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Arthropathy of Wilson's disease

Study of clinical and radiological features in 32 patients

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SUMMARY The principal clinical features and radiological findings relating to the locomotor system have been studied in 32 consecutive hospital admissions of patients with Wilson's disease. 5 of these patients were recently diagnosed and had as yet received no treatment, while 27 were routine admissions for follow-up and biochemical supervision of their illness. No patient was specifically included or excluded from the series because of the presence or absence of locomotor symptoms.

The most common radiological abnormality was a generalized increase of radiolucency, interpreted as skeletal demineralization (21 cases), followed by premature osteoarthrosis (8 cases). Changes in the spine were common and included osteochondritis, reduction of intervertebral joint spaces, osteoarthrosis, and a tendency to squaring of vertebral bodies. Other bony changes included fluffy irregularity of femoral trochanters, osteochondritis dissecans of the knees, osteophytic protrusions at bone ends, and bunches of tongue-like osteophytes at joint margins.

The symptoms associated with these radiological abnormalities comprised back pain and stiffness with restricted movement, pain and stiffness of knees, hips, and wrists, and tenderness to pressure over margins of affected joints. Joint hypermobility was also observed in 9 patients. Episodes of acute polyarthritis with serological changes were seen in 5 cases; all these episodes appeared to be related directly to treatment with penicillamine.

Since Warnock (1952) first observed osteoporosis and spontaneous fractures in a patient suffering from Wilson's disease (hepatolenticular degeneration) there have been a number of reports describing various osteoarticular lesions in this condition (Finby and Bearn, 1958; Rosenoer and Michell, 1959; Walshe, 1962; Mindelzun *et al.*, 1970; Feller and Schumacher, 1972; Kaklamanis and Spengos, 1973). While certain features such as premature osteoarthrosis with periarticular fragmentation of bone and generalized osteoporosis are recognized as being common in this disease there is marked lack of agreement as to the frequency of other equally distinctive lesions such as osteochondritis, accessory bone ossicles, spontaneous fractures, and vertebral degeneration. To take a particular example, severe rickets was a presenting feature of Wilson's disease years before the onset of neurological symptoms in a case reported by Morgan *et al.* (1962). Other cases associated with rickets or osteomalacia have been described by Mehta and Shinde (1965) and by Cavallino and Grossman (1968). One further possible example was reported by Stowers and Dent (1947). The original diagnosis was 'adult Fanconi syndrome with cirrhosis of the liver', Wilson's disease was diagnosed retrospectively by Dent and Stowers (1965) on somewhat tenuous evidence.

In an attempt to clarify further the picture of osteoarticular lesions in Wilson's disease it was decided to make a routine study of all cases seen in the course of a year at Addenbrooke's Hospital, Cambridge. Particular attention was paid to the correlation between clinical findings and radiological changes, if any, observed either at the time of study or earlier when the patient was first seen.

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Patients and methods

The study comprises 32 patients (16 male and 16 female) seen during the course of a year at Addenbrooke's Hospital, Cambridge. 5 were seen on their first admission for confirmation of diagnosis and management and the remaining 27 during the course

of follow-up admission for assessment of progress and for biochemical control. No patient was selectively included or excluded from the study because of the presence or absence of rheumatic symptoms. The patients were examined both clinically and radiologically. Ages ranged from 7 to 45 years (Table 1). Specific questions were asked relating to locomotor abnormalities, joint stiffness (including both morning stiffness and gelling*), pain, swelling, cramps, paraesthesiae, and a family history of arthritis. In the examination of the locomotor system attention was paid to abnormal postures and movements, to the muscles, and to the synovial joints.

Joint hypermobility was assessed according to the following criteria: dorsiflexion of the wrist to 90°, opposition of the thumb to the forearm, hyperextension of the knee beyond 10°, dorsiflexion of the ankle >15 degrees beyond the right angle. We also looked for abnormalities of the palate, heart, lens, metacarpal index (normal 8), and for homocystine in the urine.

The radiological survey included views of the spine, hands, wrists, elbows, shoulders, pelvis, knees, ankles, and feet in every case on first visit and, if deemed necessary, at the time of assessment. To this extent the study must be considered retrospective. Thus in assessing osteoporosis we were not able to measure bone density systematically as the films were taken at different times and with varying views and techniques. In our findings we refer to 'loss of bone density' rather than to the more precise term of osteoporosis.

Other investigations were the latex and Rose-Waaler tests, antinuclear factor, and LE cells, serum proteins and, in a limited number of cases, immunoglobulins. Also serum calcium, phosphorus, and alkaline phosphatase, and 24-hour urinary calcium excretion. At the earlier visits alkaline phosphatase was estimated in King–Armstrong units/100 ml, but were later measured in IU/l. In Table 4 results of earlier findings have been converted to IU but, in view of the difference in technique, no attempt has been made to submit this investigation to statistical analysis.

Results

The principal clinical, rheumatic, serological, and radiological findings for all patients are summarized in Table 1. Cases 15 and 16 (sibs), 24, 30, and 32 were assessed on first referral, all the others were readmissions.

*By 'gelling' we mean stiffness after immobility in degenerative joint disease; this is by no means synonymous with the morning stiffness of active inflammatory joint disease.

CLINICAL FEATURES

Symptoms or signs relating to the locomotor system occurred in 24 of the 32 patients (75%). The commonest symptoms were those suggesting mild or moderate (occasionally severe) premature osteoarthrosis, that is pain, stiffness, and gelling of the affected joints. Pain was most frequent in the knees (9 patients) and spine (6 patients). In patients with symptoms relating to the knees examination usually showed tenderness at the joint margins or on patello-femoral compression and this was associated with crepitus in 2 cases; occasionally stiffness on passive flexion and extension was also noted. In the spine extension was the movement most often limited and in 2 patients stiffness of the elbows was associated with inability to fully extend the joints. 8 patients had never complained of joint pains and in these no locomotor abnormality was found. A correlation between these clinical findings and the radiological abnormalities is given in Table 2.

Joint hypermobility, not previously recorded in Wilson's disease, was found in 9 patients according to the criteria listed earlier, but other evidence suggesting either arachnodactyly or homocystinuria was not found. Attacks of acute polyarthritis, in many ways resembling rheumatic fever or acute rheumatoid arthritis, and associated with positive serological tests for rheumatoid or antinuclear factor, were seen. These episodes appeared to be related directly to penicillamine therapy and were observed in 5 female patients (Cases 3, 9, 12, 18, 23; Table 1) in this series. As this is not strictly a feature of Wilson's disease it is mentioned here only briefly. In 4 of these patients it was possible to continue with penicillamine, albeit in a reduced dose, but one (Case 9) suffered a severe recurrence after a rest period.

No clinical evidence of rickets or osteomalacia was observed and the plasma calcium, phosphorus, and phosphatase values in no case suggested such a diagnosis, nor did the radiological changes.

RADIOLOGICAL FEATURES (TABLE 3)

Bone density

Generalized loss of bone density was observed in two-thirds of the patients. It was usually of moderate severity, being most evident in the hands, feet, and spine and was characterized by radiolucency, cortical thinning, and prominence of the trabecular pattern. There were no radiological features which suggested osteomalacia (such as concave vertebrae or Looser's lines) nor did we observe changes suggestive of either active or healed rickets. 5 patients had suffered a fracture either before or after the diagnosis of Wilson's disease had been made (Cases 12, 13, 17, 28, 31); in only one (Case 28) did the history of

Table 1 *Clinical details of 32 patients with Wilson's disease*

Case no.	*Sex*	*Age at onset (years)*	*Age at examination (years)*	*Years on penicillamine*	*Clinical features*		*Duration of joint symptoms (years)*	*Rheumatic features*	*Serology (maximum titres)*	*Radiological features*
					At start of therapy	*At time of examination*				
1	M	12	15	2	Mild choreic syndrome, clumsy; no evidence of liver damage	Very well	Nil	No symptoms, joint hypermobility	Rose + 1/500 ANF − ve	None
2	M	10	23	7, irregular	Onset with severe hepatic disease, later severe dystonia and mental disturbance, severe dysarthria	Moderately disabled dystonic	?	Occasional pains left thigh	Rose − ve ANF − ve	Generalized osteoporosis; premature OA, left hip
3	F	—	19	3	Presymptomatic younger sib; abnormal liver function tests; later developed penicillamine arthropathy	Very well, apart from joint pains	6	Lumbar backache 6 yr; general arthralgia, a.m. stiffness 2 yr; probable penicillamine reaction	Rose + 1/32 ANF + 1/640 LE occasionally + ve	None
4	M	17	29	5	Severe tremor of all 4 limbs, speech defect	Symptom free		Back pain, limited movement knees, articular tenderness, aching legs on standing	Rose − ve ANF − ve	Squaring vertical bodies, premature OA knees
5	F	22	36	10	Severe tremor all limbs, titubation, later vit D overdose, renal damage, renal osteodystrophy	Neurological recovery, residual renal damage	5	Pain, tenderness, stiffness knees, episodic pain right hip, pain in wrists, incomplete extension of elbows	Rose − ve ANF − ve	Premature OA knees; fluffy irregularity of trochanters; wrists: chondrocalcinosis or bone fragmentation (Fig. 10); tongue-like osteophytic projections at elbow (Fig. 8);
6	M	11	20	2	'Hepatitis' with fluid retention followed by severe dystonia and dysarthria	Much improved	Nil		Rose − ve ANF − ve	Generalized loss of bone density
7	M	—	20	6	Presymptomatic younger sib; developed penicillamine nephropathy after 6 yr	Symptom free; recovery of renal lesion	?	Backache, limited movement	Rose − ve ANF − ve	Generalized loss of bone density; vertebral wedging T 9–11, Schmorl's node L 4, reduction of disc space L 4–5
8	M	20	32	4	'Hepatitis' followed 8 yr later by severe pseudosclerosis with very disabling tremor	Some improvement, tremor still disabling	5	Pain in feet and ankles	Rose − ve ANF − ve	Generalized loss of bone density; premature OA throughout spine, premature OA hips, fluffy irregularities of trochanters (Fig. 7)
9	F	—	19	9	Presymptomatic younger sib; abnormal liver tests at onset; penicillamine arthropathy after 9 yr, now on TETA 2HCl	Only problem is arthropathy	2	Stiff painful fingers, severe a.m. stiffness; dorsal ganglion on wrist, clinical appearance of RA; hypermobile joints; symptoms related to penicillamine	Rose − ve ANF + 1/160 LE − ve	Generalized loss of bone density

Table 1—*continued*

Case no.	*Sex*	*Age at onset (years)*	*Age at examination (years)*	*Years on penicillamine*	*Clinical features*		*Duration of joint symptoms (years)*	*Rheumatic features*	*Serology (maximum titres)*	*Radiological features*
					At start of therapy	*At time of examination*				
10	M	17	23	1	Initial symptom stiff, painful knees, followed by tremor and speech defect	Neurological recovery still has arthritic symptoms	6	Stiff painful knees, leg cramps, knee click on extension, articular tenderness	Rose − ve ANF − ve	Osteochondritis dissecans knees (Fig. 4); patellar erosions premature OA hips, irregular articular surfaces of medial MCP joints (Fig. 2)
11	M	13	26	12	Presented with fever, parkinsonism, dysarthria, splenomegaly	Sympton free	?	Aching buttocks and thighs, joint hypermobility	Rose − ve ANF − ve	Generalized loss of bone density
12	F	15	18	3	Acute onset of severe dystonia and dysarthria	Much improved, slightly choreic	?	Fractured neck of femur from minor trauma; stiff knees, slight spinal stiffness; joint hypermobility; occasional arthritic pains of hands and feet with high ESR, possible penicillamine reaction	Rose − ve ANF ±	Generalized loss of bone density; premature OA knees; Schmorl's nodes thoracic and lumbar spine
13	F	13	16	6	Anarthria, clumsiness, involuntary movements; developed penicillamine-induced thrombocytopenia after 6 m, maintained on Trien 2HCl subsequently	Sympton free	?	Leg cramps	Rose −ve ANF − ve	Generalized loss of bone density
14	F	15	36	14	Weakness of legs, tremor of arms, speech defect, spontaneous movements, splenomegaly	Symptom free	21	Stiff, painful knees, joint hypermobility	Rose − ve ANF − ve	OA hips, generalized loss of bone density
15	M	13	13	6 m	Hepatitis-like illness	Symptom free	Nil	None	Rose − ve ANF − ve	Generalized loss of bone density
16	M	—	7	Nil	Presymptomatic younger sib of Case 15		Nil	Joint hypermobility	Rose − ve ANF − ve	Prominent growth lines (Fig. 1), generalized loss of bone density
17	M	9	20	7	Initial symptom 'hepatitis' followed by haemolysis, then severe neurological signs with spontaneous movements	Symptom free	>13	Backache and limited movements, stress fracture of tibia at age 13 yr	Rose − ve ANF − ve	Schmorl's nodes in dorsal and lumbar spine (Fig. 5), generalized loss of bone density
18	F	10	18	8	Repeated haemolytic crises; no CNS signs	Symptom free	6	Episodes of polyarthritis with ESR (60 mm/h), leucopenia and + ve serology; probable penicillamine reaction	Rose − ve ANF + 1/160 LE cells + ve	Age 12, narrow L5 disc space (Fig. 6); fluffy irregularity of trochanters

Table 1—*continued*

Case no.	Sex	Age at onset (years)	Age at examination (years)	Years on penicillamine	Clinical features		Duration of joint symptoms (years)	Rheumatic features	Serology (maximum titres)	Radiological features
					At start of therapy	At time of examination				
19	F	21	22	1	Tremor, drooling, speech defect, festination	Minimal residual tremor	1	Cramps, dorsolumbar backache, stiff knees, with click on movement	Rose − ve ANF − ve	Irregularities on joint surfaces of lower thoracic and upper lumbar vertebrae; compression of L1
20	F	—	19	11	Presymptomatic, abnormal liver function tests; elder brother died of Wilson's disease	No symptoms	>5	Aching, clicking knees, slight increase in joint hypermobility	Rose − ve ANF − ve	Generalized loss of bone density
21	F	7	12	4	Anorexia, weight loss, malaise, abdominal pain, bleeding, splenomegaly	Symptom free	1	Painful wrists, tenosynovitis of extensor tendons to fingers, patellar crepitus, patellofemoral tenderness, no pain in knees	Rose − ve ANF − ve	Generalized loss of bone density
22	F	8	18	1 + 3	Abdominal pain, splenomegaly, later CNS signs, responded to penicillamine, stopped severe relapse before drug restarted	Advanced neurological disease, renal infection, staghorn calculi	Nil	Nil	Rose − ve LE − ve	Generalized osteoporosis, high urinary Ca, staghorn calculi
23	F	7	27	15	Liver damage and haemolysis followed by choreic syndrome	Exaggerated accessory movements	6	Attacks of rheumatoid-like joint pains, on and off since age 22, related to restarting penicillamine after interruption of treatment; better during pregnancies	Rose + 1/128 ANF + 1/20 LE ± (occ)	Generalized loss of bone density, prominent growth lines; squaring of vertebrae; osteophytes of thoracic and lumbar spine
24	M	21	32	<1	Rapid onset of tremor, spasticity anarthria	Bedridden, helpless, with contractures	?	Severe dystonia with contractures	Rose − ve ANF − ve	Knees, fluffy cortices, and patchy osteoporosis as in Sedeck's atrophy
25	M	27	31	1	Severe intention tremor, mild speech defect	Minimal residual tremor	2	Aching of arms and legs since starting penicillamine, no joint abnormalities detected	Rose − ve ANF ± 1/10	L5 disc narrow, atypical tongue-like osteophytes growing from long bones in ankles, calcaneal spurs (Fig. 9), fluffy irregularities of trochanters
26	F	12	27	14	Severe dystonia, tremor, dysarthria	Symptom free	>5	Painful knees, slight patellofemoral crepitus, joint hypermobility	ANF − ve LE − ve	Osteochondritis dissecans of femoral condyles
27	M	40	45	4	Insidious onset of tremor leading to parkinsonism, also psychotic symptoms	Minimal residual tremor	Nil	None	Rose − ve ANF − ve	Generalized loss of bone density; anterior osteophytes L1 and L2
28	M	15	35	15	Severe dysarthria, dystonia, drooling	Mild dysarthria and dystonia	„	None	ANF ± 1/10 LE − ve	Generalized loss of bone density, prominent growth lines, Schmorl's node T11

Table 1—*continued*

Case no.	*Sex*	*Age at onset (years)*	*Age at examination (years)*	*Years on penicillamine*	*Clinical features*		*Duration of joint symptoms (years)*	*Rheumatic features*	*Serology (maximum titres)*	*Radiological features*
					At start of therapy	*At time of examination*				
29	F	12	26	13	Tremor, dysarthria, severe spontaneous movements, intellectual deterioration	Mild dysarthria	,,	None	Rose – ve ANF ± 1/10	Generalized loss of bone density, squaring of vertebrae
30	M	15	19	Nil	Bedridden, drooling, dysarthric, very sick; cogwheel and lead-pipe rigidity	As previous column	,,	Joint hypermobility	ANF – ve	Generalized loss of bone density, squaring of vertebare
31	F	16	24	2	Very severe tremor of arms and head, unsteady gait	Symptom free	13	Severe pains in knees, patellofemoral crepitus	Rose – ve ANF – ve	Generalized loss of bone density, osteochondritis dissecans of medial articular surface of right tibia
32	F	14	22	Nil	Haemolytic crises and hypersplenism, splenectomy followed by tremor, anarthria and rapid CNS deterioration	As previous column	Nil	None	ANF – ve	None

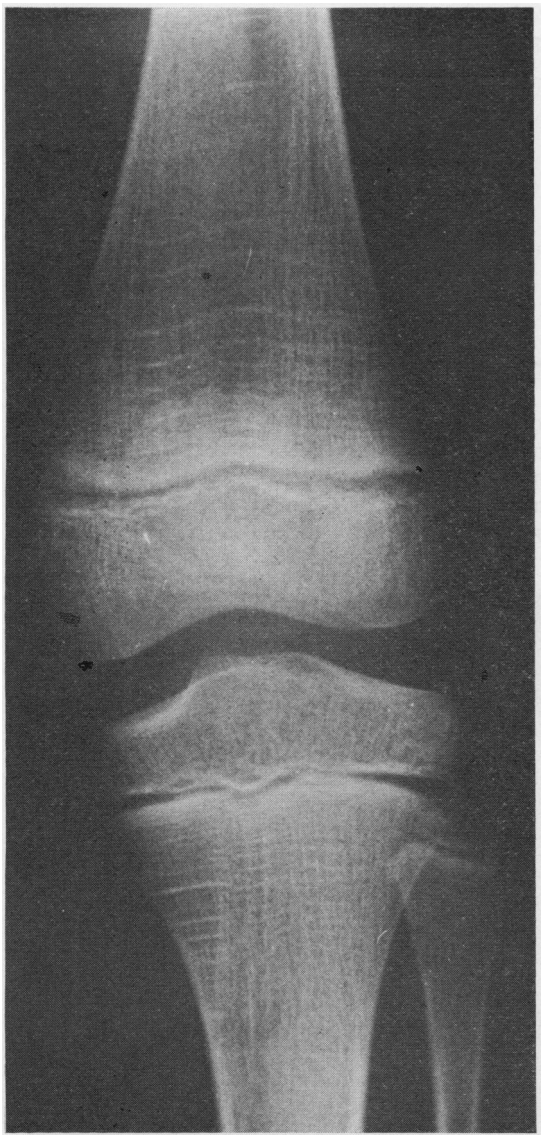

Fig. 1 *Prominent growth lines in the knees of a 13-year-old boy (Case 16).*

trauma seem to correspond with the severity of the injury thus giving further evidence to support the diagnosis of osteoporosis. The patient with perhaps the most severe loss of bone density, when assessed radiologically (Case 22) had bilateral staghorn renal calculi and a nonfunctioning right kidney, a state of affairs suggesting a very severe hypercalciuria at an earlier stage of her illness. Prominent growth lines, bands representing period of arrested growth, were a prominent feature of 3 cases (Fig. 1).

Articular changes

Premature osteoarthrosis of the peripheral joints was noted in 8 cases, but in only one were the hands involved. In Case 10 there was narrowing of the joint spaces and irregularity of the cortices of the medial metacarpophalangeal joints, changes closely resembling those seen in haemachromatosis (Fig. 2). Changes involving the hips (Fig. 3) were seen in Cases 4, 5, and 8. Osteoarthrosis of the knees was seen in 3 patients and osteochondritis dissecans of the same joints in a further 3. A particularly well marked example was seen in Case 10 (Fig. 4), an Indian male who complained of severe pain in the knees several years before neurological symptoms indicated the true nature of his disease. An appearance radiologically indistinguishable from Sudeck's (post-traumatic) bone atrophy was seen in one knee joint in Case 24, a 22-year-old male suffering from advanced Wilson's disease with severe dystonia and flexion contractures of the arms and legs.

Changes in the spine

Six patients complained of spinal stiffness or backache. Changes resembling those of spinal osteochondritis, well marked Schmorl's nodes with an occasional tendency to wedging of the vertebral bodies, or irregularity of the contiguous surfaces, were seen in 5 patients. In Case 17 several radiographs taken in childhood had shown Schmorl's nodes (Fig. 5) before the diagnosis of Wilson's disease was established. Premature spinal osteoarthrosis was striking in a 32-year-old man who had widespread anterior spondylosis though he had no

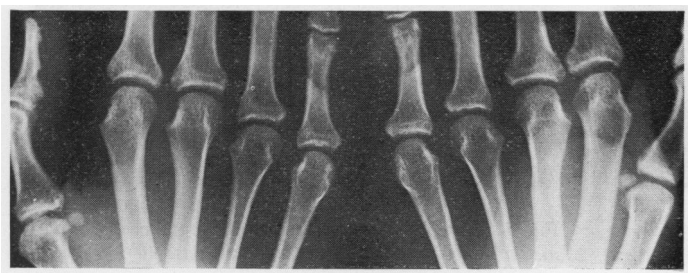

Fig. 2 *Premature degenerative changes in the metacarpophalangeal joints, most marked distally (Case 10).*

Table 2 *Correlation of rheumatic symptoms and radiological features*

Rheumatic features	*Radiological features*	*Case no.*
Pain/stiffness of knees (9 patients)	Premature osteoarthrosis	4, 5, 12
	Osteochondritis dissecans	10, 26, 31
	Normal *x*-ray	14, 19, 20
Pain/stiffness of spine (6 patients)	Vertebral squaring	4
	Osteochondritis	7, 12, 17, 19
	Normal *x*-ray	3
Pain/stiffness of hips (2 patients)	Premature osteoarthrosis	2
	Fluffy periostitis of trochanter	5
Wrist pain (2 patients)	Chondrocalcinosis/bone fragmentation	5
	Normal *x*-ray	21
Pain in feet/ankles (1 patient)	Normal *x*-ray	8
Hypermobility (9 patients)		1, 9, 11, 12, 14, 16, 20, 26, 30

Table 3 *Radiological features in 32 patients with Wilson's disease*

	No. of patients
Generalized osteoporosis	21
Prominent growth (Harris's)lines	3
Premature osteoarthrosis (peripheral joints)	8
Osteochondritis of spine	5
Reduction of intervertebral disc spaces	4
Osteoarthrosis of spine	3
Fluffy irregularities of femoral trochanters	4
Osteochondritis dissecans of knees	3
Tendency to squaring of vertebrae	4
Tongue-like osteophytic protrusions at bone ends	2

corresponding symptoms. A tendency to squaring of the vertebral bodies (that is, increase in the height of the vertebrae without a corresponding increase in the anteroposterior diameter and with loss of the anterior concavity) was seen in some patients. This

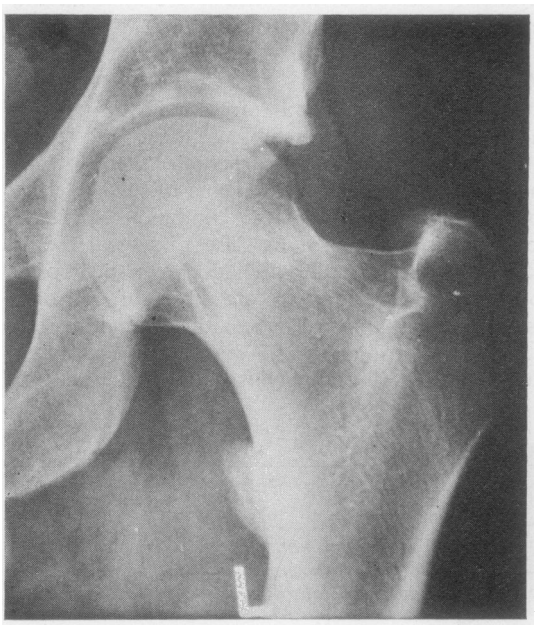

Fig. 3 *Loss of medial joint space of hips, early osteoarthrotic changes (Case 8).*

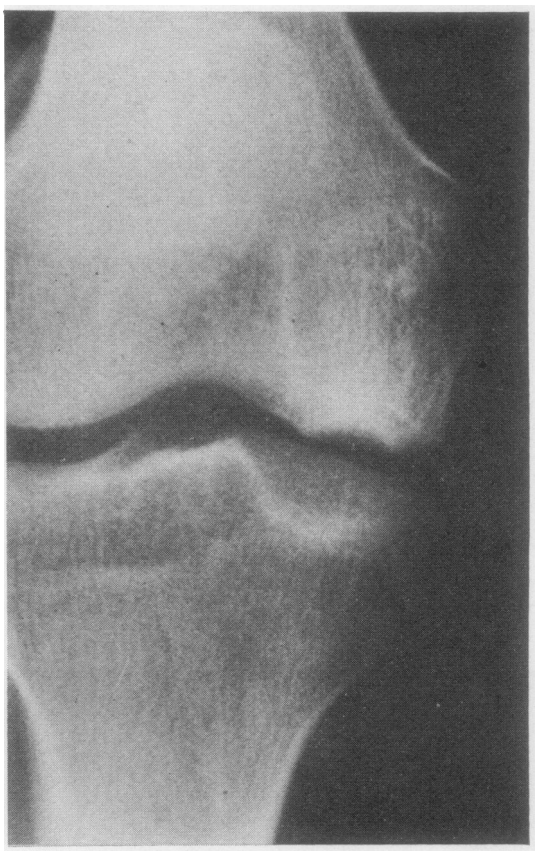

Fig. 4 *Large erosions (osteochondritis dissecans in the medial tibial condyles of both knees (Case 10).*

Table 4 *Plasma calcium, inorganic phosphorus, alkaline phosphatase, and 24-hour urine calcium excretion (mean±SE)*

	Mean age (years)	*Plasma Ca (nmol/l)*	*Plasma P (nmol/l)*	*Alkaline phosphatase (IU/l)*	*Urine Ca (nmol/24 h)*
1st visit (32 patients*)	17·1	2·40±0·04	1·20±0·05	35±14	74·7±8·7
Time of assessment (32 patients*)	23·1	2·35±0·02	1·20±0·05	74±8	50·1±8·0
Significance		<0·05	<0·05		<0·05

*As the 5 new patients were seen only once their findings are included in both sets of findings.

Table 5 *Frequency of radiographic abnormalities in various joints*

	No. of instances
Hands and wrists	
Irregularity of articular surfaces of MCP joints	1
? chondrocalcinosis, ? subchondral bone fragmentations	1
Elbows	
Tongue-like osteophytic protrusions	1
Spine	
Osteochondritis	5
Anterior spondylosis	3
Reduction of intervertebral disc spaces	4
Vertebral squaring	4
Hips	
Degenerative changes	4
Fluffy irregularity of trochanters	4
Knees	
Degenerative changes	3
Osteochondritis dissecans	3
Erosion of lateral borders of patellae	1
Appearances resembling Sudeck's atrophy	1
Ankles, heels, and feet	
Tongue-like osteophytic protrusions	1
Fluffy (compound) calcaneal spurs	1

appearance closely resembles the vertebral squaring seen in ankylosing spondylitis. Another occasional finding was narrowing of the intervertebral disc spaces, here illustrated in a 12-year-old girl (Fig. 6).

Other changes

A distinctive radiological change seen in 4 patients was a fluffy appearance of the femoral trochanters, probably representing periosteal reactions at tendon insertions (Fig. 7).

Tongue-like osteophytic protrusions from bony prominences were seen at the elbows in one patient (Case 5) (Fig. 8) and at the ankles in another (Case 25). This patient also had bilateral fluffy calcaneal plantar spurs of the compound variety (Fig. 9). The changes at the elbows in Case 5 resembled a bunch of bananas growing from the lateral humeral epicondyle and olecranon. It is uncertain whether the opacities seen in the wrists of this patient represent chondrocalcinosis or subchondral bone fragmentation, no other similar example was seen (Fig. 10). The findings are summarized in Table 5.

BIOCHEMICAL FINDINGS

The widespread age range, from 7 to 45 years, makes interpretation of the plasma levels of calcium, phosphorus, and alkaline phosphatase difficult as higher levels for these parameters would be expected during periods of active growth. Values suggesting rickets or osteomalacia were not recorded but

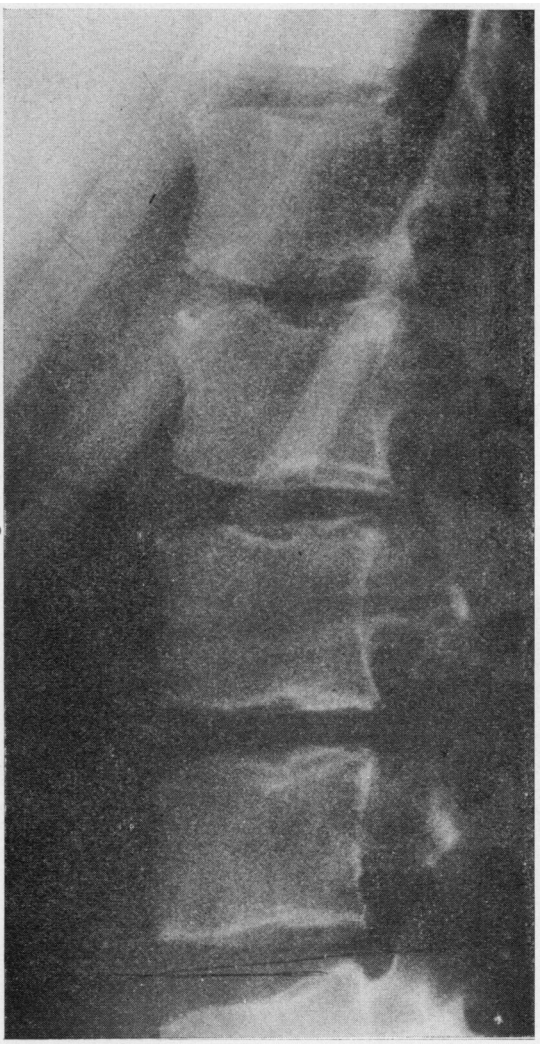

Fig. 5 *Multiple Schmorl's nodes in thoracic and lumbar spine in a 13-year-old boy (Case 17).*

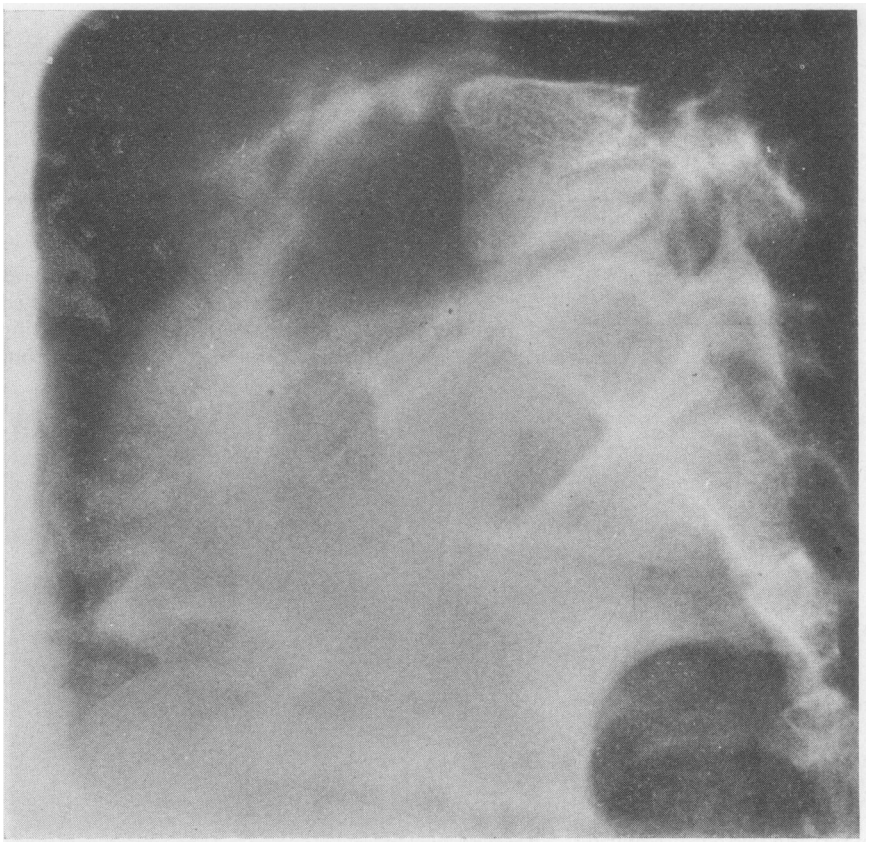

Fig. 6 *Narrowing of L5-S1 intervertebral disc space in a 12-year-old girl (Case 18).*

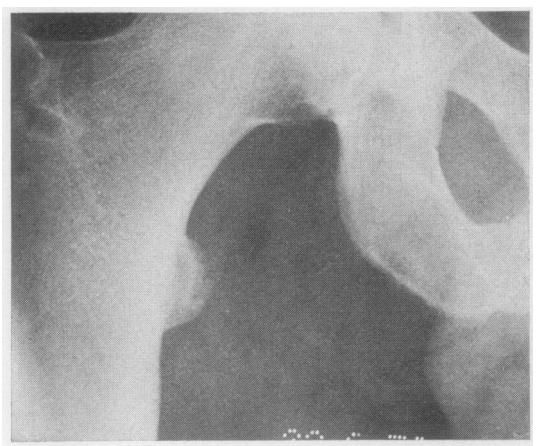

Fig. 7 *Fluffy irregularities (periostitis?) of lesser trochanters in a 30-year-old man (Case 8).*

urinary calcium values, on a normal ward diet, tended to be high on the initial visit and lower when seen for reassessment, but the difference was not significant (Table 4).

SEROLOGICAL CHANGES

The Rose–Waaler test was strongly positive in 3 patients and antinuclear factor positive (titre $>1/80$) in 5 patients at some time. These serological abnormalities were thought to be related to penicillamine therapy and were not seen in any patients before treatment was given. Immunoelectrophoresis of serum proteins, carried out on sera from 6 patients, was normal.

Discussion

As in earlier reports we found premature osteoarthrosis to be a frequent feature in our patients. Usually of mild or moderate degree, the degenerative changes were on occasions severe and could be

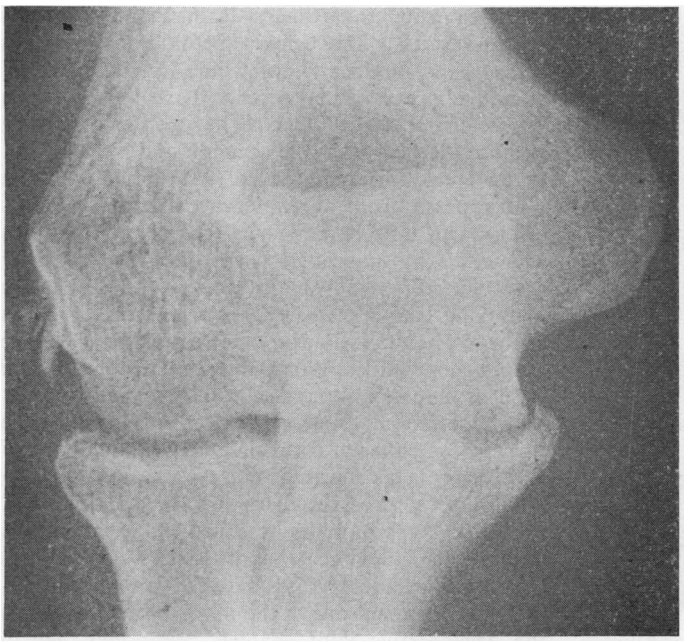

Fig. 8 *Small tongue-like osteophytes protruding from lateral epidondyle and olecranon (right elbow) (Case 5).*

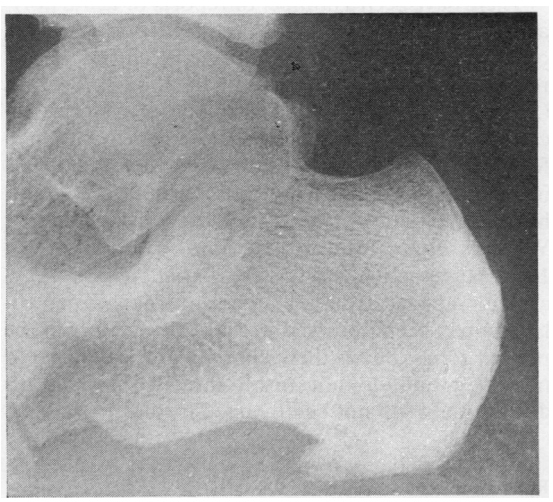

Fig. 9 *Bilateral fluffy calcaneal spurs of 'compound' appearance (Case 25).*

associated with disabling symptoms. Unlike the arthropathy of haemochromatosis, the larger joints and spine are mainly affected in Wilson's disease. It is interesting though that in one of our patients degenerative changes were found involving the medial metacarpophalangeal joints similar to the changes reported by Hamilton *et al.* (1968) in haemochromatosis. Effusions of the knee joints, as reported by Kaklamanis and Spengos (1973) were not seen in this series. These workers reported finding a noninflammatory exudate on aspiration of the joint but punch biopsies of the knee in 7 cases showed microvillus formation, vascular changes, and infiltration with chronic inflammatory cells. Chondrocalcinosis of the joints (Boudin and Pepin, 1959; Feller and Schumacher, 1972) was seen in the wrist joints of one of our patients though it is possible that the changes represented bone fragmentation as previously described (Finby and Bearn, 1958).

There seems little doubt that of the other radiological abnormalities found in patients with Wilson's disease, generalized loss of bone density, most obvious in the hands, feet, and spine, does occur in the majority of patients and is further testified to by the high incidence of fractures noted in the present series, 5 in 32 cases. The loss of bone density probably results from the loss of calcium and phosphorus in the urine (Bearn *et al.*, 1957; *Lancet*, 1962). Rickets or osteomalacia was described by Finby and Bearn in a quarter of their patients (7 out of 27), though the evidence for the diagnosis seems less than complete in 4. The Fanconi syndrome has also been reported in Wilson's disease by Morgan *et al.* (1962) and, in a less well documented case by Dent and Stowers (1965). We have not seen this clinical syndrome which must be a rare accompaniment of this disease.

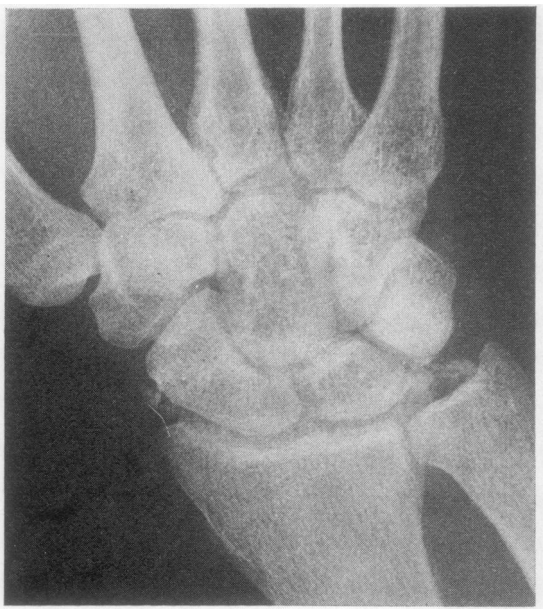

Fig. 10 *Opacities in the right wrist joint: ? chondrocalcinosis, ? subchondral bone fragmentation (Case 5).*

It also appears that Schmorl's nodes and other changes of osteochrondritis of the spine are a relatively common feature of Wilson's disease, although it must be remembered that these are changes frequently seen in the spines of adolescents and men and women in their twenties. However, as Rosenoer and Michell (1959) pointed out, the usual regions of the spine affected in Wilson's disease, mid-dorsal and lumbar, are not those typical of Scheuermann's disease. Osteochondritis dissecans has also been described previously (Rosenoer and Michell, 1959; Walshe, 1962; Mindelzun *et al.*, 1970; Kalkamanis and Spengos, 1973). Although usually in the knees, this condition affected the medial aspect of the talus in one of Rosenoer and Michell's patients. The finding of periostitis at tendon attachments causing a fluffy irregular appearance of the trochanters does not seem to have been mentioned previously in the literature. This may be a periosteal reaction of a type similar to that occurring in some cases of psoriatic arthritis and Reiter's disease, with which may be associated localized episodes of pain (Case 5).

Other features we have noted are small groups of tongue-like osteophytes protruding from bone ends and squaring of the vertebral bodies giving an appearance similar to that seen in ankylosing spondylitis. It is possible that some of these abnormalities may result from a direct toxic action of copper on the chondroblasts at the epiphyses and in the intra-articular cartilages. In this connection it is of interest that the urinary peptides of Wilson's disease, the significance of which has long been a standing source of controversy, have recently been characterized and shown to be proline-containing peptides derived from the skeleton and indicative of excess breakdown in this tissue (Asatoor *et al.*, 1976).

It appears, from our observations, that Wilson's disease can now be added to the list of conditions known to be associated with joint hypermobility (hypermobility syndrome). Whether this is due to metabolic changes affecting the ligaments such as occurs in homocystinuria, or else perhaps a feature by patients with the Wilson's disease gene in double dose, is a matter for conjecture. One possibility is that hypermobility may be induced by penicillamine therapy, as collagen formed under the influence of this drug lacks normal tensile strength due to disruption of cross linkages (Morris *et al.*, 1969). However, hypermobility was present in 2 patients before penicillamine therapy was started. As hypermobile joints predispose to early osteoarthrosis, this may represent one of the mechanisms leading to the degenerative joint changes commonly seen in patients with this disease.

There have been a number of reports of acute polyarthritis or a lupus-like syndrome occurring as a result of penicillamine therapy (Harpey *et al.*, 1974) and reversed by drug withdrawal. In 1968 one of us (J.M.W.) reported 2 such cases, one of which is included in the present series (Case 18). Arthralgia, fever, pericarditis, pleurisy, and nephritis with LE cells in the blood and a positive test for antinuclear factor have been recorded in patients given penicillamine for Wilson's disease and for cystinuria (Boudin *et al.*, 1971; Rassmussen, 1971; Oliver *et al.*, 1972). Polyarthritis, apparently related to treatment with penicillamine has been observed in 5 female patients in the present series, but as these changes are secondary to treatment and do not result directly in Wilson's disease, they will not be discussed further.

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