,, (bilateral)
H. after treatment	39	9·7	4·3	5·5				Coll. femoris
P.	48	11	3·8	21·7	12	77	+	Os pubis, os ischii (bilateral)
A.	37	10·2	2·4	11·2	15			Os ischii (bilateral)

On the radiographs clear *Umbauzonen* are visible in the pelvis and femoral neck (Special Plate, Figs. 1 and 2). Similar radiological abnormalities are found in non-tropical sprue, a case of which is illustrated in Figs. 3A and 3B of the Special Plate. This patient had low levels of calcium (7 mg. per 100 ml.) and inorganic phosphate (2.1 mg. per 100 ml.), with increased alkaline phosphatase (21.4 King–Armstrong units) and low excretion of calcium in the urine. The deterioration in her condition during the period 1951–6, when she had withdrawn from treatment, is clearly visible.

While it is true that to-day the forms of osteomalacia which are due to deficient nutrition or disturbed absorption are not very prevalent in Western Europe, the possibility of their occurrence should not be overlooked. A satisfactory body weight certainly does not exclude this pathogenesis, as the deficiency in question is usually qualitative rather than quantitative.

The *x*-ray abnormalities described above may also occur in the absence of nutritional deficiency or disturbed absorption in the small intestine, and the causes of this deserve mention.

Non-nutritional Causes

Renal Tubular Dysfunction

A disturbance of renal tubular function, with insufficient reabsorption of inorganic phosphate, may give rise to the same picture. Concentration by the kidney is normal, and so is glomerular function. In these patients absorption of calcium from the intestine is also disturbed, urinary calcium excretion being low (Snapper, 1957). Serum calcium is normal, inorganic phosphate decreased, and alkaline phosphatase increased. Excretion of inorganic phosphate in the urine is not remarkably high, but high enough when compared with the low serum level. As this form of osteomalacia does not react to vitamin-D treatment it is sometimes referred to as vitamin-D-resistant osteomalacia. In this disease the radiological abnormalities (*Umbauzonen*) already described have repeatedly been found. It may occur in a milder form, so that the patient reaches adult age before it is discovered, but often such patients have already suffered from rickets in their youth as a manifestation of the underlying metabolic upset (Anderson *et al.*, 1952).

In addition to the disturbance of inorganic phosphate reabsorption, the reabsorption of glucose (renal glycosuria) and/or amino-acids (aminoaciduria) may also be affected; in the latter case sometimes of only one amino-acid—namely, glycine (Rose, 1956). When the picture is one of aminoaciduria it is called Lignac–De Toni–Debré–Fanconi syndrome. Sometimes the disease is not of a hereditary nature, and the radiological and biochemical manifestations of osteomalacia do not appear until the age of 16 years or more.

Inability of Renal Tubules to Produce Acid Urine, Combined with Disturbed Formation of Ammonia, Causing Acidosis

As a compensatory mechanism in this disorder sodium, potassium, and calcium are utilized as bases for the excretion of the acid radicals. The increased excretion of calcium and phosphate brought about in this way causes osteomalacia. This picture is observed in cases with congenital dysfunction of the distal convoluted tubules or chronic pyelonephritis, and also after administration of large doses of sulphanilamide (Snapper, 1949).

Idiopathic Hypercalciuria

This abnormality is caused by disturbed tubular reabsorption of calcium, so that much calcium is excreted in the urine and nephrolithiasis develops (Klotz *et al.*, 1955). An opportunity has recently arisen to study this condition in a 15-year-old boy who came under treatment for attacks of abdominal pain and haematuria.

On a diet containing 280 mg. of calcium a day the 24-hour urinary calcium excretion was 317 mg. Calcium was deposited in several renal calices (Special Plate, Fig. 4). The calcium and inorganic phosphate levels were normal (9.9 and 2.5 mg. per 100 ml. respectively), but alkaline phosphatase was increased (19 King-Armstrong units). No skeletal defects were demonstrable radiologically. Renal function was normal (phenolsulphonphthalein test (Rowntree) 70%; urea clearance 60%), as also was the alkali reserve of the blood (48.3 vols.%).

In addition to those mentioned above there are other, rarer, causes of osteomalacia—for example, disturbed formation of alkaline phosphatase by the osteoblasts—which cannot be dealt with here.

Prolonged Corticosteroid Treatment

Marked osteoporosis, and also osteomalacia, may develop after prolonged treatment with corticotrophin or cortisone, as we have recently observed in several cases.

One patient, a 53-year-old man with rheumatoid arthritis, had been treated for three years successively with corticotrophin, cortisone, and (for the last year) 15–25 mg. prednisone per day. *X*-ray examination showed marked atrophy and decalcification of the skeleton, in particular of vertebrae, one of which showed a fracture with wedge-shaped compression (Special Plate, Fig. 5). The serum calcium was 9 mg. per 100 ml., inorganic phosphate 3.2 mg. per 100 ml., and alkaline phosphatase 15 King-Armstrong units. After loading with 945 mg. calcium (according to Nordin and Fraser, 1956; see below) the four-hourly retention was 78.3% and the 12-hourly excretion only 16.7%. The picture is therefore characteristic of osteomalacia.

In recent years several cases of osteoporosis with fractures (of vertebrae, femoral neck, ribs, pelvis) have been described in patients treated with cortisone or corticotrophin for rheumatoid arthritis, pemphigus, bronchial asthma, or lupus erythematosus (Curtiss *et al.*, 1954; Turiaf *et al.*, 1956; Vignon *et al.*, 1956). The fractures sometimes occurred as early as two months after treatment was started, and in such cases the previous condition of the skeleton and the dosage of corticosteroids play their part. The cause of these skeletal abnormalities can be sought in antianabolic influences involving the proteins. Not only does urinary nitrogen excretion increase as a result of hormonal treatment, but also the excretion of calcium (Sprague *et al.*, 1950; Eliel and Heaney, 1954; Luft *et al.*, 1954) and phosphate (Roberts and Randall, 1955). Of great importance is the considerable loss of calcium in the stools (Sprague *et al.*, 1950; Anderson *et al.*, 1952; Lichtwitz *et al.*, 1955; Morgan *et al.*, 1956). It is probable that this is due to an increased excretion via the intestines (Morgan *et al.*; Lichtwitz *et al.*) rather than to decreased absorption (Anderson *et al.*). The possibility that osteomalacia may also develop must therefore be reckoned with. Support for this opinion was provided by the fact that our patient had an increased blood alkaline phosphatase, and also by the result of the calcium loading test, in which calcium retention was 78%. On the other hand, the blood alkaline phosphatase might not be increased, any tendency for it to rise being controlled by the corticotrophin (Bardawill *et al.*, 1951). In our patient the alkaline phosphatase level rose after discontinuation of treatment.

An increased serum alkaline phosphatase has also been found in cases of Cushing's syndrome. As the mechanisms of action of the glucocorticoids are many the effect on the skeleton will depend on which of these mechanisms predominates. If the loss of calcium in the stools (due to the increased excretion) preponderates over the anti-anabolic action on the osteoid tissue a picture of osteomalacia will arise. In most cases, however, the anti-anabolic action probably predominates, so that the resultant picture is one of osteoporosis.

Diagnosis

A differentiation must be made between osteomalacia and osteoporosis; in the latter the growth of the bone matrix is disturbed, so that there are no osteoid zones. This is one of the possibilities to be kept in mind when dealing with menopausal women. It is not always easy

to distinguish between osteoporosis and osteomalacia. Not infrequently causes for both affections may be present—for instance, after prolonged treatment with corticotrophin or cortisone. When nutrition is inadequate there are often multiple deficiencies. In the elderly a deficiency of vitamin D and of calcium may occur; protein depletion is also a possibility. So that suitable treatment may be instituted it is necessary to determine which processes are responsible for the faulty calcification of the skeleton. In typical osteoporosis the decalcification is rarely localized in the long bones, and the plasma concentrations of calcium, phosphate, and alkaline phosphatase are normal.

Early diagnosis is most important. Although increase in alkaline phosphatase occurs early in osteomalacia, it is not pathognomonic for this disease. One of the earliest manifestations is atrophy, in the form of a thinning of the cortex, of the bones of the hand; the other radiological abnormalities of the skeleton occur only later.

Finlay *et al.* (1956) have recently described some useful diagnostic tests. These are based on the fact that, after intravenous infusion of calcium in osteomalacia, the calcium rapidly disappears from the blood, while only small amounts are excreted in the urine. In osteoporosis the calcium disappears more slowly from the blood and is excreted in the urine in normal quantities. In osteomalacia from 62% to 88% of the calcium injected is retained, while in osteoporosis retention is normal (50% to 62%) or even below normal. We have applied these tests in a number of cases, and the results are shown in Table II. From

TABLE II.—*Results of Calcium Infusion Tests*

	Serum			Calcium Infusion Test (Finlay, Nordin, and Fraser)		
	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (K.-A. Units)	Serum Calcium after Infusion (mg./100 ml.)	12-hour Excretion in Urine (%)	4-hour Skeletal Retention (%)
Normal	9–11	2·5–3·5	<10		33–53	50–62
Sprue:						
Patient J.	6·0	2·1	21·4	8·3	3·8	73·9
,, B.	8·6	3·5		9·7	2·0	87·3
Idiopathic hypercalciuria	9·9	2·5	19·0	11·3	17·4	71·0
Prolonged steroid treatment (vertebral fracture)	9·0	3·2	15·0	10·2	16·7	78·3
Osteoporosis:						
Patient R., 84 yrs.; senile	10·6	2·8	7·9	15·3	43·6	25·0
,, L.; immobile ..	10·6	3·0	5·0	16·3	28·8	31·4
,, S.; neurofibromatosis ..	10·3	2·5	7·0	14·1	36·8	39·1
,, B., 66 yrs.; senile	9·5	2·5	9·0	14·2	26·6	45·1

this it may be seen that calcium retention in the two patients with osteomalacia in non-tropical sprue was 73.9% and 87.3% respectively. The case of primary hypercalciuria, in which radiological abnormalities of the skeleton had not yet developed, had a calcium retention of 71%. In the case with marked decalcification after prolonged treatment with corticotrophin, cortisone, and prednisone, the calcium retention was 78%.

Treatment

The various forms of osteomalacia described above require greatly different treatment. In vitamin-D deficiency it is evident that this vitamin should be administered, but the dosage varies with individual patients between 2,000 and 10,000 i.u. per day. The patient's reaction must therefore be studied. If treatment is adequate some relief of pain is usually obtainable within a few weeks, but it may be several months before clinical cure can be expected.

Vitamin D can be given as such or in the form of cod-liver oil. An ample supply of calcium is also necessary—for example, by the consumption of at least 1–1.5 litres of milk per day. When there is a disturbance of absorption this should be treated; but this subject cannot be entered into here other than to point to the great advances made in the treatment of non-tropical sprue by the prescription of a gluten-free diet, as witness the excellent results obtained by Weyers and van de Kamer in coeliac disease. The diet should not contain wheat, rye, or oats, therefore bread made from these cereals should not be eaten; gluten-free bread—for example, prepared from buckwheat—or Liga wheat-free cakes are, however, allowable. We usually give two hot meals a day from which macaroni, spaghetti, vermicelli, sausage, etc., are excluded. Rice and buckwheat are allowed. We have obtained very favourable results with this regimen in adults, the stools becoming practically normal and with a much reduced fat content. To combat the osteomalacia vitamin D is given, usually in the form of 10,000–25,000 i.u. of calciferol. If the defective absorption persists, then a single injection of vitamin D in massive dosage (500,000 i.u.) may be given. Total body irradiation with ultraviolet light is of great use.

In renal tubular osteomalacia results can be obtained only with massive doses (400,000–600,000 i.u.) of vitamin D; hence the name vitamin-resistant osteomalacia. In this connexion it should be borne in mind that, although these cases are resistant to vitamin D in therapeutic dosage, large doses may still produce toxic effects. Thus the gap between toxic and therapeutic doses is small. It is therefore advisable to start with 50,000 i.u. per day and gradually increase the dosage until the blood phosphate level has risen to 2.5–3 mg. per 100 ml. Efforts should then be made to find the minimum maintenance dose. Sometimes a dosage of 200,000–400,000 i.u., equivalent to 5–10 mg. calciferol, is necessary, but this may give rise to toxic manifestations. The patient should therefore be carefully observed; as soon as he complains of nausea, vomiting, or polydipsia or polyuria, treatment must be stopped and an extensive clinical examination carried out. Vitamin-D intoxication will be referred to later.

Rose (1956) and others have reported very good results with "A.T.10" (dihydrotachysterol) in patients with "resistant osteomalacia." The patients recovered, the plasma phosphate and alkaline phosphatase levels returned to normal, calcium balance became positive (the calcium content of the faeces falling considerably), and the osteoid zones of the bony skeleton became calcified. These authors are therefore of the opinion that A.T.10 exerts an excellent antirachitic action in the human subject. In Rose's case of renal tubular osteomalacia the dosage was 5 mg. pure dihydrotachysterol per day for 13 days, then 2.5 mg. for 10 days, and finally a maintenance dose of 1.5–1.25 mg. (=0.3–0.25 ml. of the oily solution).

Dent and Harris (1956) advise that treatment should be withheld in mild cases, such as are occasionally found among the relatives of patients with more severe disease, unless suspicious symptoms appear. The patient observed by McCance (1947), after treatment with a high dosage of vitamin D, continued in good health without further treatment (Dent and Harris, 1956).

In patients with renal tubular osteomalacia and acidosis the latter must be treated with a mixture of citric acid and sodium citrate—for example, 120 ml. per day of a solution containing 16 g. citric acid and 12 g. sodium citrate. In each case, however, the dosage must be designed to promote a rise in alkali reserve to 50–60 vol.% (bicarbonate level 25–27 mEq/l.). In these cases account has to be taken of the fact that the hypopotassaemia is usually more severe than the hypocalcaemia.

In idiopathic hypercalciuria the deficiency is not of vitamin D but of calcium, so that 1–1.5 litres of milk per day with calcium in the form of the lactate or gluconate (5–10 g. per day) is to be recommended. Klotz *et al.* (1955) recommend testosterone, which Selye maintains will increase the reabsorption of calcium, and Klotz *et al.* themselves consider will promote in addition "la meilleure fixation osseuse du calcium."

Prophylaxis

Prophylaxis should be considered in all cases of sprue, and of chronic pancreatitis, and in pregnancy and adolescence. In the last two categories, and in women during lactation, it is beneficial to give, for example, 800–1,000 i.u. of vitamin D per day together with ample calcium in the form of milk (0.75–1 litre per day). Patients suffering from sprue should also be given calcium in the form of milk, and, if desired, calcium gluconate with 4,000 i.u. of vitamin D per day.

With respect to this measure it should be emphasized that (1) vitamin-D requirements show great individual differences; and (2) an excess of vitamin D may give rise to toxic manifestations. The vitamin-D requirement depends on the following factors: (1) Age (growth rate). (2) The degree of exposure to sunlight (ultra-violet rays). The formation of vitamin D in the skin under the influence of sunlight likewise shows individual variations; there probably exists a relationship between this form of vitamin-D production and the colour of the skin. (3) The calcium–phosphate ratio in the diet. This ratio seems to be more favourable in human than in cow's milk, so that serious forms of rickets are only rarely observed in breast-fed children, in contrast to those who receive an excess of cow's milk. (4) Heredity also has an important bearing on the vitamin-D requirement. This does not come into play when the diet is adequate, but when the vitamin content falls to the limit of what is necessary deficiency symptoms are likely to develop in those whose vitamin-D requirement is above the average. The genetic factor is especially important at the present day, with the great improvement in nutrition that has taken place (Dent and Harris, 1956). (5) It should also be kept in mind that in certain diseases, such as sarcoidosis (Anderson *et al.*, 1954), there exists an increased sensitivity to vitamin D.

Vitamin-D Intoxication

When vitamin-D therapy is under consideration due attention should be paid to the probable toxic effects of overdosage. It is impossible to define what is a toxic dose of the vitamin, because of individual differences in sensitivity, and therefore it is important to recognize the signs and symptoms of intoxication. These are usually anorexia, nausea, vomiting, and especially polyuria and polydipsia.

It is generally held that a rise in blood calcium level is an indication of toxicity, but when this occurs there probably already exists a severe form of intoxication. In an experimental investigation in our laboratory Takens (1956) observed that, after moderate doses of calciferol had been given to rats and rabbits, a significant increase in urinary calcium excretion occurred as compared with a control series, while the blood calcium level remained normal (Tables III and IV).

TABLE III.—*Diuresis, Serum Calcium Level, and Urinary Calcium Excretion in Rats Given* 20,000 *i.u. Calciferol per kg. Daily*

Days Before (−) and After (+) Start of Calciferol Administration	Urine (ml./24 hours)			Serum Calcium (mg./100 ml.)		Urinary Calcium (mg./24 hours)		
	Rats Given Calciferol		Controls	Rats Given Calciferol	Controls	Rats Given Calciferol		Controls
	1–4	5–8	9–12			1–4	5–8	9–12
− 7	29	31	28					
− 1	24	29	32	8·5–10·2	8·9–10·4	4·7	4·8	5·4
+ 14	32	41	28					
+ 21	54	62	22	8·6–10·5	9·4–10·7	16·4	17·9	5·4
+ 28	30	38	28					
+ 35	52	61	31			17·4	17·8	7·9
+ 42	32	43	34	9·8–12·5	9·2–10·4			
+ 49	58	63	33			19·7	18·8	8·3
+ 56	66	60	21	8·6–11·3				
+ 85	62	98	26	10 –11·1		21·2	28·4	6·6
+ 99	75	79	35					
+113	83	71	20	10·6–11	8·9–10·1			

TABLE IV.—*Urinary Calcium Excretion in Rabbits Given* 20,000 *i.u. Calciferol per kg. Daily*

Days Before (−) and After (+) Start of Calciferol Administration	Calcium Excretion (mg./24 hours)			Days Before (−) and After (+) Start of Calciferol Administration	Calcium Excretion (mg./24 hours)		
	Rabbits Given Calciferol		Control		Rabbits Given Calciferol		Control
	1	2			3	4	
−19	5·6	9·8	14·4	−26	16·7	16·2	34·5
− 5	16·7	29·1	6·6	−12	22·0	10·6	15·3
+ 9	67·7	70·8	16·5	+ 2	15·8	16·2	9·5
+23	32·5	64·0	10·7	+16	76·1	294·0	8·6
+37	179·8	241·1	14·3	+30	211·4	158·9	16·6
+51	248·9	218·1	6·9	+44	203·6	135·2	12·1
				+58	179·9	133·5	13·5

Moreover, in the rats, which were allowed unlimited quantities of distilled water, a marked polydipsia and polyuria developed. The increased calcium excretion was not such that the polyuria could be attributed to it (osmotic diuresis), more especially as the rabbits, which apart from their food were not given fluids, had an increased calcium excretion but no polyuria. A rise in blood calcium is probably a much more serious sign of intoxication. We were also able to observe clinically that the Sulkowitch test became positive before the blood calcium level rose.

In order to diagnose incipient vitamin-D intoxication, therefore, it is necessary to check the diuresis and the urinary calcium excretion. An increase of the latter indicates intoxication even if the blood calcium is still normal.

Summary

The cause of osteomalacia may be of widely varying nature: in the first place vitamin-D deficiency, which may be the result of deficient nutrition, and secondly insufficient absorption of vitamin D from the intestine (non-tropical sprue, chronic pancreatitis, etc.). In these cases the absorption is usually also deficient as regards calcium. At present the picture of classical osteomalacia with marked skeletal deformation is only rarely observed in Western countries, but milder forms are not rare. Although the general nutrition is good because a sufficient number of calories is taken up, the qualitative composition of the diet does not always come up to the standard required. The development of osteomalacia is further promoted by a lack of sunshine or by pregnancies. In these cases Looser's *Umbauzonen* (Milkman's syndrome) are often observed.

It is also of importance to know that these syndromes may be caused by diseases of the kidney such as renal tubular osteomalacia (vitamin-D-resistant osteomalacia), renal acidosis, and idiopathic hypercalciuria. Prolonged treatment with corticotrophin and cortisone may cause not only osteoporosis, but also osteomalacia. The calcium loading test is of great value in the differentiation between osteoporosis and osteomalacia.

The various causes of osteomalacia should be taken into account if rational treatment is to be given. A diet rich not only in vitamin D but also calcium (milk and buttermilk) is indicated in vitamin-D deficiency, or in the case of deficient absorption. Gluten-free food is of importance in non-tropical sprue. "A.T.10" has proved to be of great value in renal tubular osteomalacia.

Prophylactic treatment with vitamin D and calcium is recommended in all cases of non-tropical sprue and of chronic pancreatitis, and in pregnancy.

With vitamin-D treatment care should always be taken to avoid vitamin-D intoxication. Constant attention should therefore be given to the initial manifestations of this condition, among which are polyuria, polydipsia, anorexia, and vomiting. Investigations in our clinic have shown that, in combination with polyuria, an increase in urinary calcium excretion probably occurs even before a rise in blood calcium level is observed.

BIBLIOGRAPHY

Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A. (1946). *Medicine (Baltimore)*, **25**, 399.
—— Henneman, P., Benedict, P. H., and Forbes, A. P. (1953). *Proc. roy. Soc. Med.*, **46**, 1077.
Anderson, I. A., Miller, A., and Kenny, A. P. (1952). *Quart. J. Med.*, **21**, 33
Anderson, J., Dent, C. E., Harper, C., and Philpot, G. R. (1954). *Lancet*, **2**, 720.
Bardawill, C. J., Gornall, A. G., Nishikawara, M., and Wightman, K. J. R. (1951). *Proceedings of the Second Clinical ACTH Conference*, Vol. I, p. 264.
Boquien, Y., and Bureau, R. (1943). *Bull. Soc. méd. Hôp. Paris*, **59**, 183.
van Buchem, F. S. P. (1949). *Ned. T. Geneesk.*, **93**, 1488.
Curtiss, P. H., Clark, W. S., and Herndon, C. H. (1954). *J. Amer. med. Ass.*, **156**, 467.
Debray, M., Provendier, M., and Granier, R. (1943). *Bull. Soc. méd. Hôp. Paris*, **59**, 181.
Dent, C. E., and Harris, H. (1956). *J. Bone Jt Surg.*, **38B**, 204.
—— and Hodson, C. J. (1954). *Brit. J. Radiol.*, **27**, 605.
Eliel, L. P., and Heaney, R. P. (1954). *Clin. Res. Proc.*, **2**, 126.
Finlay, J. M., Nordin, B. E. C., and Fraser, R. (1956). *Lancet*, **1**, 826.
Follis, R. H. (1957). *Amer. J. Med.*, **22**, 469.
de Gennes, H. (1943). *Presse méd.*, **51**, 651.
Jackson, W. P. U., and Linder, G. C. (1953). *Quart. J. Med.*, **22**, 133.
Jonxis, J. H. P. (1955a). *Maandschr. Kindergeneesk.*, **23**, 253.
—— (1955b). *Voeding*, **16**, 518.
Justin-Besançon, L. (1942). *Bull. Soc. méd. Hôp. Paris*, **58**, 328.
Klotz, H. P., Cohen, A., and Bouvry, M. (1955). *Sem. Hôp. Paris*, **31**, 3434.
Le May, M., and Blunt, J. W., jun. (1949). *J. clin. Invest.*, **28**, 521.
Lichtwitz, A., Clément, D., Parlier, R., and Delaville, M. (1955). *Sem. Hôp. Paris*, **31**, 554.
Looser, E. (1920). *Dtsch. Z. Chir.*, **152**, 210.
Luft, R., Sjögren, B., Ikkos, D., Ljunggren, H., and Tarukoski, H. (1954). *Recent Progress in Hormone Research*, **10**, 425.
McCance, R. A. (1947). *Quart. J. Med.*, **16**, 33.
Moeschlin, S. (1956). *Schweiz. med. Wschr.*, **86**, 81.
Moldawer, M. (1955). *A.M.A. Arch. intern. Med.*, **96**, 202.
Morgan, H. G., Mitchell, R. G., Stowers, J. M., and Thomson, J. (1956). *Lancet*, **1**, 925.
Nordin, B. E. C., and Fraser, R. (1956). Ibid., **1**, 823.
Pompen, A. W. M., La Chapelle, E. H., Groen, J., and Mercx, K. P. M (1946). *Hongerosteopathie (Osteomalacie)*. Wetenschappelijke Uitgeverij, Amsterdam.
Roberts, K. E., and Randall, H. T. (1955). *Ann. N.Y. Acad. Sci.*, **61**, 306.
Rose, G. A. (1956). *Brit. med. J.*, **2**, 805.
Seeliger (1923). *Arch. klin. Chir.*, **122**, 588.
de Sèze, S., and Monnié (1943). *Presse méd.*, **51**, 651.
Snapper, I. (1949). *Medical Clinics on Bone Diseases*, 2nd ed. Interscience Publishers, New York.
—— (1957). *Bone Diseases in Medical Practice*. Grune and Stratton, New York.
Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 199.
Steinbach, H. L., Kolb, F. O., and Gilfillan, R. (1954). *Radiology*, **62**, 388.
Takens, H. (1956). Thesis, Groningen.
Turiaf, J., Marland, P., Jeanjean, Y., and Depraitere (1956). *IIIe Conférence Internationale des Maladies Rhumatismales, Aix-les-Bains*, Vol. I, p. 696.
Vignon, G., Barjhoux, P., and François, B. (1956). *Rev. lyon. Méd.*, **5**, 791.

SURGICAL DIAGNOSIS OF "CHRONIC PANCREATITIS" AND CHRONIC RELAPSING PANCREATITIS

BY

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[WITH SPECIAL PLATE]

In this paper are reviewed 22 cases in which the presence of non-malignant chronic pancreatic disease has been apparently confirmed during operation. A number of these patients, in whom a histological diagnosis of "chronic pancreatitis" was made on surgical biopsy material, died later from pancreatic carcinoma. This suggests that misinterpretation of the essential underlying pathology in patients with chronic pancreatic disease may occur frequently, and justifies publication of an analysis of the principal clinical and morbid anatomical findings in the present cases.

The 22 patients under review underwent in-patient treatment at St. Bartholomew's Hospital between 1941 and 1956, and were selected from among the 39 patients with a diagnosis of either chronic pancreatitis or chronic relapsing pancreatitis recorded by the Department of Medical Statistics during this period. Of the 17 patients excluded, 12 were not subjected to laparotomy, and thus the diagnosis cannot be considered to have been established; and in five cases it appears in retrospect that the operative findings were insufficient to support the diagnosis in the absence of pancreatic biopsy material. The records of the remaining patients have been perused and information about those still living has been obtained by letter; all available morbid anatomical material and the radiographs have been re-examined.

The clinical course of these 22 cases allows their separation into two groups. Group I consists of 12 patients in whom a diagnosis of "chronic pancreatitis" was made upon the operative findings, supplemented in most cases by examination of surgical biopsy material, and who died within three years of operation. Group II includes the remaining 10 patients, in whom the clinical picture supported a diagnosis of chronic relapsing pancreatitis and all of whom survived operation for a period varying from six to 40 years.

Group I: Diagnosis of "Chronic Pancreatitis," followed by Death within Three Years of Operation

Clinical Features

The group comprised 11 males and one female. The age of onset of symptoms referable to the local condition varied between 41 and 82 years, with an

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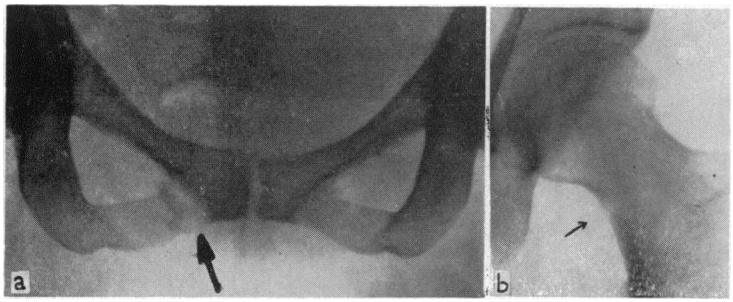

FIG. 1.—Case H. Transformation zones: (*a*) os pubis; (*b*) collum femoris.

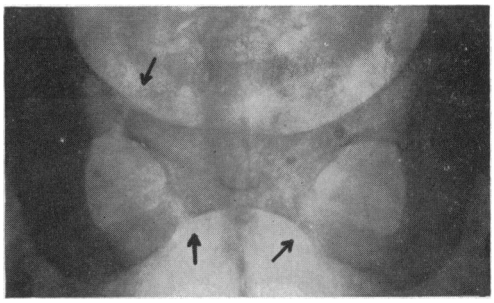

FIG. 2.—Case P. Three transformation zones.

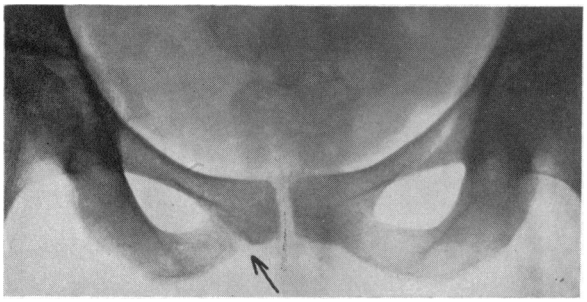

FIG. 3A.—Case J. (sprue). 1951: one transformation zone.

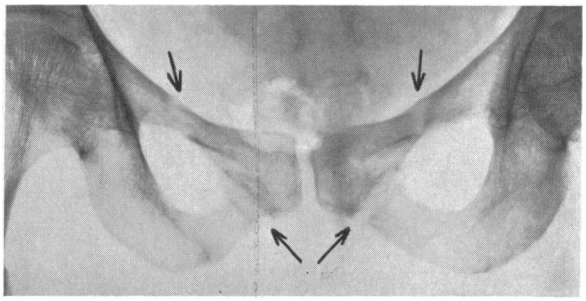

FIG. 3B.—Case J. 1956: four transformation zones; general decalcification.

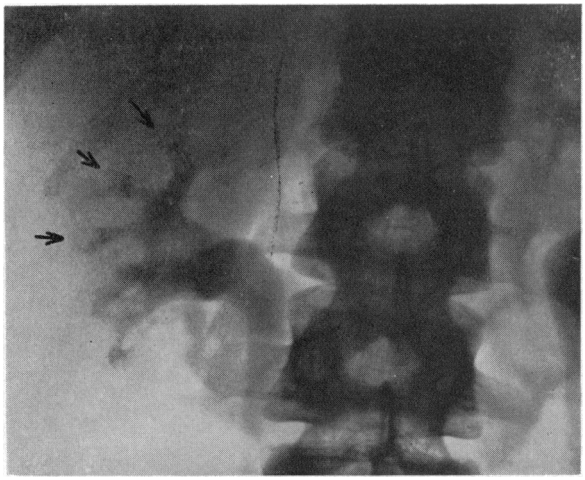

FIG. 4.—Idiopathic hypercalciuria. Intravenous pyelogram showing calcium deposition in several renal calices.

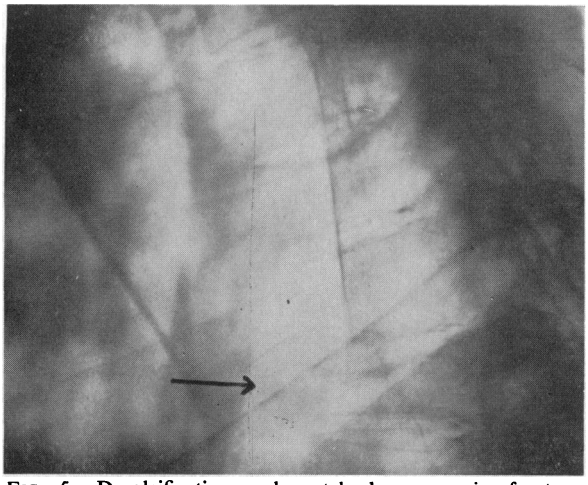

FIG. 5.—Decalcification and vertebral compression-fracture after treatment with corticotrophin, cortisone, and prednisone.

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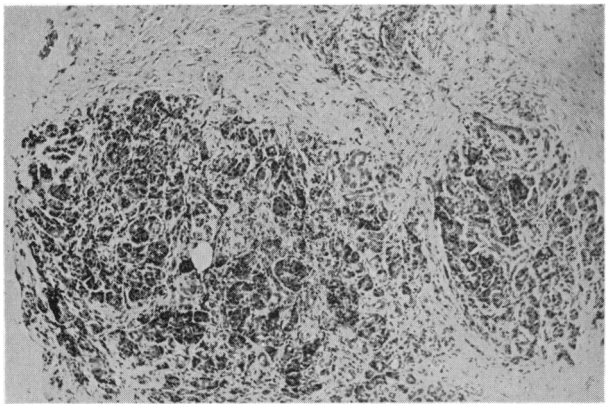

FIG. 1.—Pancreatic biopsy. Showing interlobular and interacinar fibrosis due to recent obstruction of pancreatic ducts. Male aged 67 with obstructive jaundice and mass in head of pancreas, diagnosed as "chronic pancreatitis." Death three years later from pancreatic carcinoma. (×64.)

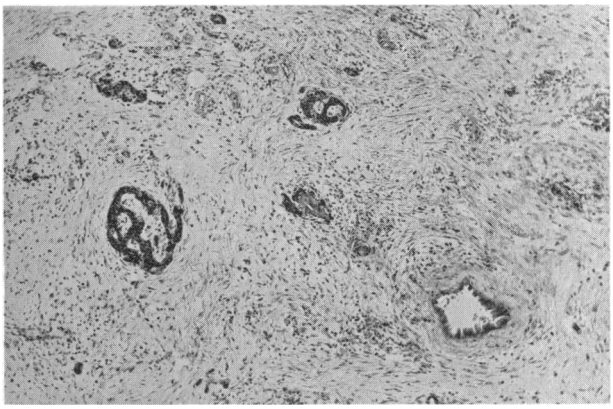

FIG. 2.—Pancreatic biopsy. Complete acinar replacement fibrosis, with scattered ductal remnants and islets of Langerhans, following ductal obstruction over many months. Male aged 64 with obstructive jaundice and mass in head of pancreas, diagnosed as "chronic pancreatitis." Death four months later from carcinomatosis. (×59.)

Figs. 3 and 4 overleaf