Ankylosing Spondylitis

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Although described over 150 years ago, ankylosing spondylitis was, until the Second World War, one of those diseases rarely diagnosed and unhelpfully described in one of our great text-books of medicine by the words 'nothing whatsoever is known of its causation and no treatment has any clear influence on the course of events'.

September 1939 put the youth of the nation into uniform, but for eight months there was no visible enemy to fight. Long route marches and physical training were prescribed to preserve the morale of the troops — measures ideally contrived to exacerbate the symptoms of ankylosing spondylitis. Doctors recruited to tend Britain's unattacked and largely healthy army were likewise under-employed, and though it took them some little time, they eventually appreciated that many of those whose backache suggested an unwillingness to serve His Majesty in a military capacity were in fact suffering from ankylosing spondylitis. Such diagnostic advance did not, however, hinder the prescription of therapeutic measures such as the plaster bed, which greatly accelerated ankylosis of the spine and gave many decubitus calculi, and radiotherapy, which provided a leukaemic risk much in excess of that enjoyed by the population at large. Moreover, this increased awareness of the disease occurred before belief in focal sepsis as a cause of rheumatic disorders had been discarded, and many lost their teeth, their tonsils and had extensive nasal surgery in an attempt to cure a disease for which there is still no treatment.

After the war a host of papers from all over the world highlighted the fact that ankylosing spondylitis is common and predominantly affects males, and made the familial incidence of the disease clear. This latter work was admirably summarised by Kellgren (1964) who indicated that the condition occurs forty times more frequently in the first degree relatives of those suffering from the disease than it does in the population at large. Moreover, studies of monozygotic twins left no doubt about the importance of genetics in the genesis of the disease, only three of ten pairs being discordant (Moesmann, 1960; Julkenen, 1962).

The next advance was the realisation that ankylosing spondylitis often appeared in patients afflicted by such relatively common diseases as ulcerative colitis, Crohn's disease, psoriasis and Reiter's disease. Many workers (Bywaters and Ansell, 1958; Fernandez-Herlihy, 1959; Acheson, 1960; Zvaifler and Martel,

1960; Wright and Watkinson, 1965) reported a high incidence of ankylosing spondylitis in chronic inflammatory bowel disease while Jayson and Bouchier (1968) and Jayson *et al.* (1970), using the opposite approach, found chronic inflammatory bowel disease in about 1 in 6 patients suffering from ankylosing spondylitis.

Macrae and Wright's family study (1973) was of particular interest, for they demonstrated not only a high incidence of ankylosing spondylitis in patients with ulcerative colitis but also in their blood relations, and the incidence in blood relations of probands with both ulcerative colitis and ankylosing spondylitis was nearly four times greater than in the blood relations of probands with ulcerative colitis only (Tables 1 and 2).

Table 1. Incidence of ankylosing spondylitis in patients with ulcerative colitis, their blood relations and their spouses (Macrae and Wright, 1973).

Group	Percentage with Ankylosing Spondylitis	
	Male	Female
91 Probands with ulcerative colitis	20.0	7.7
236 Blood relations of probands	5.1	2.6
56 Spouses of probands	NIL	NIL

Table 2. Incidence of ankylosing spondylitis in the blood relations of patients with both ulcerative colitis and ankylosing spondylitis and in the blood relations of patients with ulcerative colitis only (Macrae and Wright, 1973).

	Percentage with Ankylosing Spondylitis
Blood relations of probands with ulcerative colitis and ankylosing spondylitis	10.5
Blood relations of probands with ulcerative colitis without ankylosing spondylitis	2.8

The brilliant work of Brewerton, Caffrey and James at the Westminster Hospital and of Schlosstein and his colleagues at the University of California has shown the close relationship of the histocompatibility antigen W27 to ankylosing spondylitis and has underlined the genetic basis of the disease and demonstrated

that its complications and its association with other diseases are similarly determined.

Both the Westminster Hospital group and the Californian workers found that most patients with ankylosing spondylitis have HL-A27 but that it is present only in 8 per cent or less of controls. However, Brewerton and his co-workers found it in 52 per cent of first degree relatives of patients with ankylosing spondylitis (Brewerton et al., 1973; Schlosstein et al., 1973).

De Bruyere and Nagant de Deuxchaisnes (1975) reported a most interesting family, totalling 64, from Louvain in whom there were 6 members with ankylosing spondylitis in four generations. All affected members had HL-A27, 3 in double dose, while 27 of the 58 who were unaffected had the antigen, one in double dose.

Table 3. Incidence of HL-A27 in patients with ankylosing spondylitis in Switzerland, Italy, Yugoslavia, Sweden and Germany.

Country	Author	Patients studied	Percentage with HL-A27
Switzerland	Gerber et al., 1975	108	91.5
Italy	Luciani et al., 1975	8	87.5
Yugoslavia	Jajic et al., 1975	66	90.0
Sweden	Möller and Olhagen, 1975	?	100.0
Germany	Schattenkirchner and Albert, 1975	240	94.6

Similar high percentages of patients suffering from ankylosing spondylitis positive for HL-A27 have been reported from Switzerland, Italy, Yugoslavia, Sweden and Germany (Table 3). However, the racial incidence of ankylosing spondylitis varies, and in populations in which the disease is rare the antigen is found in fewer of the unaffected. Thus, Cleland et al. (1975) failed to find HL-A27 in 118 Australian Aboriginals in whom the disease is not known to occur, and in Negroids, Japanese and Hong Kong Chinese, in all of whom ankylosing spondylitis is very uncommon, 1 per cent or less of the population have HL-A27. On the other hand, in Pima Indians where the incidence of the disease approaches 6 per cent (Gofton et al., 1972) the antigen is present in 10 per cent of the people (Amos, 1972).

The interesting family with two members afflicted by ankylosing spondylitis reported by Dick et al. (1974) showed an affected member without the antigen and an unaffected member with the antigen, and in Van der Linden's family (Van der Linden et al., 1975) there were similar findings, so there is clearly some other genetic factor involved.

Caucasians with HL-A27 have only a 4 or 5 per cent danger of developing

ankylosing spondylitis and it seems probable that the antigen is linked to a number of immune response genes and that manifestations of the disease may be provoked by the presence of one of the conditions often associated with it, such as ulcerative colitis. This was clearly shown by Brewerton *et al.* 1974a), the proportion of patients suffering from ulcerative colitis positive for HL-A27 being very much greater in those with ankylosing spondylitis than in those with peripheral arthropathy or sacroiliitis, while those without any arthropathy show a normal incidence of the antigen. Their findings in respect of psoriasis show a similar pattern. Bluestone *et al.* (1975) investigating the incidence of HL-A27 in chronic inflammatory bowel disease and psoriasis complicated by peripheral arthritis or ankylosing spondylitis presented almost identical findings.

Juvenile chronic polyarthritis is a disease in which the prognosis is often for long uncertain and there may be much anxiety for the parents and the physician. Some may resolve completely, some become sero-positive rheumatoid arthritis with nodules, some persist as sero-negative polyarthritis while others assume the classical pattern of ankylosing spondylitis. HL-A27 has been found to be present in less than half those suffering from juvenile chronic polyarthritis but Veys *et al.* (1975) in Belgium and Schaller *et al.* (1975) in Seattle found the antigen in nearly all those whose disease went on to sacroiliitis or ankylosing spondylitis. The findings of Edmonds *et al.* (1974) were exactly the same.

Another important study from the Westminster Hospital group relates to the incidence of HL-A27 in acute anterior uveitis which commonly complicates ankylosing spondylitis or sacroiliitis but more frequently appears and recurs without identifiable reason. Of their patients 70 had no associated disease and showed an incidence of HL-A27 of 39 per cent while 90 per cent of the remaining 30, most of whom were suffering from ankylosing spondylitis or sacroiliitis, had the antigen (Brewerton *et al.*, 1974b).

In 1957, Lea and Abbatt reported a twofold increase in the number of certifications of pulmonary tuberculosis in 1,981 spondylitics pensioned on account of their disease, and eight years later Court-Brown and Doll (1965) found a 2.5 to 3 times greater than expected number of deaths from respiratory causes among ankylosing spondylitics. These were due to pneumonia, tuberculosis and 'a type of upper lobe fibrosis'. In this latter connection it must be emphasised that in Lea and Abbatt's pensioners the diagnosis of pulmonary tuberculosis was based on radiographs of the chest and not on positive sputa.

That there is a type of upper lobe fibrosis that may progress to cavitation, which is a complication of ankylosing spondylitis and totally unrelated to pulmonary tuberculosis, is beyond doubt. We have seen many examples ourselves and have found reports of over 60 such patients in the literature. They are commonly treated with antituberculous drugs despite failure to isolate the tubercle bacillus. The fibrotic process is usually bilateral but in some patients it is unilateral, the right lung being more commonly involved. In some of those with

unilateral fibrosis the other lung becomes involved after an interval of months or years. Three of our patients illustrate the main features of the condition.

Case 1. When 33 years of age, a machine operator complained of backache and increasing stoop. Clinically and radiologically he had advanced ankylosing spondylitis and was given irradiation of the whole spine and sacroiliac joints. Fourteen years later he developed exertional dyspnoea and cough and the chest radiograph showed extensive upper lobe fibrosis (Fig. 1). Pulmonary tuberculosis was suspected but eleven sputa were negative and the Mantoux test was likewise negative at 1 in 100. Despite this, antituberculous drugs were given for 15 months. After another five years had elapsed his vital capacity was only 1.20 litre (predicted 4.15 litres), his FEV_1 was 71 per cent excluding significant ventilatory insufficiency, and his carbon monoxide diffusing capacity was very low — 3.8 ml/min/mm Hg, indicating a gross transfer defect. Severe respiratory failure was confirmed by an arterial PO_2 of only 54 mm Hg and a PCO_2 of 75 mm Hg. In addition, aortic incompetence and a mild paraplegia were also evident. Fourteen months later he was admitted to hospital in a moribund state with bronchopneumonia and died within twelve hours.

Case 2. A 62-year-old sheet metal worker who had suffered from ankylosing spondylitis for 20 years was admitted to hospital because of a depressive illness. He had a fixed kyphotic spine and negligible chest expansion and obvious upper lobe fibrosis (Fig. 2). He had never been treated with radiotherapy and five sputa were negative for tubercle bacilli. He had two episodes of pneumonia from which he recovered with antibiotic therapy but the second provoked acute cor pulmonale and respiratory failure.

Case 3. A 60-year-old labourer had had symptoms and signs of ankylosing spondylitis for 25 years and had had radiotherapy (1200 rad) to the sacroiliac joints and lumbar spine. He was admitted to hospital with a right axillary vein thrombosis; physical and radiological examination showed advanced ankylosing spondylitis with the spine fixed in kyphosis. The chest radiograph showed right apical fibrosis (Fig. 3). No tubercle bacilli or malignant cells were found in the sputum but he was presumed to have a bronchial carcinoma for which he was given megavoltage irradiation. Five years later his chest radiograph is unchanged and his general condition is excellent.

Upper lobe fibrosis is unlikely to develop until ankylosing spondylitis has been present for a long time — sometimes as long as 30 years. That it is not attributable to radiotherapy is evident from the fact that many patients affected have not been so treated. Moreover, the interval between radiotherapy and the advent of
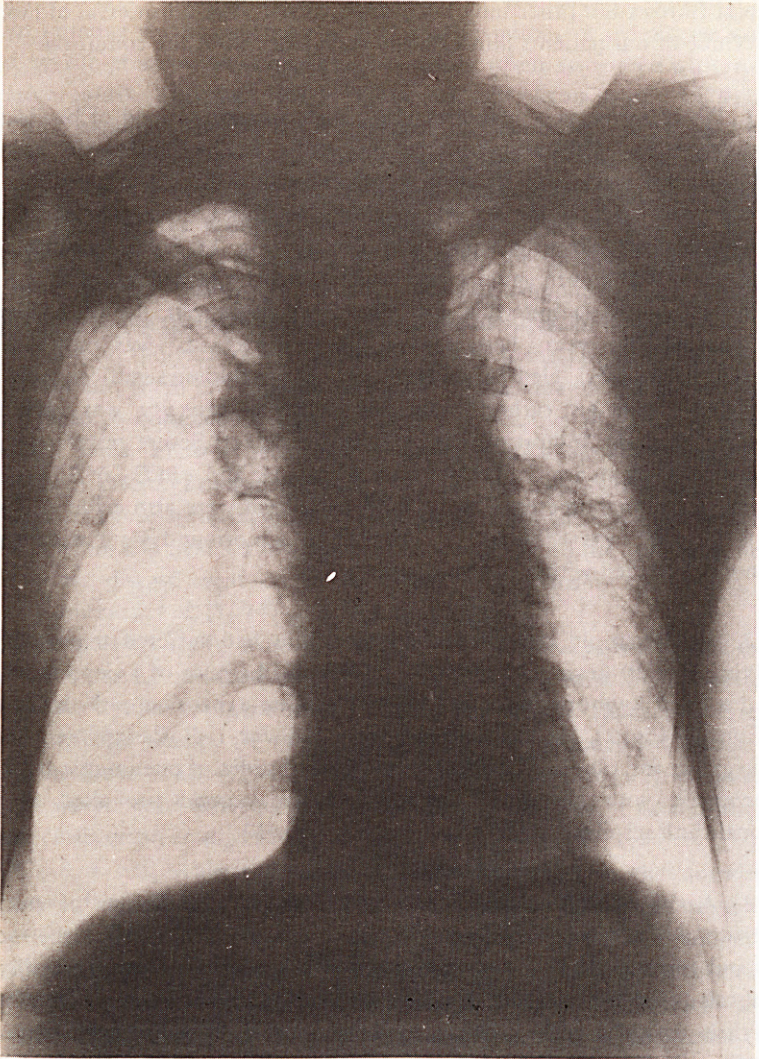
Fig. 1. Case 1. Chest radiograph showing bilateral upper lobe fibrosis.

pulmonary fibrosis is much too long and the anatomical distribution of the lung changes does not correspond to the treated area.

Symptoms are usually cough, dyspnoea and tachypnoea but haemoptysis is frequent, especially in those with cavitation, and episodes of superimposed infection, which may prove fatal, are prone to occur.
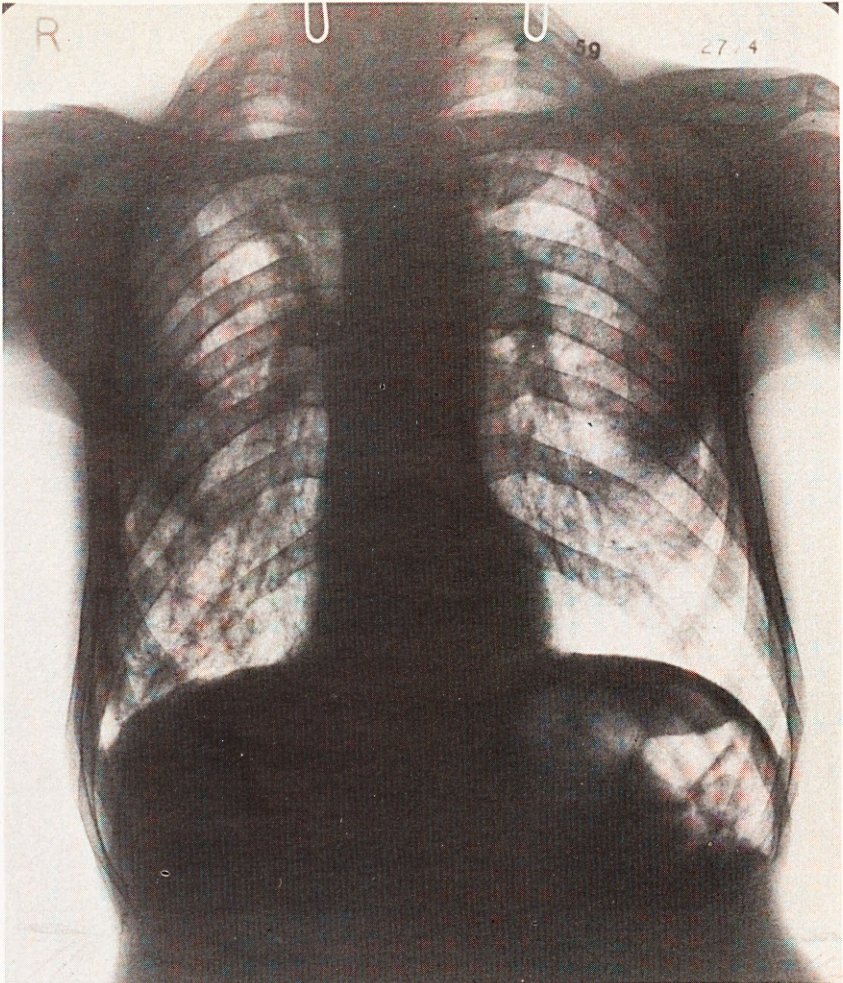
Fig. 2. Case 2. Chest radiograph showing bilateral upper lobe fibrosis.

In a high proportion of those who develop cavitation (Fig. 4) the cavity becomes colonised with aspergilli. *Aspergillus fumigatus* is the usual fungus and is identified by its presence in the sputum and by finding precipitating antibodies in the serum. The aspergilloma is, however, usually initially revealed by chest radiography or tomography showing a round opacity within a cavity.

Autopsies, pneumonectomies, lobectomies and lung biopsies have given a clear picture of the pathology of the condition, which differs from that of rheumatoid
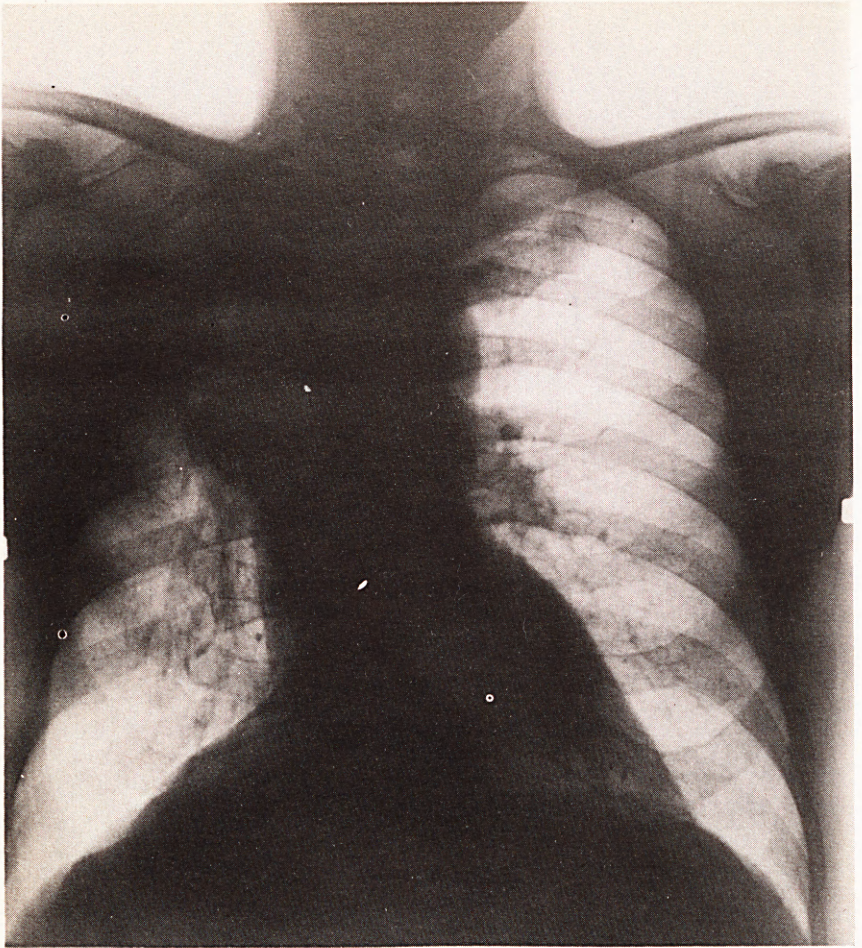
Fig. 3. Case 3. Chest radiograph showing right upper lobe fibrosis.

lung. There are dense pleural adhesions and the fibrosis is always more evident in the upper lobes than elsewhere in the lungs. It is non-specific in type, irregular in distribution and mostly interstitial, with fragmentation of elastic tissue, collagen degeneration, and an abundance of fibroblasts. Areas of chronic interstitial pneumonitis are often evident as are areas of bronchial dilatation and bronchiectasis. Fibrin and foamy macrophages are seen in remaining alveoli.

A small proportion of patients suffering from ankylosing spondylitis develop an inflammatory fibrosing lesion of the aorta and aortic valves which, histo-

Fig. 4. Chest radiograph showing cavitation in lung fibrosis associated with ankylosing spondylitis.

logically, is similar in nature to the pulmonary lesions. Presumably, both are part of the basic disease process but apart from severe and long-standing ankylosing spondylitis there are no identifiable factors especially predisposing to lung or heart involvement.

The cardiac manifestations of ankylosing spondylitis are of serious portent and

tend to be seen in the most severe forms of the disease as judged by degree of disability and peripheral joint involvement. Pathologically there is thickening and a tendency to fusion of the cusps of both aortic and mitral valves. The aortic ring is enlarged and the proximal aortic intimal surface appears raised, grey in colour and corrugated. Clinically, a systolic murmur in the aortic area is usually the first evidence of cardiovascular involvement. Later, the left ventricle enlarges and the murmur of aortic incompetence becomes audible. The left ventricle fails more rapidly than is usual in aortic valve disease of other aetiology but the insertion of an aortic valve prosthesis or other surgical procedures may grant a reprieve.

Conduction defects account for most of the other cardiovascular risks to which the victims of ankylosing spondylitis are exposed. Prolongation of the P-R interval and left or right bundle branch block are often apparent and complete atrio-ventricular dissociation may demand the insertion of a pacemaker. Of 12 patients reported by Somer and Siltanen (1975) 8 required such treatment. Massive aneurysm of the thoracic aorta and the aortic arch syndrome have also been reported, while patients with Reiter's disease may show aortic lesions and conduction defects exactly the same as those encountered in ankylosing spondylitis (Cosh *et al.*, 1973).

Few diseases have so many neurological complications and hazards as ankylosing spondylitis. Fortunately, those most frequently encountered, the muscle-wasting resulting from peripheral joint involvement and the sciatic radicular pain that is such a common early symptom, are the least serious and disabling. Loss of an ankle jerk with corresponding sensory impairment is not uncommon, particularly in spondylitics who have or have had sciatic pain, and pain, sensory loss and muscle-wasting due to cervical root lesions are also seen, though a little less frequently.

The process that ankyloses the spine and ossifies the spinal ligaments often involves the spinal meninges, for the protein content of the cerebrospinal fluid is commonly raised in the active phase of the disease (Boland *et al.*, 1948; Ludwig *et al.*, 1943). Sometimes this granulomatous process may be localised and produces a syndrome of cord compression due to adhesive arachnoiditis, often with cyst formation. Surgical efforts to decompress such lesions give disappointing results (Goldenberg and Logothetis, 1961). Such cord lesions may be associated with a granulomatous lesion of adjacent vertebrae and intervertebral discs radiologically remarkably similar to that seen in tuberculosis and brucellosis (Lorber *et al.*, 1961) but more often such vertebral and disc lesions persist as a cause of pain and radiological abnormality for years, ultimately healing spontaneously to leave the cord unscathed (Baggenstoss *et al.*, 1952). Pain may dictate surgical fusion which usually relieves symptoms (Wholey *et al.*, 1960).

When ankylosing spondylitis becomes quiescent the cerebrospinal fluid protein returns to normal but adhesive arachnoiditis may produce a cauda equina lesion with a dilated lumbo-sacral theca and posterior diverticulae (Matthews, 1968).
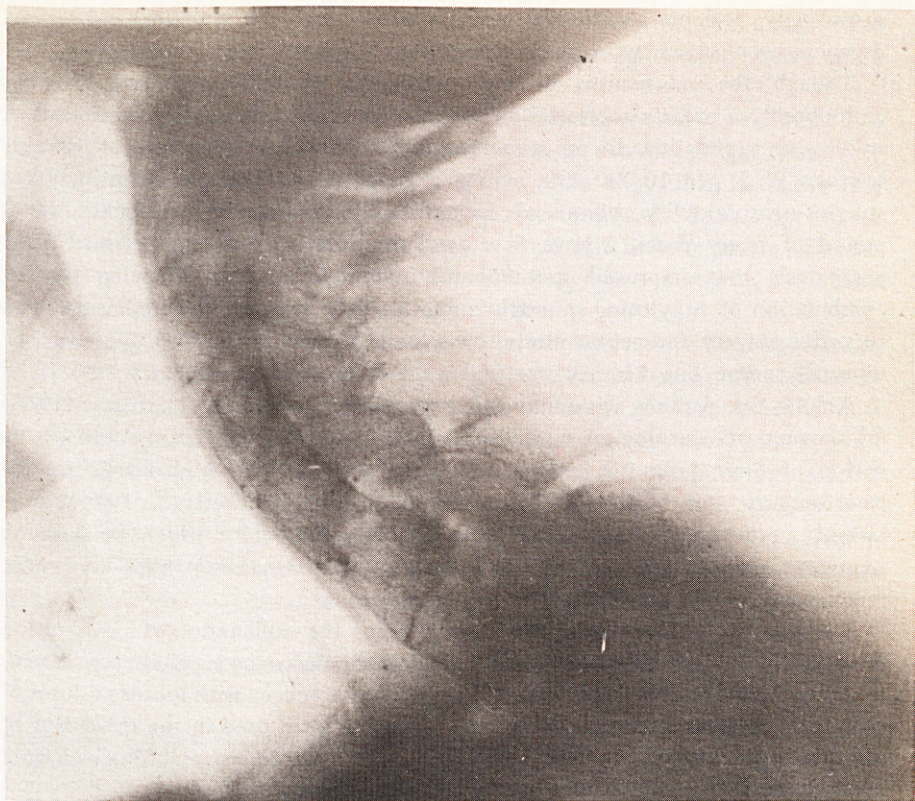
Fig. 5. Cervical spine radiograph showing severe involvement by ankylosing spondylitis and deposition of new bone along anterior surfaces of vertebral bodies.

The patient with a cauda equina lesion reported by Lee and Waters (1962) had a laminectomy without benefit. We have given nothing but symptomatic treatment to the few such patients we have seen.

Atlanto-axial dislocation, though not as frequent a complication as in rheumatoid arthritis, is not uncommon. Usually, it causes pain but no neurological symptoms or signs but it may produce parasthesiae in the upper limbs or a tetraplegia. Pain and neurological manifestations are relieved by traction, a collar or occipito-atlantal fusion.

When the cervical spine is severely involved (Fig. 5), blood flow through the vertebral arteries may be impeded and symptoms of vertebro-basilar insufficiency result. In such patients ankylosis of the cervical spine is often incomplete and some symptomatic improvement may be derived from wearing a collar. Not

surprisingly, patients so affected tend to be in middle or later life and arterial degenerative change may be partly responsible.

Though the mechanism of the relationship is quite unknown there is undoubtedly a greatly increased incidence of multiple sclerosis in the victims of ankylosing spondylitis. In the population as a whole, the incidence of multiple sclerosis is 5 per 10,000 but among a group of 45 patients suffering from ankylosing spondylitis, whom we have followed and studied carefully over a period of many years, 2 have developed multiple sclerosis and a third has a paraparesis that improved spontaneously. One young man is dying from a combination of ankylosing spondylitis and multiple sclerosis and he has also had to suffer surgery for peptic ulceration to which spondylitics also appear to be unusually prone, but this may result from the therapy given to them.

Among five patients with ankylosing spondylitis referred to Matthews (1968) on account of neurological disabilities, three had multiple sclerosis, and over a period of three years the only spondylitic referred to the Midland Centre for Neurosurgery and Neurology had multiple sclerosis (Bickerstaff, 1975). It is indeed a cruel fact of nature that one disabling disease for which we have no treatment should render its victims more prone to another disorder even more terrible and equally untreatable.

The possibility of radiation myelopathy being the explanation of a cord lesion in anyone previously treated by radiotherapy must always be carefully considered. It seems, however, that cord damage is only likely to occur with localised doses of 4,000 rad or more and such doses have not often been used in the treatment of ankylosing spondylitis. We have not encountered or traced any record of radiation myelopathy following radiotherapy for ankylosing spondylitis.

Two of our group of 45 spondylitics had a cluster of focal epileptic attacks. One had multiple sclerosis, and an area of cortical demyelinisation was presumably responsible for the episode, but in the other patient no cause was apparent and the skull radiograph, E.E.G. and brain scan were normal. One of 54 spondylitics reported by Matthews (1968) had epilepsy.

Edgar (1974) reported two patients who had received radiotherapy for ankylosing spondylitis and years later developed leg weakness due to a post-radiation sarcoma. He had traced another three similar iatrogenic victims through Professor Sir Richard Doll. All five patients had died within six months from pulmonary metastases.

A common finding in ankylosing spondylitics is a moderate and variable elevation of the serum alkaline phosphatase. We have found this in approximately half of our patients, and the 5-nucleotidase, gamma-glutamyl transpeptidase and the polyacrilamide gel electrophoresis showed it to be usually osseous in origin (Kendall *et al.*, 1973a).

When the knees are affected in ankylosing spondylitis there are usually large effusions on both sides that rapidly reaccumulate if aspirated. The synovial fluid is

remarkably similar to the synovial fluid in rheumatoid arthritis, with a high white cell count comprising polymorphs and lymphocytes, a high 5-nucleotidase and a high IgG, IgM and IgA (Kendal *et al.*, 1973b).

Our current knowledge of the aetiology of ankylosing spondylitis does not give much hope of the early advent of curative treatment but meanwhile potentially harmful therapeutic measures should be avoided as far as possible. Radiotherapy, though it may reduce pain, has been largely discarded in the knowledge that it does not arrest the disease and does carry a small but definite leukaemic risk. Steroids are useless and dangerous and the older analgesics — certainly phenacetin — have destroyed the kidneys of many spondylitics.

Although the presence of ankylosing spondylitis does reduce life expectation, the chronic disability it produces is the major problem and in this the Bechterew stoop is the cross most patients have to bear. There can be no doubt that the most important therapeutic measures are lifelong remedial exercises every morning and night to maintain a good erect posture and prevent the disabling stoop from developing.

Hip involvement is often very painful and disabling and total hip replacement may afford much relief but there are reports of hips so replaced becoming totally ankylosed by bone within a few months of operation (Wilde *et al.*, 1972).

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