Clinicopathological Conference

A Case of Early Ankylosing Spondylitis with Fatal Secondary Amyloidosis

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

Clinical History

Professor E. G. L. BYWATERS: The patient (Case No. 227423 ; P.M. 11926) was a man aged 21 at the time of his death in 1966.

His first complaint was in 1956 when at the age of 11 years he developed occasional pain with sudden onset affecting the right knee, the ankles, hips, and back. Examination at another hospital was negative and his condition improved. Two years later he complained of pain in the right knee and the hip, which became worse at night, and a general physician put forward the possibility of Still's disease. The sedimentation rate was 78 mm./hr.

In 1959 he was seen for the first time at Hammersmith Hospital following a history of attacks of fever and pain in the hips, back, thighs, and knees for about 10 months. Examination at the time showed slight limitation of movement of the left hip. There was good movement of the back, and no other joints were affected. The sedimentation rate was 50 mm./hr., and the Rose–Waaler test was negative. In the following year the right knee became swollen and the spleen palpable. The sedimentation rate was 68 mm./hr., and the haemoglobin level was 9.4 g./100 ml. He was treated with prednisone at a dose of 15 mg./day falling to 7.5 mg./day, but because of poor progress he was referred again and admitted to the M.R.C. Rheumatism Unit at Taplow in 1961.

At that time there was pain and swelling affecting the right elbow, the knees, and the left foot. There was also some limitation of the movement of the right hip. Back movements were full and free, and there was normal chest expansion (2½ in.—7 cm.). Biopsy of the knee showed mild chronic synovitis of a non-specific character. Radiographs showed slight abnormality of both sacroiliac joints with some sclerosis and doubtful erosions. The E.S.R. was 52 mm./hr., and the Rose–Waaler test was again negative. There was no proteinuria. The patient was treated with aspirin 4 g./day, prednisone 10 mg./day, and active exercises. He was discharged and followed-up during the next three years in the outpatients department. The dosage of prednisone was gradually reduced from 10 mg./day to 6 mg./day and its action reinforced with enteric-coated aspirin, phenylbutazone, and calcium supplements. During this time he was attending a rehabilitation centre with a view to radio-engineering. However, intermittent proteinuria was noticed from December 1961 onwards, and by August 1963 this had become constant. His serum albumin fell to 2.6 g./100 ml., with 3.8 g./100 ml. globulins, and a normal blood urea (23 mg./100 ml.). The clinical symptoms during this period were occasional effusions in the left knee and some pain in the right heel, where *x* rays showed erosion in the sub-Achilles bursa and peritendinous periostitis (Fig. 1). He was able to reach the floor with his finger tips.

In 1964 he was admitted to Taplow for the second time because of his proteinuria. At this time he was still able to touch the floor, but there was slight limitation of movement in the region of the thoraco-lumbar junction, and also of the shoulders, right elbow, wrists, hips, and ankles. *X*-ray of the hip showed an erosion and bilateral sacroiliitis. The E.S.R. was 100 mm./hr. He was passing protein at the rate of 1–2 g./day. Treatment with prednisone and phenylbutazone was continued. A rectal biopsy showed the presence of amyloid in the walls of the blood vessels. By June 1965 he was developing some limitation and stiffness in the neck and signs of nephrotic syndrome with oedema of the ankles. The blood urea was 20 mg./100 ml., and the cholesterol was 740 mg./100 ml.

Further Progress

In May 1966 he was admitted for the first time to Hammersmith Hospital as an emergency on account of priapism with onset the previous day. He showed traces of ankle oedema, from which he had suffered periodically for a year. His blood pressure was 120/70 mm. Hg, the serum albumin had become reduced to 0.5 g./100 ml., the blood urea was 16 mg./100 ml., and his cholesterol was 550 mg./100 ml. He was treated with Rheomacrodex for three days, followed by heparin for 10 days. After three weeks he was discharged, by which time some improvement in the priapism was noted. He was readmitted on 19 September 1966 primarily for consideration of treatment of the nephrotic syndrome. The oedema had spread from the ankles, and there was now swelling of the face and legs with ascites and pleural effusions. The spleen was enlarged. Although the serum albumin was still further reduced to 0.4 g./100 ml., and the globulin to 3.3 g./100 ml., there was still no nitrogen retention—the blood urea was 16 mg./100 ml. Examination of the joints showed limitation of movement of the hips, the neck, and of the lumbar spine. The nephrotic picture improved with treatment with a low salt and protein diet together with the use of diuretics including chlorothiazide and frusemide, cyclizine, and potassium supplements. Prednisone was continued at a dosage of between 5 and 7 mg./day.

In view of the poor prognosis it was thought reasonable to use cytotoxic agents, and he was started on a course of chlorambucil at a level of 10 mg./day reducing to 7 mg./day. This produced a satisfactory fall in lymphocytes from 2,000 to 200/cu. mm. This treatment had to be stopped after 10 days, because after a bath the patient suddenly collapsed with pallor, sweating, peripheral blood vessel constriction, and tachycardia. His blood pressure was 70/50 mm. Hg. It was not clear whether this was due to an acute pulmonary embolus or to hypovolaemia due to gastrointestinal bleeding. He was given plasma, blood, and hydrocortisone intravenously, with an immediate marked improvement, followed by digitalis, packed cells, and an increase in the daily steroid dosage to 15 mg. of prednisone. After this there was a gradual but steady increase in blood urea, which by 12 November had reached 64 mg./100 ml. Eleven days later he developed oedema of the left leg due to thrombosis of the left femoral vein. Collateral venous circulation became visible on the abdomen indicating caval obstruction. He was given treatment with heparin, but this had to be stopped because of profuse bleeding per rectum. His urinary output during this time remained satisfactory.

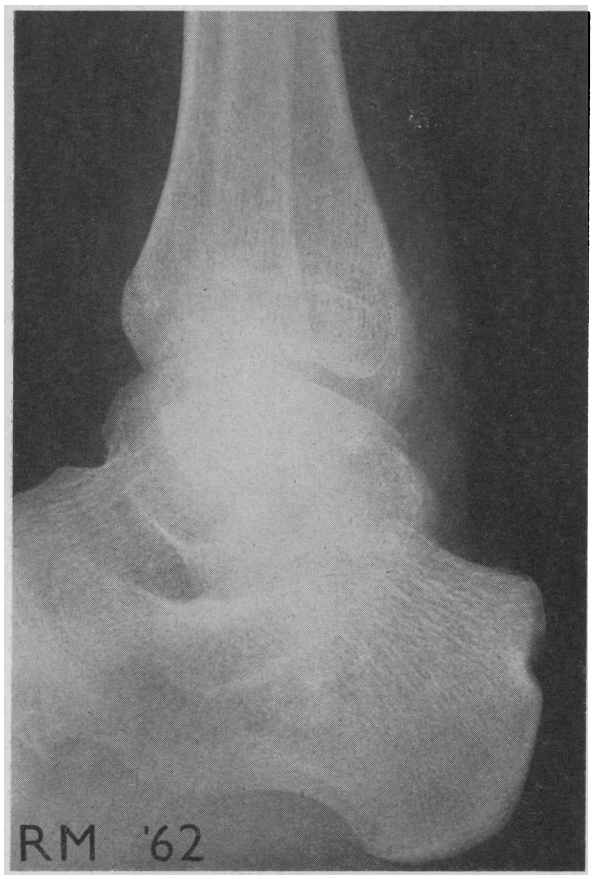

FIG. 1.—Heel radiograph, showing erosion above insertion of tendo achillis and posterior tibial periostitis (peritendinous).

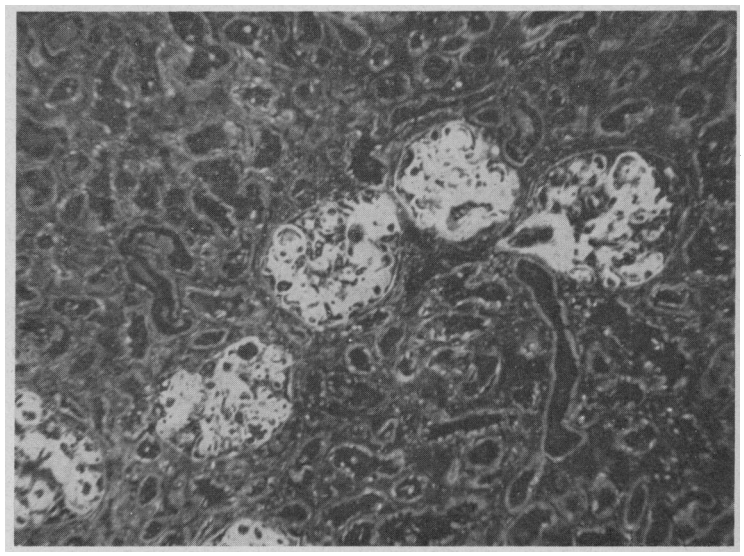

FIG. 2.—Section of kidney. Four complete glomeruli and part of two glomeruli fluorescing under ultraviolet light showing almost total replacement by amyloid. (Thioflavine T. ×70.)

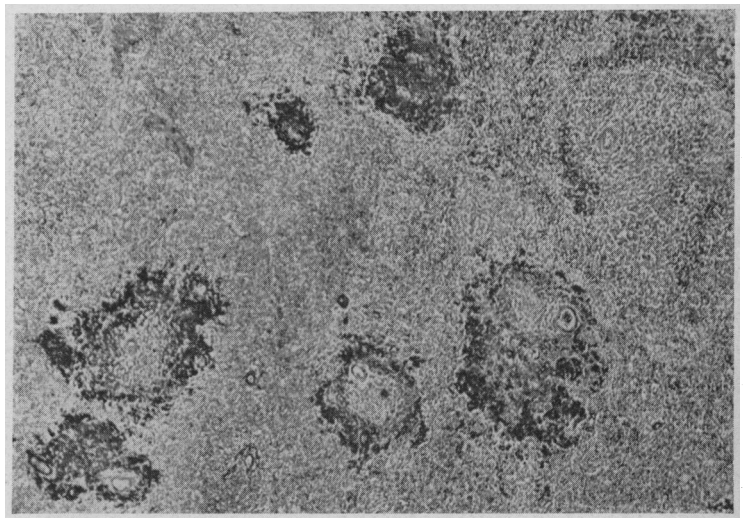

FIG. 3.—Low power view of spleen showing Malpighian bodies surrounded or replaced by amyloid. (Methyl violet. ×37.)

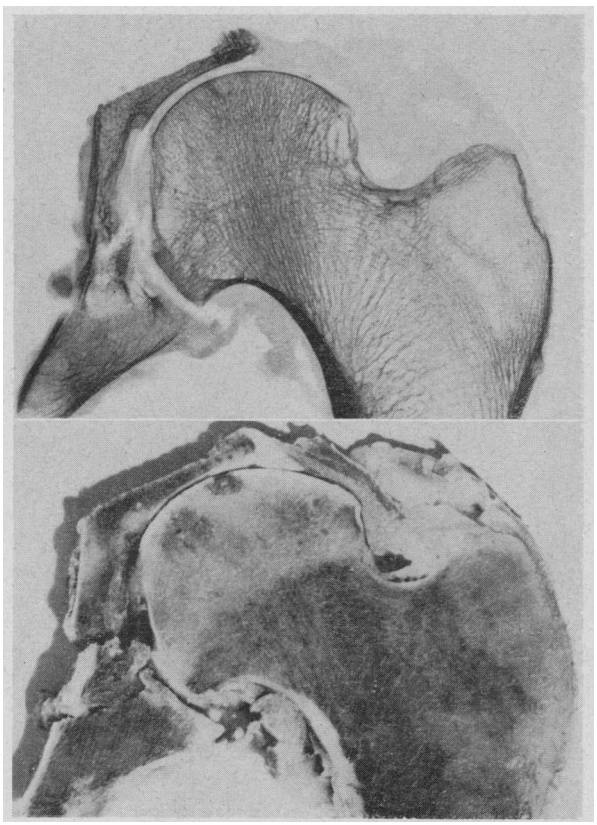

FIG. 5.—Hip in coronal section showing isolated erosion of femoral head, synovial proliferation, and acetabular erosion. *X*-ray of slice above, gross photograph below.

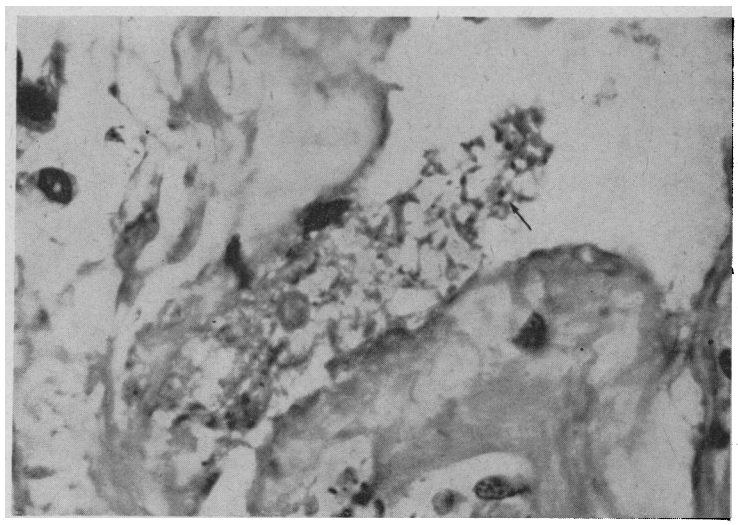

FIG. 4.—*Pneumocystis carinii*. Numerous bodies lie in foamy intra-alveolar exudate. The parasites appear as black bodies, one of which is arrowed. (P.A.S. ×312.)

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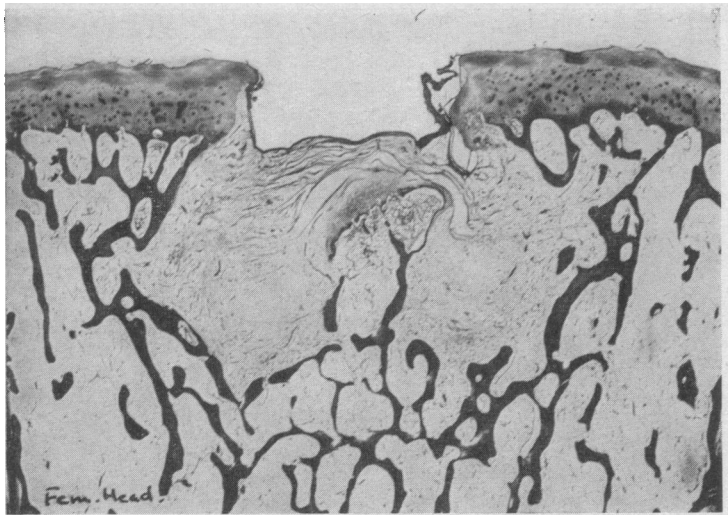

FIG. 6.—Coronal section of defect in femoral head seen in Fig. 5 showing depressed cartilage and erosion, apparently isolated. (H. and E. ×9.)

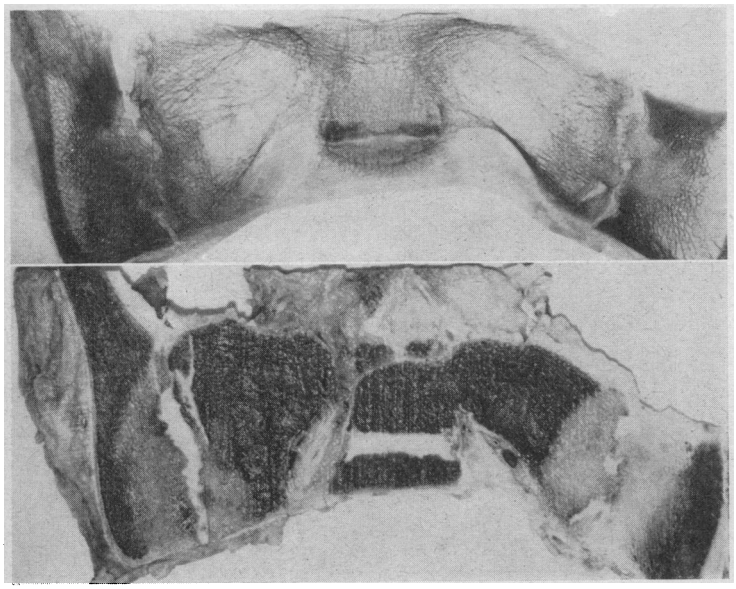

FIG. 7.—Sacroiliac joints coronal section. *X*-ray above and gross photograph of specimen below showing erosions, sclerosis of bone, fusion of cartilage, and partial persistence of epiphyseal cartilage.

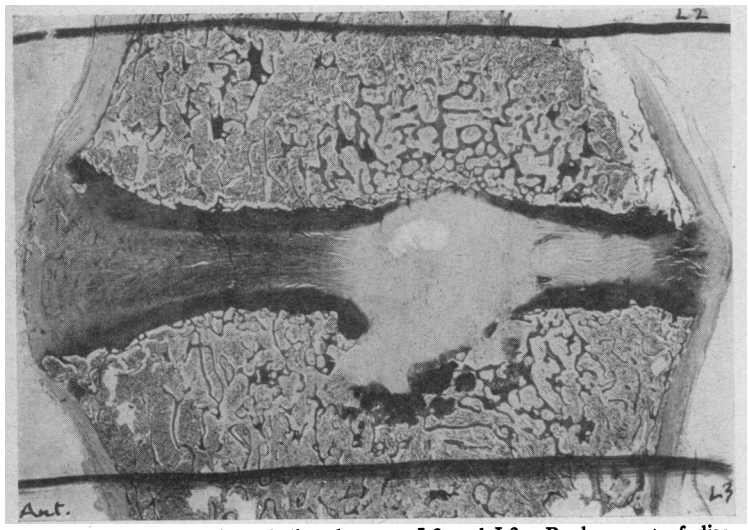

FIG. 10.—Sagittal section of discs between L2 and L3. Replacement of disc fibres by granulation tissue with surrounding sclerotic bone. (H. and E. ×2.8.)

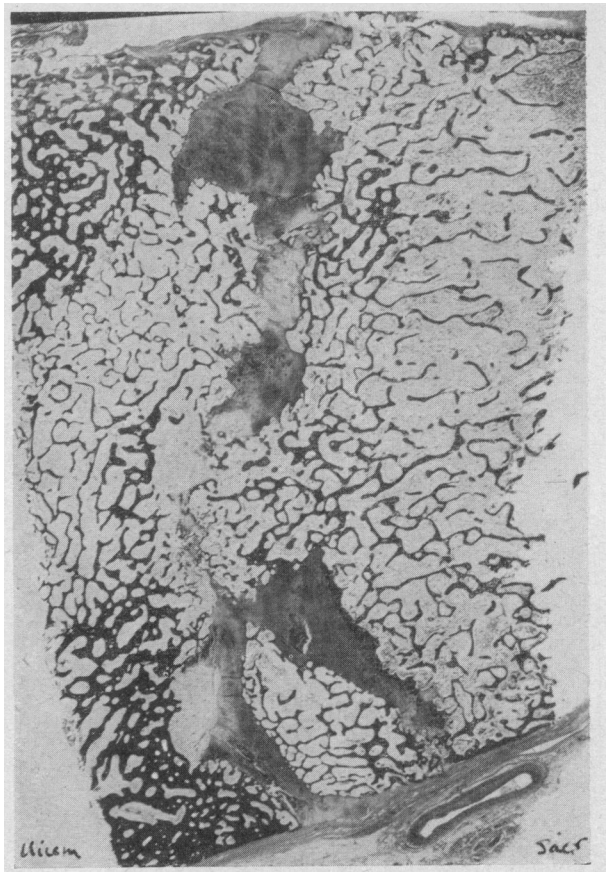

FIG. 8.—Right sacroiliac joint coronal section showing erosions, fusion, and sclerosis more marked on the ilial side (left) than on the sacral side (right). (H. and E. ×2.2.)

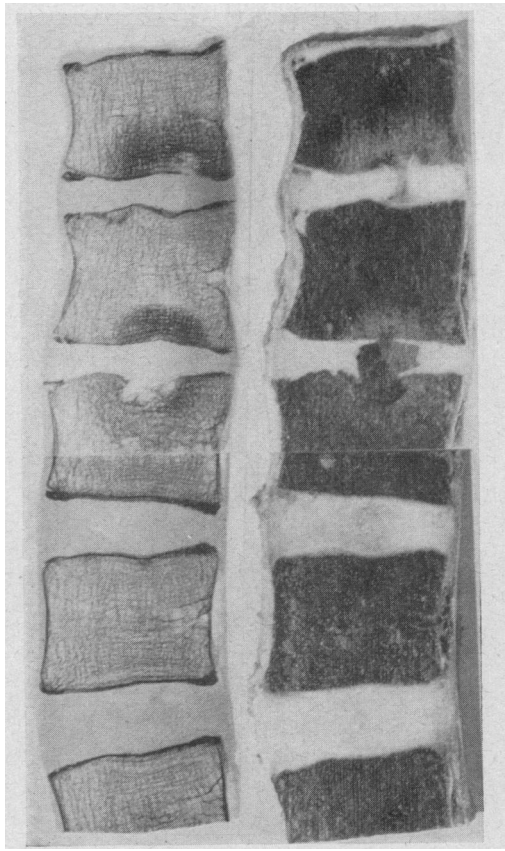

FIG. 9.—Sagittal section lumbar vertebrae 1–5, showing granulation tissue and breaching of cartilage end-plate with narrowing of discs. *X*-ray of slice on left and gross photograph on right.

Because of the probability that further emboli might break off from the caval clot he was seen by the surgeons, who advised an exploratory operation with the object of removing the clot from the inferior vena cava or of plicating it above the level of the clot formation. However, at operation the inferior vena cava was found to be solidly clotted above the level of the inferior border of the liver, and there was periphlebitis of at least four days' duration ; the abdomen was therefore closed and the boy maintained on anticoagulants, dextrose, and salt-free albumin. His condition deteriorated, however, although his blood pressure was maintained. Urine output fell, gross oedema developed, and the blood urea rose to 300 mg./100 ml. He died with hypotension on 7 December 1966, aged 21.

Clinical Diagnosis

(1) Ankylosing spondylitis with central and peripheral joint involvement.

(2) Secondary amyloidosis.

(3) Thrombosis of the vena cavae and probably of renal veins, with pulmonary emboli.

Post-mortem Findings

Dr. E. OLSEN: The body was that of a thin but well-nourished young man 170 cm. in height and weighing about 59 kg., with gross bilateral oedema of the legs and oedema of the scrotum and sacrum. A recent left lumbar incision was present.

Joints : The synovial membrane from the hip and other joints showed evidence of healed or suppressed inflammatory lesions with increased blood vessels, pigment, etc., presumably the effect of chlorambucil and five years' steroid therapy. There was erosion of cartilage both at its margins and occasionally developing through more central defects in subchondral bone.

The sacroiliac joints were obliterated and replaced in part with granulation tissue. Such areas were surrounded by dense sclerosing bone. A few of the apophyseal joints of the cervical and dorsal vertebrae were involved asymmetrically. In the upper lumbar region there was invasion of the discs by granulation tissue through defects in the vertebral plates.

Kidneys : The right kidney weighed 280 g. (normal =170 g.), the left weighed 240 g. They were large and pale with smooth cortices. On cutting, fatty streaking was seen in the cortex and medulla. No thrombi were identified in the major tributary veins. The right renal vein showed total occlusion by predominant recent thrombus. The left renal vein showed partial occlusion only. This consisted of a short extension (about 5 mm.) of thrombus from the inferior vena cava. Stains used for amyloid were methyl violet, Congo red, and thioflavine T. Histology showed almost every glomerulus to be completely replaced by amyloid (Fig. 2). Some small vessels and veins showed amyloid in the wall. The tubules showed varying degrees of atrophy with some dilatation and thyroid-like appearances. Some of the tubular walls contained amyloid. The interstitial tissue contained many fat-laden foam cells. No thrombi were detected in the intra-renal vessels.

The *penis* showed necrosis of the central arteries of the corpora cavernosa. The deep dorsal vein showed medial muscular hypertrophy and severe intimal fibro-elastic thickening, but no evidence of thrombus or amyloid in the walls.

The *spleen* weighed 275 g. (normal=170 g.). This had a typical "sago-grain" appearance. Histology showed the arterioles and Malpighian bodies to be replaced or surrounded by amyloid (Fig. 3). The pulp of the spleen showed no evidence of amyloidosis.

Adrenal glands : The right weighed 5 g. and the left weighed 5.5 g. (normal=6 g.). Both showed extensive cortical replacement by amyloid. Small vessels in the *thyroid, rectum, bladder,* and *pancreas* showed amyloid.

The *liver* weighed 1,600 g. and showed fatty changes only, apart from amyloid in an occasional portal tract vessel.

The *heart* was normal, weighing 250 g. (normal for the patient=280–360 g.), but a small vessel near the bundle of His was found to contain amyloid. The *aorta* showed widespread white mottling varying from pin-point size to about 5 mm. diameter. The lesions were not raised. Histology showed collections of lipid material in the intimal and subintimal position.

The pulmonary artery to the right *lung* was totally occluded with slightly adherent thromboembolus, which was extended into the major branches to the lower lobe. The right lung weighed 625 g. (normal=450 g.), and the left lung weighed 550 g. (normal=400 g.). Both were oedematous and congested, and small infarcts were present. Histology showed intra-areolar oedema, bronchopneumonia, and *Pneumocystis carinii* (Fig. 4).

The left popliteal, left femoral, external iliac, right and left common iliac *veins,* and the *inferior vena cava* contained thrombus extending to 5 cm. above the renal veins. The thrombus varied from organized areas (weeks old) to very recent ones (days old).

In view of the absence of histological evidence of involvement of the intrarenal veins, the total occlusion of only one renal vein, and minimal extensions from the thrombus of the inferior vena cava into the other renal vein it seems most likely that the thrombi in the renal veins were extensions of the thrombus in the inferior vena cava and unassociated with amyloid of the kidney in this instance.

Pathologist's Diagnosis

(1) Ankylosing spondylitis.
(2) Amyloidosis ("secondary" distribution).
(3) Venous thromboses (renal vein thrombosis).
(4) Pulmonary thromboembolus.
(5) Bronchopneumonia.
(6) *Pneumocystis carinii.*
(7) Aortic changes.

Pathological Changes in the Joints

Professor BYWATERS: The pathological changes in the joints are of particular interest because very little is known about the early changes of ankylosing spondylitis. Almost everyone is familiar with the late changes of the advanced case. Published accounts, as well as our own necropsy experience of about 20 cases, concern mostly patients between 40 and 70 years of age —that is, after ankylosis has been established, often for many years. This case, and one other dying recently at Taplow (also of amyloidosis) was in the early preankylosing stage. A more detailed account of these changes will be published shortly.

The *hip joint* showed chronic inflammatory changes in the synovial membrane, but these were very mild and inactive, with more blood vessels than granulation tissue, probably reflecting six-year steroid suppression as well as more recent treatment with chlorambucil. Besides marginal cartilage erosion in the acetabulum there were two buds of granulation tissue penetrating the cartilage of both the acetabulum and the head of the femur from below, apparently quite unconnected with marginal pannus (Figs. 5 and 6).

The *sacroiliac joints* (Figs. 7 and 8) were obliterated and surrounded by sclerotic bone. There was partial persistence of sacral epiphyseal cartilage. Articular cartilage was eroded

and replaced in some areas by granulation tissue spreading from and invading also subchondral bone. These areas were surrounded by dense sclerotic bone trabeculae. Elsewhere the two layers of cartilage had fused.

The *cervical spine* showed marginal erosion of the cartilage of some of the apophyseal joints by pannus. There were no syndesmophytes or bridging of the discs, but in some marginal areas the annulus fibrosus showed abnormal leashes of blood vessels.

The *lumbar spine* showed similar involvement of some of the apophyseal joints. The major lesions, however, affected the discs, although only minimal narrowing had been detected radiologically during life. These consisted of granulomatous lesions involving intravertebral discs and adjacent lumbar vertebrae 1, 2, and 3 (Figs. 9 and 10). There was destruction of the disc substance and replacement with vascular connective tissue which was seen also in the adjacent vertebrae surrounded by dense bony sclerosis. This lesion corresponds radiologically with diminution of the disc space and with a sclerotic reaction somewhat resembling that of Schmorl's nodes, but more extensive and with more reaction round it. The changes resemble somewhat those described in the spine of patients with atrophic polychondritis.[1]

Discussion

Professor BYWATERS: These pale patches on the aorta are interesting; they do not resemble the deep scarring with linear wrinkling due to changes in the media that have been seen in a small proportion (two out of 212 in our previous study[2]) of adult ankylosing spondylitis patients.

Dr. J. HOBBS: They could be the result of the nephrotic syndrome. This intimal thickening has been described[3] as the result of fatty infiltration of the aorta, and the fat cannot be seen in paraffin sections.

Professor BYWATERS: Yes. It would be interesting to know if there was any topographical correspondence of these changes with the common atheromatous fat deposit, since we have seen quite large cholesterol deposits in the skin in amyloid nephrosis.

Dr. OLSEN: There was minimal fatty streaking present—about three or four good streaks in the abdominal aorta. The pale mottling that I showed you was much more widespread.

Professor J. F. GOODWIN: I was very interested in the point that was raised about the possibility of amyloid in the heart. One of our patients with aortic regurgitation due to severe ankylosing spondylitis also had episodes of complete heart block, but I can't remember whether any amyloid deposit was found in the region of the bundle. One must distinguish, when speaking of cardiac amyloidosis, between the primary and secondary types. The type of amyloidosis which causes heart failure due to generalized involvement of the myocardium is the primary type, which I personally regard as a different disease to the secondary type. One does sometimes find isolated deposits of amyloid in the myocardium, particularly in old people, but I don't think it ever produces serious cardiac disturbance.

Professor BYWATERS: We didn't think very much of the suggestion of cardiac amyloidosis for that particular reason. It is interesting, however, that patients with this aortic lesion do develop conduction defects with PR lengthening and sometimes more, but this is not associated to my knowledge with any amyloid in the heart. It depends how thorough the search is. With modern polarizing and fluorescent methods one could perhaps find it, but I think not. The conduction defects must be due to some lasting connective tissue change.

Dr. OLSEN: They have been described as being due to fibrosis within the bundle of His, but in this case the bundle itself was absolutely normal.

Professor C. C. BOOTH: Can we come back to the original joint disorder? This patient presents with peripheral joint involvement and his initial diagnosis is Still's disease, which to me is the juvenile form of rheumatoid arthritis. Is this rheumatoid arthritis, or is it ankylosing spondylitis, and is there a difference between the two?

Still's Disease

Professor BYWATERS: We have been trying to work that out for some 20 years now, and the answer is beginning to emerge—the situation is a little less obscure now than then. There are a few cases of Still's disease or juvenile rheumatoid arthritis which are similar in every way to the adult disease: they have positive rheumatoid factor in their blood, they have nodules, and they may have vascular lesions (although these are very rare in childhood). Then again there are one or two cases—mainly like this one in boys—which when followed up for long enough go on to develop ankylosing spondylitis. In the early stages, however, they are indistinguishable from ordinary juvenile rheumatoid arthritis. The latter does not usually go on to ankylosing spondylitis, or to ulcerative colitis or psoriatic arthritis, although we have seen both. Furthermore Still's disease does not go on to adult rheumatoid arthritis. When we follow these cases of ordinary juvenile rheumatoid arthritis up they remain sero-negative—without rheumatoid factor macroglobulin in their serum. Quite a lot of adult rheumatoid is sero-negative, particularly outside hospitals, and it may be that Still's disease is related on the one hand to sero-negative adult polyarthritis and on the other hand to ankylosing spondylitis. Particularly in young boys of 11 or under, sero-negative arthritis should be suspected of being spondylitic even though the back is not affected, particularly if there is bilateral sacroiliac involvement. On the other hand, sacroiliac involvement, radiologically perhaps of a slightly different sort, is also seen in those cases of Still's disease which don't go on to ankylosing spondylitis. So we're gradually beginning to get some sort of categorization into this diagnosis of rheumatoid arthritis, but it is a slow business.

Professor BOOTH: What happens in juvenile rheumatoid arthritis with sacroiliac involvement and no radiological involvement of the spine? The point about this case is that you have got unique and beautiful demonstrations of the spinal pathology. If you took a patient with what you called juvenile rheumatoid arthritis and examined his spine as carefully as this, would you find the same sort of lesion?

Professor BYWATERS: No; we have done this in a number of cases and there are no such changes, despite the cervical spine involvement of ordinary juvenile rheumatoid arthritis.

Adult Rheumatoid Arthritis

Professor BOOTH: Yet in adult patients with rheumatoid arthritis you have also described the severe changes in the neck joints.

Professor BYWATERS: The neck changes are really quite different. As John Ball[4] has shown, the neck changes in the adult are primarily invasive—granulomata of the oncovertebral joints which invade a destroyed degenerated intervertebral disc—so that there is loss of disc space radiologically, invasion by rheumatoid granulation tissue pathologically, and undue mobility clinically. Subluxation is frequent. In ordinary cases of juvenile polyarthritis that do not proceed to ankylosing spondylitis, on the other hand, there is, first of all, involvement of the apophyseal joints in the neck by the rheumatoid process and then fusion of these joints and ultimately fusion of the bodies as well. Adults, usually elderly adults, show abnormal mobility, while juveniles show abnormal stiffness—two quite different things. Ankylosing spondylitis presents yet a different picture, a third type of spinal lesion.

Pathological Changes

Professor BOOTH: Coming on now to the interpretation of the pathological changes. What do you conceive to be the primary pathological abnormality here? Is it something wrong with the joint capsule of synovium, or something wrong with the cartilage, or what?

Professor BYWATERS: This is the key question. First of all, although 45 necropsies have been recorded in the literature on ankylosing spondylitis, most of the cases have had the disease for many years and there are very few which are early, Forestier[5] has recorded what appears to be the earliest changes, but that was in a man of 41—24 years after an onset of the disease: the rest are mainly late cases in the old, bamboo stage. In our own 21 necropsies we have only two cases with early changes, and one of these is the one I have been showing you. The late stage is that of bambooing—that is, dense ossification of the disc periphery (not calcification—ossification) and ankylosis of the apophyseal joints as well; although radiologically the latter may appear to be free, they are, in fact, ankylosed by marginal changes. The genesis of ankylosis in spondylitis has been ascribed classically to apophyseal rheumatoid change, with fusion and secondary bambooing. More recently the theory has developed that this is a metabolic disease with calcification and then ossification of the annulus fibrosus, starting at the margins of the vertebral bodies and spreading up to form the so-called syndesmophytes. This has been the theory, but examination of these one or two early cases makes it clear that the ossification which occurs (not in the anterior ligament but in the annulus fibrosus) is just the sort of ossification which could occur as a secondary phenomenon in these granulomatous areas that I have described. Forestier's case, and Aufdermaur's case No. 1[6] are the best early cases (although one was 24 years and the other was about six years from onset) and show the established lesion with a bony bridge between the two vertebrae.

New Hypothesis

I think it is possible on the basis of this and another recent early case to put forward a new hypothesis and to suggest that this disease is some change in cartilage, or some change in the body's reactions to cartilage, whereby the latter becomes an active autoimmune target, so that it gets invaded either at the margins where it joins normal connective tissue or where the normal bony layer protecting it from marrow blood vessels becomes deficient. Changes closely resembling the lesions of polychondritis are well described by Thould and his colleagues.[7]

Dr. OLSEN: I would like to ask a question with regard to the anterior longitudinal ligament. Are the changes one sees radiologically a secondary phenomenon or are they, as at one time was thought, a primary one? Cruickshank[8] stresses that the anterior longitudinal ligament is very rarely involved.

Professor BYWATERS: The anterior ligament is only rarely and lately involved. Everyone is agreed also that the major late change is ossification in the annulus fibrosus underlying the longitudinal ligaments and in the outer layers of the disc. What I was saying earlier is that I think this lesion itself may be a secondary one—ossification secondary to a preceding inflammatory change.

Priapism and Amyloid

The other thing we need to discuss is the relationship between priapism, venous thrombosis, and amyloidosis. Priapism must be a very rare complication of amyloid, but it is well associated with thrombosis, and thrombosis is well associated with amyloid, though the actual mechanism is far from clear. That is why we thought the priapism might have been due to amyloid affecting penile vessels, but it might well have been due to venous blockage spreading back from the pelvic veins.

Dr. OLSEN: That may have been so. One finds amyloid in the vessel wall associated with thrombosis, but more often the veins or arteries are not involved by amyloid at the site of thrombus formation, and it has been proposed[9] that generalized factors such as dehydration or some abnormality in the fibrinogen factor or thrombo-fibrinolytic factor may be the cause of thrombosis. Propagation of thrombus from smaller vessels may be another explanation. I believe that these patients show severe rouleaux formation when one cross-matches their blood.

Amyloid and the Kidney

Dr. HOBBS: I should like to say a few words about the degree of elevation of cholesterol in these patients. Dr. John Brown and I have shown in a series of 16 patients with rheumatoid arthritis and amyloid that six had highly selective proteinuria. Patients with such lesions have the heaviest proteinuria and thereby the most reduced serum albumin and highest serum cholesterol levels. In highly selective proteinuria the glomerulus is working at its best as a permeable membrane, and, therefore, can let more protein through. With gross impairment of permeability—for example, chronic glomerulonephritis—there is less proteinuria. The astonishing thing is that in our total series of 32 patients with amyloidosis there are nine with highly selective proteinuria. Histologically their glomeruli have looked like those seen today. Surprisingly in one-third of patients all this deposition of amyloid doesn't seem to interfere too much with the passage of protein through the glomerulus.

Dr. E. D. WILLIAMS: Have you any idea what the size of the pores is in amyloid?

Dr. HOBBS: Fig. 11 shows this patient's results, using a technique[10] where the glomerular selectivity can be judged by a visual comparison of the clearances of proteins according to their molecular weight. Suitably concentrated urine is electrophoresed on cellulose acetate alongside the donor serum. On cellulose acetate the albumin (M.W. 70,000) and transferrin (β,88,000) bands are sharp and over 90% pure, and the clearly defined α-globulins are generally small (48–54,000). The clearance formula is UV/P. For a given urine sample V is constant so that U/P compares clearances for the different

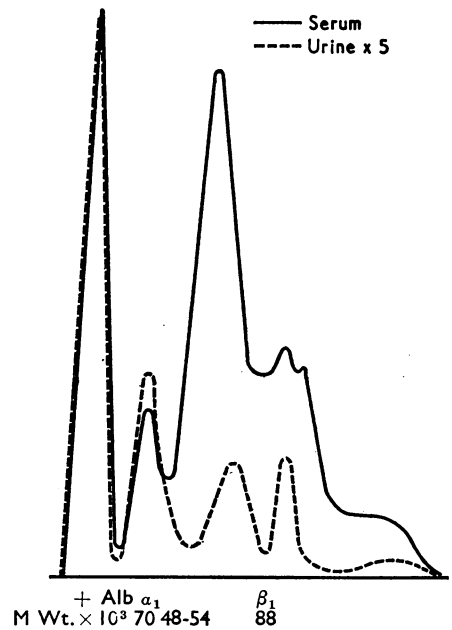

FIG. 11.—Visualization of differential protein clearance. By superimposing the scanned albumin peaks in electrophoresed serum and urine, the clearance of albumin has been set to 1.00. Relative to this the smaller α_1 (>1.00) and larger β, (<1.00) proteins show there has been renal discrimination between these fractions of closely similar size. In this patient with glomerular amyloidosis the proteinuria was highly selective.

fractions. By setting the scanner, the albumin peak areas can be made identical for urine and serum so that U/P is 1.00. Now the other fractions can be visualized in relation to an albumin clearance of 1.00. In Fig. 11 it can be seen that for $\alpha 1$, U/P is >1.00 and for $\beta 1$ U/P is <1.00: there has been discrimination between fractions of closely similar size, thus the clearance of $\alpha 1 >$albumin $>\beta 1$. This indicates a high degree of selectivity. The strips shown were made one month before death, and three other examinations over the previous two years showed the same pattern. Over three years this pattern has been seen in some 25 patients, who have all had highly selective results by the more laborious immunological methods,[11] and this technique seems equally reliable. This patient had a γG/transferrin clearance ratio[12] of 0.17; this is astonishing when you consider the appearances of the glomeruli at necropsy, and is important in that highly selective proteinuria due to amyloidosis does not respond to corticosteroid therapy.

Professor BOOTH: We will have to draw to a conclusion now. I think this has been a unique opportunity to see the pathology of this very fascinating condition, and we are privileged to have the opportunity of hearing about Professor Bywaters's unique work on this subject. Thank you very much indeed.

We are grateful to Professor J. P. Shillingford and Dr. E. D. Williams for assistance in preparing this report, and to Mr. W. Brackenbury for the photomicrographs.

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Royal College of Surgeons Tutors

The statement below has been issued by the Royal College of Surgeons:

Following the successful completion of the pilot scheme for surgical tutors, carried out with the assistance of a generous grant from the Nuffield Provincial Hospitals Trust, the College has decided, after full consultation with regional postgraduate deans, senior administrative medical officers, and others, that a full surgical tutoral scheme should now be implemented throughout England and Wales. The terms of reference for the tutors are as follows:

(1) R.C.S. tutors are appointed for a period of five years in the first instance.

(2) Their responsibilities, under the general guidance of the Council's regional representative on the Advisory Panel on the Training of Surgeons, include the following:

(*a*) To act as general adviser to those in training posts for the F.R.C.S.

(*b*) To work in close co-operation with the postgraduate dean and the clinical tutors in the region. It is of course understood that some R.C.S. tutors have also been appointed as regional clinical tutors.

(*c*) To arrange seminars, joint ward rounds, journal readings, and discussions.

(*d*) To establish and maintain facilities for study, including surgical library facilities.

(*e*) To arrange for time off for study and for attending appropriate scientific meetings.

(*f*) To encourage research in surgery, particularly in the clinical field, and to advise on the preparation of articles for publication.

The first list of tutors appointed is given below. Further lists of tutors appointed in the remaining regions will be issued in due course.

East Anglian Region.—Mr. I. Ranger (Norfolk and Norwich), Mr. C. Henriques (East Suffolk), Mr. B. Rowlands (Peterborough).

N.W. Metropolitan Region.—Mr. R. S. Murley (Mid-Herts Group), Mr. D. E. Bolt (South-west Middlesex Group), Mr. R. V. Fiddian (Luton Group), Mr. A. G. Horsburgh (West Herts Group), Mr. O. D. Morris (Ashford Group), Mr. F. A. Henley (Central Middlesex Group), Mr. J. I. Burn (St. Charles Group), Mr. D. W. Bain (Windsor Group).

S.E. Metropolitan Region.—Mr. P. Holmes (Brighton), Mr. M. Williams (Canterbury), Mr. P. J. Jennings (Medway), Mr. A. W. R. Williamson (Tunbridge Wells), Mr. A. Wheatley (Woolwich and Dartford), Mr. L. Evans (Lewisham), Mr. G. Ramsay (Bromley), Mr. M. Walker-Brash (Orpington), Mr. J. M. Powley (Eastbourne and Hastings), Mr. J. D. Maynard (Guy's Hospital).

S.W. Metropolitan Region.—Mr. W. J. D. Bradfield (Kingston), Mr. J. E. H. Pendower (Croydon), Mr. W. H. W. Jayne (Chelsea and Kensington), Mr. C. J. Anders (Chertsey), Mr. P. S. Boulter (Guildford), Mr. R. P. M. Miles (Chichester), Mr. A. E. Stevens (Redhill).

Wessex Region.—Mr. T. Rowntree (Southampton), Mr. J. Mousley (Winchester), Mr. P. Shemilt (Salisbury), Mr. W. H. G. Jessop (Bournemouth), Mr. R. T. Campbell (Portsmouth), Mr. W. A. Tucker (West Dorset), Mr. V. Gordon Walker (Isle of Wight).

Oxford Region.—Mr. G. J. Hadfield (Aylesbury and District), Mr. T. H. Cullen (Kettering and District), Mr. D. G. Lambley (Northampton and District), Mr. N. Rothnie (Reading and District), Mr. P. Huddy (Swindon/Cirencester District), Mr. P. Lord (Wycombe/Amersham District).

Wales.—Mr. R. Williams (Pontypridd Area), Mr. C. Havard (Bridgend Area), Mr. J. E. Mitchell (Swansea Area), Mr. A. H. Millard (Carmarthen Area), Mr. D. B. Griffiths (Aberystwyth Area), Mr. R. H. P. Oliver (Bangor Area), Mr. R. S. Todd (Wrexham Area), Mr. L. P. Thomas (Newport Area), Mr. H. R. Ker (Merthyr Area), Mr. O. Daniel (Rhyl Area).

Newcastle Region.—Mr. A. H. Petty (Newcastle General Hospital, Hexham and District Group), Mr. L. B. Fleming (Royal Victoria Infirmary), Mr. T. H. Tweedy (Gateshead and District Group), Mr. R. J. Rutherford (South Shields and District Group), Mr. G. J. H. Maud (Wansbeck, S.E. Northumberland, Berwick-upon-Tweed, Alnwick, and Rothbury Groups), Mr. G. H. Dunstone (Durham, N.W. and S.W. Durham Groups), Mr. D. A. Sanford (Sunderland Area Group), Mr. G. H. D. McNaught (Hartlepools Group), Mr. K. C. McKeown (Darlington and District and Northallerton Groups), Mr. A. B. Maclean (E. Cumberland Group), Mr. A. M. Loughran (W. Cumberland Group), Mr. S. Mottershead (North and South Tees-side Groups).

Sheffield Region.—Mr. F. J. P. O'Gorman (Sheffield), Mr. A. G. Butters (Barnsley), Mr. G. C. W. Baker (Chesterfield), Mr. P. H. Beales (Doncaster), Mr. P. D. Livingstone (Rotherham), Mr. P. Goodall (Derby), Mr. K. F. Wood (Leicester), Mr. J. P. Jackson (Harlow Wood), Mr. J. N. Ward-McQuaid (Mansfield), Mr. J. W. Betts (Lincoln).

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Liverpool Region.—Mr. C. R. Helsby (Liverpool).