IDIOPATHIC OSTEOPOROSIS IN THE YOUNG

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Six patients are described with idiopathic osteoporosis which began between the ages of 4 and 16 years. In four children the disorder was mild with pain in the back, vertebral collapse, qualitatively normal iliac bone biopsies, variable calcium balance and spontaneous recovery. The two remaining patients had progressive bone disease with deformity. One with a previously normal skeleton developed changes similar to those of osteogenesis imperfecta; in the other patient, who rapidly developed structural collapse associated with severe metaphyseal osteoporosis, treatment was ineffective and the histological appearances of the bone suggested osteoblastic failure. Quantitative bone histology in four patients showed no evidence of excessive active resorption; and the ratio of Type III to Type I collagen in the skin was normal, in contrast to the findings in osteogenesis imperfecta. The significance of this study in relation to previous accounts is reviewed.

Osteoporosis is the commonest metabolic bone disease of adults, but is very rare in the young. When its known causes in this age group, such as Cushing's syndrome, coeliac disease, immobilisation, osteogenesis imperfecta and homocystinuria, have been excluded, there remain occasional patients in whom the aetiology is obscure.

The most severe form of this disorder has been best described by Dent and his colleagues (Dent and Friedman 1965; Dent 1969; Brenton and Dent 1976; Dent 1977) under the name of idiopathic juvenile osteoporosis. The cardinal features that they described were: an onset just before puberty, multiple fractures, pain in the back and extremities, and radiological evidence of osteoporotic new bone and metaphyseal compression fractures. Of these the most remarkable was the formation of osteoporotic new bone, "neo-osseous porosis" (Dent 1977), characteristically at the metaphyses, but also at other sites of new bone formation such as the pelvis and femoral neck. This phenomenon presumably required the coincidence of osteoporosis and a high growth velocity. In this sense idiopathic juvenile osteoporosis resembles rickets, which is also manifest only during growth and is now well described in adolescence (Cooke *et al.* 1973).

Earlier descriptions had been given by Schippers (1939), Lindemann (1951) and Hammel (1951) and also by Catel (1954) who incorporated the pubertal onset and biconcave vertebrae into the term "Pubertäts-fischwirbelkrankheit". Although onset around puberty is usual (see Table V), Kooh *et al.* (1973) described an identical condition in childhood. Of subsequent descriptions only those of Jowsey and Johnson (1972) and Jowsey (1977) give significant quantitative information on bone histology.

These and other descriptions of idiopathic osteoporosis in the young show that the clinical features are very similar at all ages during growth (Berglund and Lindquist 1960; Schwarz 1965; Fanconi *et al.* 1966; Cloutier *et al.* 1967; Loirat *et al.* 1967; Gooding and Ball 1969; Görgényi 1969; Lapatsanis, Kavadias and Vretos 1971; Grubbauer, Stögmänn and Wendler 1976; Lachmann *et al.* 1977), and it does not therefore seem necessary to regard the idiopathic juvenile osteoporosis of Dent and his colleagues as a separate disorder.

In the present context, the term idiopathic osteoporosis of the young has been used because it covers a wider range of ages. It refers to the condition occurring in the first 20 years of life, rather than the first 50 years as used by Jackson (1958) in describing idiopathic osteoporosis in younger people; and it excludes osteoporosis in pregnancy since this may be causally related.

Probably no more than 45 patients with this disorder have been described, about half of them severely affected. It is not easily diagnosed, very little is known about the changes in the skeleton and there is no logical or effective treatment. To help with these problems, this paper describes the clinical features and investigation of a further six patients in whom symptoms of idiopathic osteoporosis began between the ages of 4 and 16 years.

HISTOLOGICAL AND BIOCHEMICAL METHODS

Routine biochemical methods were used (Smith *et al.* 1973). Bone was taken by trephine either from the iliac crest or by the transiliac route. Decalcified and undecalcified sections were prepared; quantitative histological examination was made of suitable plastic-

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embedded undecalcified sections, stained with toluidine blue and von Kossa's stain, using established point-counting procedures (Woods *et al.* 1968; Merz and Schenk 1970a). Bone area, a measure of bone volume in thin sections, was measured with a Chalkley eye-piece, and surface measurements with a grid eye-piece.

The ratio of the alpha chains of the two different genetic types of collagen, $\alpha_1(I)$ and $\alpha_1(III)$, was measured in a pepsin-digest of skin by the method of interrupted gel electrophoresis (Sykes *et al.* 1976). Since Type I collagen contains two $\alpha_1(I)$ chains whereas Type

III collagen contains three $\alpha_1(III)$ chains, the ratio of the number of molecules of Type III to Type I collagen is two thirds of the ratio $\alpha_1(III)$ to $\alpha_1(I)$.

THE PATIENTS

The presenting features of the six patients are shown in Table I, arranged according to the age at which symptoms began. In the last patient symptoms began at the age of 16 years, and continued through early adult life with progressive severe osteoporosis. No patient had a family history of bone disease or of parental

Table I. Presenting features of six young patients with idiopathic osteoporosis

Case	Date of birth	Sex	Age of onset (years)	Symptoms	Signs	Radiographs (Fig. 1)
1	1963	F	4	Intermittent pain in back	None	Vertebral collapse (two thoracic, two lumbar)
2	1963	M	7	Pain in feet, limp	Abnormal gait	Fracture of femur and radius, vertebral collapse
3	1956	M	7	Round shoulders	Kyphosis	Progressive vertebral collapse
4	1960	M	7	Pain in back	None	Multiple vertebral collapse
5	1964	F	9	Pain in back	None	Vertebral collapse
6	1943	M	16	Increasing pain in back, pain in feet	Stiff back	Gross vertebral collapse, metaphyseal osteoporosis

Table II. Investigations and course in six young patients with idiopathic osteoporosis

Case	Age when first seen (years)	Initial biochemistry*						Histology	Treatment	Course		
		Plasma (per 100 ml)			Urine (mg/24 h)		Balance† (mg/24 h)					
		Ca (mg)	P (mg)	P-ase (KA units)	Ca	THP	Ca	P	Mg			
1	10	10.2	5.2	17	100	—	+32 -8	+98 +53	+16 -7	—	Extra calcium	Improvement
2	10	10.0	4.4	12	83	—		—		—	Symptomatic and orthopaedic only	Multiple fractures. Evidence of metaphysial fractures
3	15	9.2	4.4	9	287	105		—		Normal	Laminectomy Physiotherapy	Vertebral fractures. Temporary paraplegia after injury. Progressive improvement
4	13	9.5	4.5	11	350	48	-169 -25	-195 -169	-10 +6	Normal	None	Improvement
5	10	9.8	4.8	17	80	34	+240 +252	+87 +282	+6 +25	Normal	None	Improvement
6	23	10.3	4.0	6	24	53	-137	+231	—	Several biopsies (see text) Some thin trabeculae	Numerous (see text)	Progressive skeletal collapse

*** Conversion factors**

Plasma: Calcium mg/100 ml $\times 0.25 = \text{mmol/l}$
 Phosphate mg/100 ml $\times 0.32 = \text{mmol/l}$
 Alkaline phosphatase KA units/100 ml $\times 7.1 = \text{iu/l}$
 Urine: Calcium mg/24 h $\times 0.025 = \text{mmol/24 h}$
 Total hydroxyproline mg/24 h $\times 7.6 = \mu\text{mol/24 h}$

Balance: Calcium mg/24 h $\times 0.025 = \text{mmol/24 h}$
 Phosphate mg/24 h $\times 0.032 = \text{mmol/24 h}$
 Magnesium mg/24 h $\times 0.042 = \text{mmol/24 h}$

†Two consecutive four-day periods

Fig. 1

The shape of the affected vertebrae in the six patients with the date the radiograph was taken. The mid-thoracic vertebrae are shown in all patients except one (Case 6).

Table III. The estimated daily intake of calcium and vitamin D in five patients with idiopathic osteoporosis

Case	Calcium (mg)	Vitamin D (iu)
2	864	56
3	1190	69
4	1046	55
5	627	15
6	903	102

Conversion factors

Calcium mg/24 h $\times 0.025 = \text{mmol/24 h}$
 Vitamin D mg/24 h $\times 0.025 = \mu\text{g/24 h}$

consanguinity, and all were initially of normal or above normal height for their age. There was no clinical or biochemical evidence of malabsorption, Cushing's syndrome, osteogenesis imperfecta, hypogonadism or chromosomal disorder. Biochemical studies were done when the patients were first seen in Oxford (Table II). The estimated intake of vitamin D and calcium, and the results of quantitative bone histology are given in Tables III and IV. The radiographic appearance of the spine in all patients is shown diagrammatically in Figure 1. The relative proportion of the $\alpha_1(\text{III})$ and $\alpha_1(\text{I})$ chains in the collagen derived from the skin of four patients and from age-matched controls is shown in Figure 2. Short clinical histories are given for two patients (Cases 2 and 6). In the remaining patients the symptoms disappeared when growth ceased but in Case 3 the deformity persists.

Table IV. Quantitative bone histology in four patients with idiopathic osteoporosis, showing the percentage of one area to another

Case	Date of biopsy	Matrix/section area	Osteoid/section area	Osteoid/total bone area	Surface osteoid/total trabecular surface	Maximum number of osteoid lamellae	Crenated surfaces/total surface	Osteoclasts/total surface	Osteoblasts/total surface
3	1971	15.4	0.7	4.5	52.0	3	20.0	1	2
4	1972	—	—	—	—	—	—	0	0
5	1974	20.5	0.4	1.9	50.0	3	12.0	1	5
6	1969	9.4	0.2	2.1	53.0	2	12.0	0	0
	1970	16.3	0.2	1.2	35.0	1	18.0	2	2
	1971	—	—	—	—	—	—	0	0
	1972	10.6	0.1	0.9	15.0	2	44.0	1	1
Normal values (see text)	Mean	22.8*	0.58†	0–6.85†	13.8†	4 or less‡	5.3§	2.7§	5.0†
	SD	4.29	0.29		6.2		1.69	1.7	2.9

*Merz and Schenk (1970a), †Merz and Schenk (1970b), ‡Woods *et al.* (1968), §Schenk, Merz and Müller (1969)

Fig. 2

The ratio of $\alpha_1(\text{III})$ to $\alpha_1(\text{I})$ collagen from the skin of four young patients with idiopathic osteoporosis compared with control values for 10 normal subjects aged 12 to 18 years (mean $\pm$ SD = 0.22 ± 0.06). Biopsies from the patients were taken at the following ages: Case 1, 14; Case 2, 15; Case 4, 19; Case 5, 15.

Case 2. This boy first noticed pain over the dorsum of both feet and around the heels at the age of seven years. He walked slowly, "like an old man". Two years later he fractured the right radius and subsequently the shaft of the left femur (Fig. 3). The femoral fracture healed slowly and refractured six months later after a fall. Radiographs in 1973 showed collapse of several vertebrae (Fig. 1). A subsequent radiograph (Fig. 4), after a fracture of the lower end of the femoral shaft, showed evidence of metaphyseal compression at the lower end of the femur and in the upper tibia. Since then he has broken all his long bones and those in his hands and feet. Radiographs (Figs 5 to 7) demonstrated narrow diaphyses with thin cortices contrasting with the widened misshapen metaphyses and disorganised growth plates. By December 1978 he was confined to a wheelchair. Apart from multiple fractures there was nothing to suggest osteogenesis imperfecta. No bone biopsy was done. Analysis of skin collagen (Fig. 2) gave a ratio of $\alpha_1(\text{III})$ to $\alpha_1(\text{I})$ of 0.16; this ratio is normal for this age (Sykes, Francis and Smith 1977).

Case 6. In this patient osteoporosis began at the age of 16 and progressed until his death at the age of 29. In 1968 his erythrocyte sedimentation rate was 38 millimetres in the first hour, and radiographs suggested fusion of the sacro-iliac joints. Ankylosing spondylitis was diagnosed and radiotherapy given, producing temporary improvement. By 1969 he had lost 10 centimetres from his maximum height of 186 centimetres, had pain in his back and ankles and limped with short steps. Radiographs showed widespread

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Case 2. Radiographs showing the development of changes in the long bones. Figure 3—The left femur at the time of fracture in 1972. Figure 4—A subsequent fracture at the lower end of the femoral shaft, with evidence of compression of the femoral and tibial metaphyses (1974). Figure 5—The appearance of the left femur in 1975. Figure 6—The left tibia in 1973. Figure 7—The right tibia in 1977, demonstrating the long thin diaphyses and the widespread disorganised metaphyses. The appearances on the left were almost identical.

rarefaction in the metaphyses which rapidly progressed (Figs 8 to 10). He had multiple vertebral fractures (Fig. 1) and probably also had partial metaphyseal fractures, but the osteoporosis became so severe that it was difficult to be certain of this. Bone biopsy of the iliac crest in 1969 showed a small amount of osteoid composed of one to two lamellae. There was no evidence of excessive bone-cell activity but a few trabeculae were smaller than normal. The bone marrow was normal. The calcium balance was negative (Table II). Sufficient intravenous calcium was given to produce sustained hypercalcaemia (Pak *et al.* 1969); this had a temporary effect on the calcium balance which became +351, +513 and +478 milligrams per day in three four-day periods during calcium administration, but fell to +68 milligrams per day (over eight days) as soon as the calcium supplement was stopped, and six months later was -145 milligrams per day in two consecutive four-day periods. The osteoporosis progressed with temporary response or no response to treatment with dihydrotachysterol, thiazide diuretics (during which the daily calcium balance varied between -131 and -319 milligrams), diphosphonates (EHDP) and many different analgesics. Radiographs of the long bones showed considerable endosteal bone resorption but repeated investigations for

malignant disease were negative. By 1972 he had lost 43 centimetres in height. He became increasingly breathless and eventually died. Necropsy failed to demonstrate the immediate cause of death, but the radiographic changes were confirmed (Fig. 11). Histological examination showed that the vertebral trabeculae were very thin or absent. There was no cellular evidence of excessive bone resorption. Bone formation appeared to be reduced but in some areas there were foci of immature bone. There was no evidence at any time of leukaemia, myeloma or neoplastic disease.

DISCUSSION

Since previous accounts of idiopathic osteoporosis in the young are scattered, and often deal with single cases, they have been brought together in Table V. It is apparent that in most patients symptoms begin just before puberty, earlier in girls than boys (Brenton and Dent 1976), and as often in the peripheral skeleton as in the back. Pain in the ankles, difficulty and slowness in

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Case 6. Figure 8—The left ankle in 1969, showing rarefaction in the area of the metaphyses. Figures 9 and 10—The change in appearance of the hands between 1969 (Fig. 9) when there was slight metaphyseal rarefaction only and 1972 (Fig. 10) when there was extensive periarticular loss of bone. Figure 11—Radiographs taken at necropsy show extensive endosteal bone resorption.

Table V. Previous accounts of idiopathic osteoporosis in the young

Author	Age (years)	Sex	Symptoms	Fractures		Calcium (mg/24 h)		Bone biopsy	Treatment	Comments
				Vertebrae	Metaphyses	Urine	Balance			
Schippers (1939)	7	F	Pain in ankle	+	-	-	-	-	Oral calcium and phosphate	Waddling gait
Lindemann (1951)	11	F	Pain in back	+	-	-	-	-	Plaster cast and oral calcium	Difficulty in rising from the floor
Hammel (1951)	13	M	Pain in back	+	-	-	-	-	Plaster cast	Plasma calcium 11.4 mg/100 ml
Catel (1954)	13	M	Abnormal gait, slow and stiff; pain on jolting	+	-	-	-	From ulna: inflammation and appearance of aplastic anaemia	Plaster bed	Unable to rise from ground unaided and had to climb up himself
Berglund and Lindquist (1960)	12	M	Pain in feet	+	-	Normal	-160	-	Calcium vitamins and norethandrolone	Calcium-47 "accretion" rate normal in both patients
	12	M	Pain in back	+	-	Normal	0	Increased cellular activity	Nortestosterone	
Schwarz (1965)	16	M	Fracture in long bone	+	-	-	-	Osteoporosis	Anabolic steroids and oral calcium	Sustained positive calcium balance with calcium loading
	18	F	Fracture in long bone	+	-	-	-	Osteoporosis	Oral calcium	
Dent and Friedman (1965)	11	F	Recurrent fractures	+	+	350	-350	Gross osteoporosis	Dihydrotestosterone and methyl testosterone	
	8	F	Pain in knees	+	+	188	+90	-	Vitamin D and stilboestrol	Also transfusion from patient with marble bone disease
	9	F	Pain in ankles, not possible to walk	+	+	96	-125	-	Dihydrotestosterone	
	9	M	Pain in back	+	-	91	+290	-	None	
	11	M	Pain in arms, legs and back	+	-	238	-168	-	Dihydrotestosterone	
	9	F	Pain in feet and difficulty in walking	+	-	118	0	-	None	
Fanconi <i>et al.</i> (1966)	11	F	Pain in back after somersault	+	-	Normal	-	From spinous process of T3 and sternum		
	15	M	Pain in feet	+	+	570	-	From iliac crest and rib	Parathyroid exploration	Parathyroid hyperplasia of water-clear cells
Cloutier <i>et al.</i> (1967)	12	F	Pain in back after injury	+	-	371	0	"Excess resorption" (microradiography)	None	

Loirat <i>et al.</i> (1967)	11	F	Pain in back after fall	+	+	Normal	-50	Reduced bone mass	Calcium and vitamin D	Calcium balance became positive
Gooding and Ball (1969)	13	F	Pain in knees and ankles; severe pain in left hip	+	-	—	-137	From rib: bone formation rate low (tetracycline-labelled); no cellular abnormality	—	Pain in left hip, probably due to compression of articular surface
Görgényi (1969)	10	F	Pain in back after fall	+	-	Normal	—	—	Oral calcium and anabolic hormone	Patient obese. Review of 18 other cases
Lapatsanis <i>et al.</i> (1971)	8	F	Pain in feet and difficulty in walking	-	-	Normal	-80	—	—	Balance in both patients positive on recovery
	11	M	Pain in spine and unable to walk	+	+	800	-1200	Thin cortex	—	—
Jowsey and Johnson* (1972)	11	M	Fractures	+	?	183	—	"Excess resorption surface"	None recorded	—
	12	M	—	No details	?	253	—	Normal	—	—
	13	M	Pain in back for 6 months	?	+	188	—	formation surface (microradiography)	—	—
	18½	M	Pain in back for 8 years	+	?	125	—	—	—	—
	21	M	Fractures for 13 years	+	?	90	—	—	—	—
Kooh <i>et al.</i> (1973)	1½-12	11 patients† 6M, 5F	Pain in ankles and back	+(9)	+(9)	Sometimes increased	Negative (3)	Thin scalloped trabeculae, "osteoblast arrest"	Calcium and anabolic steroids	On phenytoin for epilepsy
Grubbauer <i>et al.</i> (1976)	12	M	Limping	+	+	Up to 400	—	Osteoblasts, osteoclasts, bone mass and mineralisation all reduced	Vitamin D,	Radioactive calcium absorption high. Patient obese
Lachmann <i>et al.</i> (1977)	12	F	Pain in back	+	-	Normal	—	Routine histology normal	High calcium intake	—
<i>Reviews with no individual details</i>										
Dent (1969)	3 patients aged 8-13 years		Good radiographs of new osteoporotic bone							
Brenton and Dent (1976)	17 patients		Includes previous cases. Describes variable severity							
Houang <i>et al.</i> (1978)	14 patients		All previously described							

*Excludes one patient with pseudoglioma and one of Cloutier *et al.* (1967)

†No individual details

walking and an abnormal gait are characteristic features. Pain in the back may follow injury or jolting. Radiographs show multiple compressed or biconcave vertebrae and often metaphyseal compression fractures of the long bones. The erythrocyte sedimentation rate may be raised. Biochemical measurements vary with the stage of the disease and the degree of immobilisation: hypercalciuria is not uncommon, and the calcium balance may be zero or negative when it should be positive. The bone has seldom been examined, except occasionally by microradiography, and the results are conflicting. No useful treatment has been described. Spontaneous recovery is usual, leaving variable deformity and the radiographic hallmarks of healed osteoporosis. Only in severe disease is eventual height significantly reduced.

Individual accounts contain additional points of interest. Dent and Friedman (1965) showed the difficulty in excluding acute leukaemia, and one treatment among several that they used was to transfuse plasma from a patient with the mild form of dominantly inherited osteopetrosis. Dent (1969) and Brenton and Dent (1976) emphasised the diagnostic importance of the formation of osteoporotic new bone, particularly in the metaphyses but also subperiosteally, for example in the pubic rami and in the femoral neck; and Houang *et al.* (1978) discussed the radiographic appearances.

The diagnostic importance of limping, abnormal gait, or refusal to walk was emphasised by Kooh *et al.* (1973). Previously Lindemann (1951) had noted a patient who was unable to rise from the ground without "climbing up himself", a symptom of proximal muscle weakness; Catel (1954) had a similar patient and also noted an extraordinarily slow and stiff gait in another of his patients. Kooh *et al.* (1973) considered that the bone biopsy on one of their patients indicated "osteoblast arrest": tetracycline labels, present only in areas of osteoblastic activity, showed bone mineralisation at the rate of 35 microns over 10 days, which is below normal for a child. However, Jowsey and Johnson (1972) showed by microradiography that resorption surfaces were increased whereas formation surfaces were within the normal range, but the osteoid width was reduced. The significance of these findings is uncertain since the "normal" ranges given are variable (Jowsey and Johnson 1972; Jowsey 1977), there are other inconsistencies (Cloutier *et al.* 1967), and the microradiographic appearance of excess bone resorption can result from failure of bone formation. Bradford *et al.* (1976) and Jowsey (1977) suggested that Scheuermann's kyphosis might follow mild juvenile osteoporosis, and in three patients again provided microradiographic evidence of increased bone resorption; in considering the mean extent of the resorption surface, the difference between control subjects and patients with Scheuermann's disease did not appear to be significant.

In examining two 12-year-old boys Berglund and

Lindquist (1960) found a normal accretion rate (measured by calcium-47) but a calcium balance which was either negative or zero; since histological sections of the spinal process in one patient showed "intensive metabolism of the bone with dominance of the resorption processes" it was concluded that the disorder was predominantly due to excessive bone resorption. One patient of Fanconi *et al.* (1966) sustained a spontaneous fracture of the sternum when descending the stairs; another had an exploration of the parathyroids which demonstrated hyperplasia of the water-clear cells only, and also had hypercalciuria (up to 570 milligrams per day). Görgényi (1969) stated that histological examination might show thinner than normal trabeculae, with a diminished number of osteoblasts, but no figures were given to support this claim. Cloutier *et al.* (1967) recorded a girl aged 12 years in whom the osteoporosis caused compression of the spinal cord. Lachmann *et al.* (1977) found an increased absorption of oral calcium-47 in another girl aged 12, suggesting that malabsorption of calcium was not the cause of the osteoporosis. Finally, Grubbauer *et al.* (1976) recorded a boy aged 12 who was receiving anticonvulsants and developed fractures of the vertebrae and metaphyses; his urinary calcium measured 400 milligrams a day, and there were no features of rickets.

In most accounts the difficulty in excluding mild osteogenesis imperfecta has been emphasised, the results of biochemical measurements have been variable, and the interpretation of bone histology controversial. Our investigations may help with these problems.

Present series

In our patients the osteoporosis extends over the whole range of severity. Four (Cases 1, 3, 4 and 5) had a mild transient form of the disease which might be labelled "idiopathic adolescent kyphosis" or "Scheuermann's disease". It is not known how many adolescents with kyphosis have an episode of osteoporosis; but the abnormal calcium balances in two patients (Cases 1 and 4) demonstrate the co-existence of a generalised metabolic disorder.

Differential diagnosis. The two case histories illustrate the main diagnostic problems in idiopathic osteoporosis in the young, namely the exclusion of mild osteogenesis imperfecta and of neoplastic infiltration of the skeleton. *Osteogenesis imperfecta.* The clinical features which make mild osteogenesis imperfecta unlikely, though still possible, are the absence of a positive family history, short stature, blue sclerae, abnormal teeth or deafness. Two other diagnostic aids are the radiological appearances and biochemical examination of skin collagen.

Brenton and Dent (1976) state that in severe idiopathic juvenile osteoporosis the width of the long bones is normal, although the cortex may be thin, and metaphyseal fractures are common; whereas in osteogenesis imperfecta the bones are often abnormally

thin, may appear excessively long, and metaphyseal fractures are rare. There are individual exceptions. In our Case 2 the rarefaction and distortion of the left femur after the first fracture could be attributed to local immobilisation but later radiographs showed multiple vertebral fractures and suggested abnormal new bone formation at the metaphyses. The long bones, especially the tibia and fibula, subsequently acquired the shape considered characteristic of osteogenesis imperfecta, with narrow diaphyses, widened metaphyses and apparent disorganisation of the growth plates. The shape of the skull is often abnormal in osteogenesis imperfecta, but in this patient was normal.

The ratio of the two different genetic types of collagen in the skin, expressed in terms of the alpha chains derived from them, is significantly increased in mild osteogenesis imperfecta (Sykes *et al.* 1977; Fujii, Kajiwarra and Kurosu 1977); this increase may result from defective formation of Type I collagen, the only collagen in bone. An increased ratio of $\alpha_1(\text{III})$ to $\alpha_1(\text{I})$ collagen in the pepsin-digest of skin would therefore strongly suggest mild osteogenesis imperfecta, but a normal ratio would not definitely exclude it. In our patients the ratio was normal. Three out of four biopsies were, however, taken from patients who appeared to have recovered completely from their osteoporosis (Cases 1, 4 and 5) and it could be argued that the collagen ratio might have been abnormal at the time of the bone disease. However, if these patients did have osteogenesis imperfecta the inherited abnormality would have persisted, even if the bone disease was in remission.

Neoplastic infiltration. In Case 6 the rapid appearance of widespread periarticular metaphyseal osteoporosis and subsequent endosteal resorption suggested leukaemia (see Wynne-Davies and Fairbank 1976), or possibly myeloma, but no evidence of these disorders was ever found. It is not clear why rarefaction was localised to the metaphyses, but this could be related to the continuing increased rate of bone turnover in this region in comparison to other parts of the skeleton.

Biochemistry. In our patients the plasma alkaline phosphatase level was within the normal range for the age of the patient (Round 1973), and the available measurements of urinary hydroxyproline were also normal (Clark 1977). Only in Case 4 was there an increase in the urinary calcium level, which could not be attributed to immobilisation. In three out of four patients the calcium balance was zero or negative at a time when it should have been positive. These findings agree with those of most previous authors; Jowsey and Johnson (1972), however, found that the levels of plasma alkaline phosphatase and urinary total hydroxyproline appeared to be increased, but the normal considerable temporary increase in urinary hydroxyproline level that parallels the increased rate of growth before puberty (Clark 1977) was not then appreciated.

Histology. The qualitative histological appearance of the bone was normal in three out of four patients. In Case 6 there was progressive thinning of the trabeculae, shown in the first biopsy in 1969, six months later, and at necropsy (Table IV). This occurred without any cellular evidence of increased bone resorption and in the presence of very few osteoblasts. Examination of the vertebrae also showed some areas of immature bone formation, considered to be a response to injury; these had not apparently formed the basis for a more mature type of bone and the behaviour was said to be similar to that found in osteogenesis imperfecta.

Quantitative measurements were made on some sections; these were taken from iliac trabecular bone, with the exception of the necropsy specimen in Case 6. When the results are compared with the normal values given by Schenk, Merz and Muller (1969) and Merz and Schenk (1970a,b) for the age range 20 to 30 years, and similar details provided by other authors (Woods *et al.* 1968; Meunier *et al.* 1973), there are two points to note: first, there is no well-established range of values in normal adolescents, and second, when assessing the surface covered by osteoid, various authors (Merz and Schenk 1970b; Krempien *et al.* 1972) disregard the first osteoid lamella, so that their values for this measurement are considerably below ours. Thus, in a personal series of biopsies from 24 adults with qualitatively normal bone, the osteoid as a percentage of the total surface area was 36.42 ± 3.49 (SD). In our patients bone volume, represented by the matrix area in thin sections, was 2 SD below the adult mean in two biopsies. The percentage of crenated surfaces, which represent past and present bone resorption, was above normal in all biopsies, but the number of osteoclasts was not increased. This suggests that formation has been defective, and the low number of osteoblasts is compatible with this. The final set of results in Case 6 refer to vertebral trabecular bone. Since we find little difference between the quantitative measurements for vertebral and iliac trabecular bone, the observations on the vertebrae of this patient probably have the same significance as those obtained by previous iliac biopsy.

From our results it seems that the principal cause of bone loss is a failure of bone formation. This does not support the contention of Jowsey and Johnson (1972) that bone resorption is excessive.

Cause

The cause of this condition is obscure but there are clues. One is the reversibility of the osteoporosis. Osteoporosis produced by an adrenal cortical tumour (Albright and Reifenstein 1948), by immobility and by space flight (Pace 1977) is also reversible. How force through the skeleton stimulates the osteoblasts is unknown, although piezoelectric signals are a possibility (Becker 1978). Young patients with idiopathic osteoporosis have not been immobilised (except during treatment), but the

skeleton behaves as if it has. This could be due to temporary osteoblastic failure.

Another clue is the slow, stiff and painful gait, and the difficulty in rising from the ground. Such symptoms could be entirely due to pain and fracture in the metaphyses, but might, as in osteomalacia, result from a disorder or deficiency of vitamin D. In our patients the intake of vitamin D and calcium was low, but this is very common in Britain, and no evidence of osteomalacia was found. Dent and Friedman (1965) thought that idiopathic juvenile osteoporosis was unlikely to result from calcium deficiency but described a five-year-old boy whose osteoporosis might be due to his low intake of 150 milligrams of calcium daily; the osteoporosis improved when the calcium intake was increased (Dent 1977). Rickets that was thought to be due to calcium deficiency was described by Kooh *et al.* (1977). Bone

disease due to calcium deficiency in the young must be an extreme rarity; young patients with idiopathic osteoporosis may suffer from malabsorption of calcium, but whether this is the cause of the bone disorder, or its effect, is unknown. Since current work suggests that the metabolism of vitamin D and calcitonin is altered during times of physiological stress, of which growth is one, further investigations of these hormones in the osteoporosis of young people is indicated.

It is not yet clear whether the primary disorder in idiopathic osteoporosis of the young is a deficiency of osteoblasts or an excess of osteoclasts. There is little evidence of excessive bone resorption, apart from that obtained by microradiography; but there cannot be complete failure of osteoblast activity because new osteoporotic bone is formed at the metaphyses. This distinction could be therapeutically important.

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