THE AETIOLOGY OF
ANKYLOSING SPONDYLARTHITIS

by
D. E. P. Forbes
M.B., Ch.B.

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Dietary Deficiencies
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INTRODUCTION

The object of this thesis is to bring under consideration the aetiology of ankylosing spondylarthritis.

In the first section the literature on the subject is reviewed. The factual findings and characteristics of the disease which are relevant to the deduction of its causation have been extracted and correlated. The collected evidence is used to assess the part that various conditions play in the aetiology of ankylosing spondylarthritis and the views of the different writers concerning the aetiology are dealt with.

In the second section the relevant findings of the writer after an investigation of 26 cases of ankylosing spondylarthritis are set out. (A brief history of the main symptoms and physical findings in the cases are set out in the appendix. A photograph of an X-ray film of each case is included).

The third section consists of a summary of the evidence drawn from the literature and the cases, followed by a discussion and the conclusions reached.

In this thesis the term ankylosing spondylarthritis is used to describe a chronic disease of the vertebral column, the characteristics of which are here set out. The disease occurs most frequently among young adult males. The onset is usually insidious but may be acute. The course of the disease is prolonged, usually lasting over many years. It may be progressive without remissions, but in the majority of cases exacerbations and remissions occur. Among the main symptoms are pain and stiffness in the back. These are often accentuated after being in bed or remaining still for some hours and are relieved by gentle exercise. According to some authorities the early stages are characterised by vague wandering pains in the limbs and body. There are also general systemic manifestation among which are lassitude, depression and loss of weight.
The sacro-iliac joints and the joints between the vertebral arches are involved in the early stages of the disease and later these joints become ankylosed and there is calcification of the longitudinal ligaments of the vertebral column.

In the Report of The B.M.A. Committee on the Causation and Treatment of Arthritis and Allied Conditions (1933) the disease is classified as spondylitis ankylopoietica. At least ten other synonyms have been commonly used to describe this disease but as the true diarthrodial joints of the vertebral column appear to be first affected the term ankylosing spondylarthritis seems to be the most satisfactory and is the one used in this paper.
SECTION I

INCIDENCE

GENERAL INCIDENCE

There is a widespread impression that ankylosing spondylarthritis is becoming more common, and that the increasing incidence became marked during the last war (Fletcher, 1944; Wyatt, 1945; Buckley, 1945;)

Schmorl in 1932 (cited by Dunham & Kautz, 1941) found 8 cases among 10,000 specimens of vertebral columns in the Dresden Collection, an incidence of 0.08%.

Bachman in 1930 (cited by Dunham & Kautz, 1941) in a series of 2561 X-ray films of the spine found 41 clear-cut cases, an incidence of 1.6%.

Dawson (1935) and Tyson (1937) both found an incidence of 1 case of ankylosing spondylarthritis for every 13 cases of rheumatoid arthritis seen. However, Graham & Ogryzlo (1947) reported that the ratio of ankylosing spondylarthritis cases to rheumatoid arthritis cases was a little under one to three.

Boland (1946) stated that in an Army General Hospital 7.5% of all patients admitted for medical treatment had rheumatoid spondylitis (ankylosing spondylarthritis). He also stated that at the Army Rheumatism Centre, Army and Navy General Hospital, 18.1% of 6,000 consecutive admissions for all types of rheumatic disease had rheumatoid spondylitis. The diagnostic criteria were not fully stated. On the other hand Campbell (1947) found 12 cases in 1,000 rheumatic cases seen at a spa, and 2 cases in 1,000 general medical out-patients, the latter being an incidence of 0.2%.
From the above figures it is impossible to tell whether the actual incidence of ankylosing spondylarthritis is increasing; what is certain is that it is being diagnosed with greater frequency than previously. This is probably to be explained by a change in the criteria on which a diagnosis is based, the general knowledge that this is not a rare disease, and the stress now laid on the importance of early diagnosis and treatment.

SEX INCIDENCE

The sex incidence varies very markedly in different series, but in no series are there more women than men.

The largest series recorded is that of Polley & Slocumb (1947), who, in over 1,000 cases seen at the Mayo Clinic, found there were 931 males and 104 females, an approximate ratio of $M : F = 9 : 1$.

The lowest male preponderance was found by Fletcher (1944) who, in a series of 68 cases found a ratio of $M : F = 9 : 8$. No reason is apparent in this instance to account for the low male preponderance, but the sources from which the cases were drawn are not mentioned.

On collecting the cases from thirteen sources* 1,999 male cases and 336 female cases were found, an approximate ratio of $M : F = 6 : 1$.

FAMILIAL INCIDENCE

It is generally recognised that ankylosing spondylarthritis occurs occasionally in more than one member of the same family.

The evidence of the reports of the earlier writers such as Bechterew, Marie & Astié (cited by Hadley, 1940) must be discounted in establishing the familial incidence of the disease as it cannot be certain that the cases to which they referred were cases of ankylosing spondylarthritis.

Of the later writers, its occurrence has been reported in twin brothers by Ehrlich (cited by Dawson, 1935); in identical twins by Ray (1932) and Campbell (1947); in two brothers by Geilinger, Fischer & Vontz (both cited by Hadley, 1940), Weil & Allolio, Reynolds (both cited by Stecher & Hauser, 1946), Blair (1942), Scott (1942) and Campbell (1947); and in successive generations by Geilinger, Fischer & Vontz (both cited by Hadley, 1940), Burckhardt (cited by Dawson, 1935), Herrick & Tyson (1941), Scott (1942) and Campbell (1947). Even the later writers record insufficient details to make the diagnosis of ankylosing spondylarthritis definite. This insufficiency of evidence is commented upon by Stecher & Hauser (1946) who, in a study of the literature up to 1946 found only three instances of an occurrence in brothers where there was sufficient evidence to prove without doubt that they were suffering from ankylosing spondylarthritis. They add a report of their own of its occurrence in brothers, with sufficient details to substantiate the diagnosis. Tegner & Lloyd (1949) report the disease in all three children, two brothers and a sister, of one family and from a study of the case notes, all three appear to be definite cases of ankylosing spondylarthritis.

No accurate estimate of the frequency with which more than one member of a family is affected can be made from a study of the literature, but from the fact that the large majority of authors record having seen it themselves in only one instance it may be supposed that the happening is rare.
For instance, in 100 cases reported by Fischer & Vontz (cited by Hadley, 1940) in only one family is more than one case recorded. Scott (1942), on the other hand, from approximately 400 cases under review, reported having seen four instances of the disease affecting two siblings and one instance of its occurrence in a father and son. The most frequent familial incidence was reported by Campbell (1947), who in a review of 25 cases, found that two pairs of his patients were siblings, and that two patients gave a history of another sibling being affected with a similar disease to themselves. In one of these cases there was also a history of an uncle suffering from the same disease.

OCCUPATIONAL INCIDENCE

There is no evidence in the literature of any particular occupational incidence.

Geilinger (1918) stated that the disease often occurred in labourers, shoemakers and porters, but gave no figures. Golding (1936) in his series found that 75% were sedentary workers and 25% manual or outdoor workers. Bach (1939) found that sedentary workers appeared to be more frequently affected than others.

INCIDENCE IN THE ARMED FORCES

Proebster (cited by Dunham & Kautz, 1941) called attention to the fact that many patients attributed the onset of their disease to war service, but Wolff (cited by Dunham & Kautz, 1941) investigated a number of such cases and found that in almost every case episodes of pain in the spine or one or more attacks of acute peripheral arthritis had preceded their entry into the armed forces.
No figures of the incidence in the armed forces as compared with civilian life are available. Boland (1946) found that 7% of all cases admitted to a general service hospital had ankylosing spondylarthritis. Campbell (1947) gave the incidence as 0.2% in general medical out-patients. This agreed with Herrick & Tyson's (1941) figure of 0.2% of all new cases seen. At first sight the wide discrepancy between these figures appears to suggest that service in the armed forces in some way increases the liability to ankylosing spondylarthritis, but this is not necessarily so, and may certainly be partly accounted for by the fact that a large number of the susceptible age group would be serving in the forces.

McWhirter (1943) made the interesting observation that of a 104 patients with ankylosing spondylarthritis seen by him between 1942 and 1944 61% were in, or had been discharged from, the armed forces. He then investigated a series of cases with seminoma of the testis and found that 65% of them were in, or had been, in, the forces. He concluded that service life was certainly not the cause of either condition, but he thought it possible that the abnormal strains and conditions of service life might make ankylosing spondylitis manifest itself earlier than it would otherwise do. Boland (1946) also held this opinion.

Campbell (1947) compared the age of onset in members of the armed forces with that of civilians and found that the age in civilians was higher. This finding is of doubtful value, however, as it is impossible to know to what extent the age group of the two series from which the cases were drawn differed.

**EXPOSURE AND CHILLING**

Proebster (cited by Dunham & Kautz, 1941) and Fritz (1936) considered that acute or chronic chilling was an important factor in the aetiology of ankylosing spondylarthritis, but if this is so it seems strange
that no increased incidence has been observed in occupations entailing these stresses.

TRAUMA

Wehrsig (cited by Dunham & Kautz, 1941) maintained that trauma, acute or chronic, was a factor in the aetiology of 25% of cases. Buckley (1935) found a history of injury in 17 (11.5%) of 150 cases but in only 12 (8%) was there a clear association with the onset. Baker, Rinehart, Mettier & Bruckman (1939) found that a definite injury was the immediate cause of the primary symptoms in 8 (5.2%) out of 153 cases. Krebs & Vontz (cited by Dunham & Kautz, 1941) stated that the disease could progress asymptotically until some trauma occurred.

Boland & Present (1945), on examining 100 cases for a precipitating cause, found none in 80% and various different factors in the remaining 20%.

CLIMATE

Buckley (1935) stated that climatic conditions had no special bearing on the incidence. Parr & Shipton (1946), in an analysis of the regional incidence in Australia, showed that the disease occurred in various very different types of climate, and concluded that climate had no influence on the incidence of the disease. There is no evidence in the literature which conflicts with these views.
TYPE OF INDIVIDUAL AFFECTED

Bach (1939) stated that patients attacked were often of the asthenic type, whereas Buckley (1945) considered that there was a tendency for robust and virile rather than weakly individuals to be affected. He pointed out that this fact is often overlooked because the disease saps the vigour of the patient.

Scott (1942) found that 95% of his cases were exceptionally interested in sport and were originally keen athletes. He also said that he found a higher proportion of swimmers and divers among the patients than in the general population. Parr & Shipton (1946) found it attacked both athletic and non-athletic individuals with no special stress on the former.

AGE AT ONSET

The age at onset given by authors who recorded sufficient details to allow their findings to be presented in tabular form can be seen in Table 1. From this table it is apparent that the commonest age at onset was between the twentieth and thirtieth year, but that in a considerable number of cases the onset occurred before the age of twenty. After the third decade the number of commencing cases became progressively less, but in a few cases the onset did not become apparent until after the age of sixty. The age at onset as stated by other workers confirms these findings (Golding, 1936; Forestier, 1939; Dunham & Kautz, 1941).
### TABLE 1

Age at onset in years of 1,521 patients with ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Author</th>
<th>under 20-</th>
<th>30-</th>
<th>40-</th>
<th>50-</th>
<th>60+ or over</th>
<th>not known</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Mc Whirter (1945)</td>
<td>33</td>
<td>86</td>
<td>34</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>168</td>
</tr>
<tr>
<td>Fletcher (1944)</td>
<td>7</td>
<td>19</td>
<td>13</td>
<td>15</td>
<td>8</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>Fischer &amp; Vontz*</td>
<td>3</td>
<td>44</td>
<td>32</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Buckley (1935)</td>
<td>25</td>
<td>57</td>
<td>41</td>
<td>24</td>
<td>3</td>
<td>0</td>
<td>150</td>
</tr>
<tr>
<td>Polley &amp; Slocumb (1947)</td>
<td>244</td>
<td>518</td>
<td>170</td>
<td>86</td>
<td>17</td>
<td></td>
<td>1035</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>312</strong></td>
<td><strong>724</strong></td>
<td><strong>290</strong></td>
<td><strong>172</strong></td>
<td><strong>23</strong></td>
<td></td>
<td><strong>1521</strong></td>
</tr>
<tr>
<td><strong>Percentage</strong></td>
<td><strong>22%</strong></td>
<td><strong>47%</strong></td>
<td><strong>19%</strong></td>
<td><strong>11%</strong></td>
<td><strong>1%</strong></td>
<td></td>
<td><strong>100%</strong></td>
</tr>
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* Cited by Comroe (1944).
CHANGES IN THE BLOOD

SERUM PROTEINS

Pemberton & Scull (1943) found that the protein fraction of the plasma was often abnormal, the fibrinogen and globulin levels being raised and the albumen level being low. Parr & Shipton (1946) agreed with these findings, and stated that the raised globulin level was due largely to an increase in the euglobulin fraction. They found that the total proteins might be altered slightly or not at all, while the albumen:globulin ratio was lowered or even reversed. Simpson & Stevenson (1949) on the other hand found no significant alteration of the serum protein levels in 27 cases of ankylosing spondylarthritis.

ERYTHROCYTE SEDIMENTATION RATE

It is agreed by all observers that the erythrocyte sedimentation rate (E. S. R.) is raised in the great majority of patients during the active phases of the disease. It is only concerning a few minor points that different views have been expressed.

Dunham & Kautz (1941) stated that it was not then known whether the sedimentation rate was raised in the very early stages of the disease. Comroe (1944) stated that the E.S.R. was rapid even in the early stages, and that as improvement occurred it tended to fall to normal in a large percentage of cases. Boland & Shebesta (1946) agreed that the E.S.R. was a fairly good gauge of the activity of the disease process, but stated that in 15% to 20% of mild but clinically active cases it might be normal. Parr & Shipton (1946) also stated that the E.S.R. might be normal in slowly progressive disease.

Polley & Slocumb (1947) found a normal E.S.R. in 176 (19%) of 949 cases. In 27% of their cases
the E.S.R. was over 60 mm. per hour.

THE BLOOD CELLS

The red cells

Many authors (Dunham & Kautz, 1941; Comroe, 1944; Parr & Shipton, 1946) have mentioned that some degree of anaemia is common in ankylosing spondylarthritis. The anaemia is of a hypochromic normocytic or microcytic type.

The white cells

Dunham & Kautz (1941) and Comroe (1944) stated that an inconstant leukocytosis might occur. Parr & Shipton (1946) agreed with this finding and also stated that in 50% of their cases there was a "shift to the left" of the neutrophil cells. In the series of Campbell (1947), which consisted of 25 cases, he reported that in 2 cases there was an eosinophilia of over 5% but he gave no absolute figures.

PATHOLOGY

POST - MORTEM REPORTS AND BIOPSY MATERIAL

Dunham & Kautz (1941) reviewed the work of Marie, Léri, Simmonds and Fraenkel, who, at the end of the nineteenth and at the beginning of the present century, described the post-mortem findings on cases of ankylosing spondylarthritis. All these workers noted the great involvement of the posterior articulations of the spine.
In 1903 Siven (cited by Guntz, 1933) described the post-mortem findings of a case in which the small intervertebral joints were completely ossified, but in which the process was not so far advanced in some of the costo-transverse joints. From his findings he concluded that the ankylosis of the small joints was due to an inflammatory process, and that the changes which occurred in the discs, in which there was no evidence of inflammation, were unrelated. Guntz (1933), who investigated the spines of 9 advanced cases of ankylosing spondylarthritis, and one case in which the disease was in the developing stage in the spine, reached a similar conclusion. As Guntz’s description of the histological examination of the early stages of the process in the spine has had such an influence on the views of later workers, it should be pointed out that the history of the case was not typical of ankylosing spondylarthritis, and that there was complete bony ankylosis of the hips, knees and other peripheral joints with only early changes in the spinal joints. From the advanced changes in the peripheral joints one would have expected the changes in the spine to have been those of a late stage of the disease process, but this was not so. Some authors distinguish between ankylosing spondylarthritis and rheumatoid arthritis of the spine, and those who take this view would probably regard this case as representing the latter condition. However, as is stated below (Page 21), there does not appear to be sufficient evidence at present to regard ankylosing spondylarthritis and rheumatoid arthritis affecting the spine as two separate pathological entities, and, unless further pathological proof of this is provided in the future, it is justifiable to accept this case as representing the changes which occur in the intervertebral joints in ankylosing spondylarthritis.

Freund (1942) described the changes in a specimen which consisted of the first to the fourth lumbar vertebrae including two complete vertebrae and three complete discs. It is questionable whether the case was one of ankylosing spondylarthritis as only an extremely inadequate history was reported.
The patient, a male, died at the age of sixty-seven due to a hypernephroma. It is stated that he had been complaining of pain and stiffness in the joints for six years prior to his death, and that for a lesser period his back had been very stiff but not painful. However, Freund felt himself to be justified in considering that it was a case of spondylitis ankylopoietica (ankylosing spondylarthritis), mainly because there were lesions of all the intervertebral joints together with osseous bridging between the vertebrae.

Freund reported at that time that there were no records of any detailed microscopical examinations of the discs, and their relationship to the vertebrae, in ankylosing spondylarthritis. He gave an account of the changes found in the discs in the specimen he examined.

Beadle (1931), in a paper on the intervertebral discs based on work carried out in the pathological department of the Friedrichstädtter Krankenhaus at Dresden, recorded some observations on Bechterew's Disease of the spine (ankylosing spondylarthritis), and Schmorl & Junghanns (1932) also reported the findings on this disease. La Chapelle (1946) reported the histological findings in some disc tissue removed at operation on an advanced case.

If the descriptions of all the workers mentioned above in this sub-section are taken in conjunction, the changes that occur in the apophyseal joints and in the discs can be summarised, as all are in agreement about the main findings.

In the intervertebral, costo-vertebral, and costo-transverse joints the following changes occur. There is an exudation into the joint cavity, followed by the spread of connective tissue into the joint space from the capsule and possibly also from the underlying bone. In the connective tissue are congested blood vessels and collections of small round cells.
The cartilage becomes eroded, bony trabeculae grow into and across the joint space, and bony ankylosis occurs. The histological features are insufficient to elucidate the aetiological factors concerned, but suggest a chronic inflammatory process. As distinct from these changes, no evidence of an inflammatory process occurring in the intervertebral discs has been found. Freund noted congested blood vessels in the connective tissue which was replacing the disc tissue, but he, rightly, did not consider this to be evidence of inflammation. No changes occur in the discs until late in the disease process, when they may become thinned. They may then be replaced by connective tissue, and eventually by bone of the same consistency as the spongiosa.

THE X-RAY APPEARANCES AS AN INDICATION OF THE PATHOLOGICAL PROCESS

THE SACRO-ILIAC JOINTS

It is generally agreed that the earliest X-ray signs of the disease process occur in the sacro-iliac joints, but opinions vary on the question as to whether these joints must be affected before a diagnosis of ankylosing spondylarthitis is made. Most authors think that a small percentage, varying from 1% to 10%, of cases may have ankylosing spondylarthitis without evidence of sacro-iliac changes. The sacro-iliac involvement is almost always bilateral.

The changes that occur in the sacro-iliac joints are well described by Scott (1942), Forestier (1939), Boland & Shebesta (1946) and Rolleston (1947). They disagree about minor points only. From the descriptions it is seen that the pathological process causes the loss of well defined articular cortex, irregularity of the joint margins and irregular increase and decrease in the bone density around the joints.
Later there is a loss of the joint space, trabeculae growing across and leading to complete bony ankylosis. The earlier changes are presumably due to the destruction of the hyaline and fibrocartilage of the joints.

While considering the sacro-iliac joint changes the work of Sashin (1930) is of interest. In 257 unselected post-mortem examinations, following various causes of death, both sacro-iliac joints were removed. 114 specimens were macerated and examined and 143 were examined in the fresh state. Bony ankylosis of the joints was found to be present in 51% of males between the ages of thirty and fifty-nine, and in only 6% of females in the same age group. In the over sixty age group bony ankylosis was present in 82% of the males and 30% of the females. Unfortunately the corresponding radiographic appearances of the joints were not recorded. Brooks (cited by Sashin) examined the sacro-iliac joints of 95 males and 300 females. The age, and method of selection, of the cases was not given. He found complete bony ankylosis in 37% of the males and 9% of the females. Sashin pointed out that the main concern in the male pelvis is stability, whereas in the female pelvis mobility is important.

THE INTERVERTEBRAL JOINTS

That the involvement of the apophyseal joints is of major importance in ankylosing spondylarthritis has been demonstrated by post-mortem examinations, and this has been confirmed by radiological evidence. However, owing to the difficulties of interpreting the radiographic appearances, many workers, including Forestier (1939), Scott (1942), Roland (1946), and Polley & Slocumb (1947) considered that for the practical purposes of diagnosis the changes were unreliable. For this reason very much less attention has been bestowed on the intervertebral than the sacro-iliac joints.
Oppenheimer has carried out a great deal of work on diseases of the apophyseal joints and their radiological appearances, and he described the changes seen in atrophic arthritis of the apophyseal joints including rhizomelic spondylosis (ankylosing spondylarthritis). From his description, and those of other authors, notably Boland (1946), it can be seen that the X-ray appearances in the apophyseal joints are of the same type as those seen in the sacro-iliac joints, and are suggestive that both are produced by the same pathological process.

THE COSTO-TRANSVERSE JOINTS

It was pointed out by Rolleston (1947) that changes in the upper costo-transverse joints can be seen fairly easily in antero-posterior projections of the cervico-dorsal region. From his description it is clear that the appearances may be caused by the same pathological process as that which occurs in the posterior intervertebral joints.

OSTEOPOROSIS

Decalcification of the spine and pelvis and sometimes of the long bones, has been noted by many observers. Disease may produce osteoporosis. However, it is agreed by most authors that in ankylosing spondylarthritis the decalcification is most apparent while the process in the apophyseal joints is active, and that normal density may be regained after ankylosis of these joints has occurred. It therefore seems likely that the osteoporosis is closely connected with the pathological process, and is not merely a form of disuse atrophy.

Oppenheimer (1938, and 1940)
DISC CHANGES AND LIGAMENTOUS CALCIFICATION

It is generally recognised that continuous areas of calcification joining the outer aspects of the vertebral bodies are commonly seen in the later stages of ankylosing spondylarthritis, but what causes these appearances is not agreed. Most observers have assumed that the appearances are due to calcification of the paravertebral ligaments and this is most probably the case. However, Buckley (1935) considered it more likely that the ossification occurred in the edges of the discs rather than in the ligaments, and in another paper (1945) he put forward the view that the outer fibres of the annulus fibrosus became calcified. This view was confirmed by Freund (1942) who thought that what, from the radiographic appearances, might be regarded as ligamentous ossification was actually ossification in the discs. In the case that he described radiological evidence of bony bridging could be seen, but on examination of the specimen no definite calcification of the paravertebral ligaments was present. He also noted that the radiographs in his case showed irregular opacities in the discs with irregularity of the upper and lower surfaces of the vertebrae, and he found on histological examination that these appearances were accounted for by areas of ossification in the discs. In any case, the opinion stated by Scott (1942) that the discs are not involved in the disease seems to be untrue. He stated that he based his view on experience gained from autopsies and the examination of Egyptian skeletons. He gave no details of the examinations, but said that no calcification of the discs had ever been found.

While discussing calcification of the discs and ligaments the work of Oppenheimer (1942) on the subject must be mentioned. He examined clinically and radiologically 282 persons with calcification or ossification of vertebral ligaments, and repeated his examinations on many of the cases several times. He pointed out that this was not a distinct disease; it was usually a secondary phenomenon, and occurred, in the presence of vertebral rarefaction, when the tension or mobility of the ligaments was diminished.
In his view it was not a cause, but was sometimes the result, of vertebral immobility.

THE HIP AND SHOULDER JOINTS

Changes may occur in the hip and shoulder joints in ankylosing spondylarthitis.

Polley & Slocumb (1947) found that the hip joints were involved in 28% of their large series of cases, and in three-quarters of these the involvement was bilateral. In one quarter of the cases with hip-joint involvement (7% of the total series) the shoulders were also involved.

McWhirter (1945) described the changes in the hip joints as a narrowing of the joint space with decalcification of the adjacent bone, with the possibility, later, of either obliteration of the joint space or preservation of the joint space with ossification of the capsule.

Buckley (1935) stated that damage to the articular cartilage of the hip joints occurred very early, but that the chief factor limiting movement was ossification of the rim of fibrocartilage around the edge of the acetabulum, and the formation of a bony ridge around the head of the femur at the margin of the articular cartilage. However, in a later paper (1945) he mentioned the X-ray appearances in an ankylosed hip joint in ankylosing spondylarthitis; the head of the femur appeared to be almost intact and there were trabeculae running from the pelvis to the shaft of the femur along the lines of stress.

Dunham & Kautz (1941) stated that in their experience the changes in the hip and shoulder joints resembled a severe atrophic arthritis, although in a few instances there was considerable exostosis formation and calcification about the hip joints.
Miller (1936) considered that the hip changes were caused by osteoarthritis due to abnormal posture.

From the above it seems that the changes which may occur in the hip joints vary very considerably. In some cases the changes resemble those of atrophic arthritis; in others the changes suggest osteoarthritis, and sometimes complete bony ankylosis occurs.

THE PERIPHERAL JOINTS

When changes in the peripheral joints occur they resemble those of rheumatoid arthritis. This question is discussed more fully below, in the sub-section on the relationship between rheumatoid arthritis and ankylosing spondylarthritis (Page 21).

IN VolvEMEN T OF OTHER JOINTS

Dunham & Kautz (1941) stated that occasionally the temporo-mandibular joints were included in the ankylosing process. They added that ankylosis of the sternoclavicular joints had been reported, but was rare. They gave no references in this connection.
THE RELATIONSHIP BETWEEN ANKYLOSING SPONDYLARTHITIS AND RHEUMATOID ARTHRITIS

There is so far no agreement as to whether ankylosing spondylarthritis and rheumatoid arthritis should be considered as the same or separate entities.

Guntz (1933), Dawson (1935), Forestier (1939), Edström (1940), Hench et al. (1941), Dekkers (1943) and Boland & Shebesta (1946) considered that ankylosing spondylarthritis belonged to the disease group of chronic atrophic rheumatic arthritis, whereas Scott (1942) and Buckley (1943) considered that ankylosing spondylarthritis was definitely not a form of rheumatoid arthritis and that there was no relationship between the two conditions. Bach (1939), Osgood (1940) and Freund (1942) were also of the opinion that the two conditions were probably separate entities.

EVIDENCE OBTAINABLE FROM PERIPHERAL JOINT INVOLVEMENT

The figures given by various workers of the number of cases of ankylosing spondylarthitis which have peripheral joint involvement vary enormously. This is mainly accounted for by a difference in view as to what should be regarded as ankylosing spondylarthitis. For instance, Buckley (1945) stated that in over 200 cases of true ankylosing spondylarthitis he had never seen the small joints affected in any case. But this may be explained by the fact that he drew a distinction between ankylosing spondylarthitis and rheumatoid arthritis spreading to the vertebral joints and would thus have classified any case in which there was a peripheral onset with later involvement of the spine as rheumatoid arthritis affecting the spine, and not ankylosing spondylarthitis. He in fact mentioned two such cases in which the hands and feet were affected and said that they were cases of rheumatoid arthritis spreading to the vertebral joints.
Miller (1934) apparently recognised a similar distinction. He stated that rheumatoid arthritis involving the spine produced the pathological changes recognised as spondylitis ankylopoietica (ankylosing spondylarthritis), but that a patient with spondylitis ankylopoietica did not necessarily have rheumatoid arthritis of the spine. Many workers would not agree with this statement. Boland (1946) for instance, said that the clinical and radiographic findings in the spine were the same whether or not the peripheral joints were involved.

Unless and until the changes in the vertebral joints can be shown to differ in ankylosing spondylarthritis and rheumatoid arthritis involving the spine, there seems no good ground for distinguishing one from the other. If a case presents demonstrable changes in the spine which fulfil the criteria laid down for making a diagnosis of ankylosing spondylarthritis, then the only logical course appears to be to regard the case as such, irrespective of which of the other joints are involved or of the time at which they became involved.

McWhirter (1945), in agreement with Buckley (1945), was of the view that patients with ankylosing spondylarthritis did not get rheumatoid changes in the small peripheral joints. In his experience, although a few patients in the early stages of the disease might suffer from pains in the distal joints of the limbs these joint pains were as a rule transient and not progressive; the proximal joints might be involved in the later stages, but the hands never showed typical rheumatoid changes.

Polley & Slocumb (1947), on the other hand, found that 286 (28%) of 1035 cases of ankylosing spondylarthritis had rheumatoid involvement which had produced residual damage in the peripheral joints. A further 22% had had transitory symptoms referable to the peripheral joints.

Boland (1946) stated that typical peripheral rheumatoid arthritis co-existed with rheumatoid spondylitis in approximately 25% of cases. He considered that the small joints of the hands and feet were affected as often as the larger joints of the limbs.
He cited the work of Polley which he said demonstrated that peripheral joints so involved showed histopathological changes identical with those found in rheumatoid arthritis without spondylitis.

Other workers who found that the small peripheral joints of the limbs showed changes typical of rheumatoid arthritis in a smaller percentage of cases than Boland include Tyson (1937), Dunham & Kautz (1941), Swaim (1939), Edström (1940) and Dekkers (1943). Fischer (cited by Herrick and Tyson, 1941) found associated changes in the smaller joints characteristic of rheumatoid arthritis in 29% of a series of 98 cases.

Thus the main weight of the available evidence is that peripheral arthritis is present in many cases of ankylosing spondylarthritis, and that when these changes occur the arthritis is indistinguishable from typical peripheral rheumatoid arthritis.

AGE AT ONSET

The age at onset is approximately the same in ankylosing spondylarthritis and rheumatoid arthritis. In the former the maximum incidence occurs in the twenty to thirty age group (see Page 9), and in the latter it occurs between the ages of twenty and forty (Comroe, 1944).

SEX INCIDENCE

The sex incidence in the two diseases is different. It was stated above (Page 4) that from an analysis of a large number of cases it was found that the sex ratio of cases of ankylosing spondylarthritis was M : F = 6 : 1.
It is generally recognised that rheumatoid arthritis occurs more frequently in females than in males.

FAMILIAL INCIDENCE

In a report from the 7th International Congress of Rheumatic Diseases by a Special Correspondent (1949) it was reported that Stecher, Solomon & Wolpan found that rheumatoid arthritis occurred in the fathers, mothers and sisters of rheumatoid arthritis patients in a significantly higher proportion than it did in the relatives of patients with spondylitis, or in the controls. Spondylitis occurred in the brothers and sisters of spondylitis patients and of rheumatoid arthritis patients more than it did in any other group. (It is stated that the figures had been statistically analysed and shown to be significant, but no figures were quoted). The latter finding suggests a relationship between ankylosing spondylarthritis and rheumatoid arthritis.

ASSOCIATED DISEASES

Edström (1940) found that in seven unselected consecutive cases of ankylosing spondylarthritis nursed in the Rheumatic Diseases Department at Lund, six were typical cases of chronic rheumatic infectious arthritis. He said that they showed other manifestations of an association with a rheumatic syndrome. These took the form of arthritis, peritendinitis, bursitis, endocarditis, pleuritis, iritis, conjunctivitis, nephritis, gastritis, secondary anaemia, subcutaneous nodules and changes in the skin and nails. As a part of the clinical picture of chronic infectious arthritis, the spondylarthritis syndrome of prespondylitic type, appeared.
The sacro-iliac joints, and in some cases the symphysis pubis, were involved. Also present were a rectangular shape to the vertebral bodies, decreased cartilage distance in the intervertebral joints without much obliteration of the joint slits, and slight calcification of the ligaments.

SUBCUTANEOUS NODULES

Edström (1940), discussing the same series of cases, reported that one of the cases had subcutaneous nodules, but from the facts reported it is difficult to be certain that this was a definite case of ankylosing spondylarthritis. In a paper by Hench et. al. (1941) it was pointed out that the demonstration of subcutaneous nodules in an unequivocal case of ankylosing spondylarthritis would go far to settle the controversy as to the relationship between the two diseases. Campbell (1947) stated that rheumatic nodules had never been found in ankylosing spondylarthritis, and up to the present no unequivocal record of this occurrence has been found. As eight years have now passed since Hench's observation, this may be regarded as evidence against there being a very close relationship between ankylosing spondylarthritis and rheumatoid arthritis.

IRITIS

The occurrence of irido-cyclitis in association with ankylosing spondylarthritis has been noted by many authors. Buckley (1935) found a history of iritis in 8 (5.3%) out of 150 cases and Scott (1942) noted its occurrence in 20 (7%) of about 300 cases. Campbell found a history of its occurrence in 24% of cases, and other authors (Golding, 1946; Fritz, 1936) have given a figure for the incidence which falls between these percentages.
Irido-cyclitis also occurs in association with rheumatoid arthritis. Berens, Angevine, Guy & Rothbard (1938) gave the incidence as being from 2.5% to 4.5%. It therefore appears that it occurs rather more frequently in ankylosing spondylarthritis than in rheumatoid arthritis. Boland (1946) is in disagreement with this conclusion, stating that it occurred in approximately the same proportions in the two diseases.

LABORATORY DATA

Blood changes

The changes in the haemoglobin, the red cells and the white cells are similar in rheumatoid arthritis and ankylosing spondylarthritis.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate is raised in the active stages in both diseases, but Polley & Slocumb (1947) reported that it tended not to be so high in rheumatoid spondylitis (ankylosing spondylarthritis) as in peripheral rheumatoid arthritis. However, in 27% of their cases of rheumatoid spondylitis the rate was over 60 mm. per hour.

Serum Proteins

Parr & Shipton (1946) stated that the changes in the serum proteins were similar in the two diseases, with a reduction in the albumen and an increase in the globulin and fibrinogen.
They found, however, that the increase in the fibrinogen was usually greater in ankylosing spondylarthritis than in rheumatoid arthritis.

Scull, Bach & Pemberton (1939) in a paper on the serum proteins in rheumatoid disease, showed statistical analyses of the levels of the total protein, albumen and globulin in the sera of 177 cases of rheumatoid diseases, 10 of non-rheumatoid diseases and 15 normals. The "rheumatoid" group is subdivided into various groups including 48 cases of severe atrophic arthritis and 14 cases of spondylitis. On comparing the levels in these latter two groups it is seen that in both there is a lowering of the albumen and a raising of the globulin level. The biggest difference between the two is shown in the globulin levels. In the severe atrophic group the level is 129% of normal and in the spondylitic group 148% of normal. There are no marked differences in the other levels. On studying the globulin levels more closely, it appears that the large scatter of the levels in the severe atrophic cases and the small number of the spondylitis cases makes a comparison of the mean levels of these groups misleading, and suggests that in fact there is very little difference between the two groups.

Simpson & Stevenson (1949) carried out plasma protein estimations in 5 cases of ankylosing spondylitis. They found that little abnormality was shown except an occasional high total protein figure and a consistently high value for fibrinogen. The albumen and globulin levels and the albumen:globulin ratio were always within normal limits. They stated that these results were in contrast to the findings in rheumatoid arthritis, in which abnormal plasma proteins were found in approximately 50% of cases. However, the number of cases was small, and no clinical findings concerning the cases were reported. It can be seen that the evidence of the different workers is conflicting.
Plasma Phosphatase Activity

Buckley (1945) stated that in arthritis the plasma phosphatase activity was not increased, whereas in spondylitis a moderate increase was usual. The plasma phosphatases in ankylosing spondylarthritis are dealt with fully below (Page 54), and the conclusion drawn from the literature is that there is never more than a slight increase in level in ankylosing spondylarthritis.

Streptococcal Agglutinins

Comroe (1944) reported that streptococcus agglutinins were not increased in patients with ankylosing spondylarthritis in contrast to their increase in more than half of the patients with rheumatoid arthritis of the peripheral joints. He did not state the type of streptococcus involved. He cited Dunham & Kautz (1941) as his reference for this statement, but in their article there is no such statement.

17 - Ketosteroid Excretion

Davison, Koets & Kuzell (1947) stated that there seemed to be a trend to a greater excretion of 17-ketosteroids in ankylosing spondylitis in males, whereas in typical polyarticular rheumatoid arthritis in females this tendency was not demonstrated.

They found that the average urinary excretion of 17-ketosteroids in 13 male patients with ankylosing spondylarthritis, all of which were typical cases without peripheral joint involvement, was 27.3 mg. in 24 hours as compared with an average value of 14 mg. for normal males.
In 11 females with rheumatoid arthritis the average urinary excretion was 12.8 mg. as compared with an average of 10 mg. for normal females.

These findings suggest that there is some difference in the two disease processes, but it would have been more conclusive if it had been possible to compare the excretion in the two diseases in the same sex.

PATHOLOGY

From the small amount of evidence available in the literature (see above, Page 14) it seems that the pathological changes in the intervertebral and costo-vertebral joints in ankylosing spondylarthritis are similar to the changes that occur in the joints affected in rheumatoid arthritis.

Boland (1946) stated that specimens removed from the apophyseal joints during the active phases of the disease revealed microscopical findings similar to those seen in peripheral rheumatoid arthritis. For this statement he referred to the paper by Dunham & Kautz (1941) and to a personal communication (unpublished data) from J.E. Flynn to the author. Study of the paper by Dunham & Kautz reveals no statement to this effect, except in so far as the findings of Guntz (1933) are quoted.

Desmarais, Gibson & Kersley (1948) reported on muscle biopsies, taken from 56 cases of typical idiopathic rheumatoid arthritis and 17 cases of spondylitis ankylopoietica (ankylosing spondylarthritis). Round cell foci and bloodvessels changes were seen in the sections of muscle from 34 (60.7%) of the 56 cases of rheumatoid arthritis. In all specimens from the 17 cases of spondylitis ankylopoietica the results were negative.
Simpson & Stevenson (1949) reported that muscle biopsies were taken from 18 cases of ankylosing spondylarthritis and that the changes which occur in rheumatoid arthritis were present in none.

Bach (1949), in a report on the Seventh International Congress on Rheumatic Diseases held at New York, stated that the papers read there revealed a general agreement that rheumatic fever, rheumatoid arthritis, ankylosing spondylarthritis and lupus erythematosus were closely related, both in their clinical manifestations and in the findings at biopsy and necropsy. No references were given.

RESPONSE TO TREATMENT

Gold Therapy

Most authors think that cases of ankylosing spondylarthritis and cases of rheumatoid arthritis respond differently to gold therapy.

Cecil, Kammerer & De Prume (1942) found that a remission or great improvement was shown in 66% of 235 cases of rheumatoid arthritis treated with gold salts whereas only 1 (14%) of 7 adequately treated cases of ankylosing spondylarthritis was benefited. Other authors who agree that gold therapy is not as effective in the treatment of ankylosing spondylarthritis as in rheumatoid arthritis are Bach (1939), Dekkers (1943), Boland & Present (1945) and Buckley (1945).

X-Ray Therapy

In contrast to the response to gold therapy, almost all investigators have found that X-ray
therapy produces much better results in ankylosing spondylarthritis than in rheumatoid arthritis.

Probably the best papers on the subject are those of Smyth, Freyberg & Peck (1941) and Smyth, Freyberg & Lampe (1941). It was stated in the first paper that it was found that, in a group of 74 cases of rheumatoid arthritis treated with X-ray therapy, 44% should show no subjective or objective benefit, 30% showed subjective benefit only, and 26% showed improvement attributable to X-ray therapy, although in only 14% of cases was this of a significant grade. In many cases, by the use of lead screening at some treatments, the relief of pain was shown to be of psychogenic origin. Of 15 cases of rhizomelic spondylitis (ankylosing spondylarthritis) there was subjective and objective improvement in 74% of cases. They also found that in 85% of the rheumatoid arthritis group the erythrocyte sedimentation rate was either increased or remained unchanged following treatment, whereas in 40% of the spondylarthritis group the rate decreased. In the second paper the results of X-ray treatment of 52 cases of ankylosing spondylarthritis are reported, and these confirm those of the preceding paper, 72% showing subjective and 50% objective improvement. It was also shown, by the use of lead screens, that the improvement was not due to psychological reasons as no screened patient showed any significant improvement.

No author has offered any explanation as to why there should be this difference in the response to X-ray therapy, but Baker (1945) felt that it indicated that the cellular changes in the two diseases were different.

Treatment with 17-hydroxy-11-dehydrocorticosterone

Hench, Kendall, Slocumb & Polley (1949) reported the effect of 17-hydroxy-11-dehydrocorticosterone on 14 cases of rheumatoid arthritis. One of the cases had polyarthritis and rheumatoid spondylitis (ankylosing spondylarthritis). The clinical response in this case was similar to that in the other cases. This suggests
that the two diseases have a similar basis.

The points in favour of, and against, regarding ankylosing spondylarthritis and rheumatoid arthritis as the same entity will now be summarised briefly:

**Points In Favour :-**

a) When changes occur in the intervertebral joints in rheumatoid arthritis they cannot be distinguished clinically or radiologically from those occurring in ankylosing spondylarthritis.

b) Peripheral joint changes may be present in cases of ankylosing spondylarthritis, and when they are, they cannot be distinguished from the joint changes in peripheral rheumatoid arthritis.

c) The age at onset in the two diseases is similar.

d) The familial incidence suggests a relationship between ankylosing spondylarthritis and rheumatoid arthritis.

e) Irido - cyclitis occurs in association with both diseases.

f) Similar changes take place in the blood cells, and the erythrocyte sedimentation rate in both diseases. The evidence concerning changes in the serum proteins is conflicting.

g) The response to 17 - hydroxy - 11 - dehydrocortico-sterone is similar.

h) Papers read at the Seventh International Congress on Rheumatic Diseases suggested a relationship between rheumatic fever, rheumatoid arthritis, ankylosing spondylarthritis and lupus erythematosus.
Points Against :-

a) The sex incidence is different in the two diseases.

b) There is a difference in the urinary excretion of 17-ketosteroids.

c) There is a difference in the response to gold therapy and X-ray therapy.

d) Subcutaneous nodules may be present in rheumatoid arthritis; they have been reported in only one case of ankylosing spondylarthritis, and this was a doubtful case.

e) There is scanty evidence that streptococcal agglutinins are absent in ankylosing spondylarthritis, but present in many cases of rheumatoid arthritis. This work needs confirmation.

f) Muscle biopsies show typical changes in 60% of cases of rheumatoid arthritis. These changes apparently do not occur in ankylosing spondylarthritis.

Thus it can be seen that there are some unexplained differences between the two diseases, but the evidence at present available suggests that the processes involved in the two conditions are essentially similar.

RELATIONSHIP OF ANKYLOSING SPONDYLARTHRITIS TO RHEUMATIC FEVER

Fischer & Vontz (cited by Dekkers, 1943) found that 14% of 98 cases of ankylosing spondylarthritis had suffered from acute polyarthritis (rheumatic fever), and out of 9 cases described by Dekkers 2 (22%) had had rheumatic fever.
Dunham & Kautz (1941), in their review of 20 cases, found that 2 (10%) had had rheumatic fever some years prior to the onset of spondylarthritis and one case had definite evidence of a lesion of the mitral valve.

Bach (1939) found a definite history of rheumatic fever in 4 (8%) of 50 cases.

Thus out of a total of 177 cases quoted by the above authors 22 cases had had rheumatic fever, giving a percentage of 12.4%.

In the previous section it was seen that the evidence points to an essential similarity between ankylosing spondylarthritis and rheumatoid arthritis. As there is also evidence that rheumatic fever and rheumatoid arthritis are related, this may be regarded as indirect evidence of a relationship between rheumatic fever and ankylosing spondylarthritis.

The evidence supporting the view that rheumatic fever and rheumatoid arthritis are related will now be given.

Rosenberg, Baggenstross & Hench (1943), in a review of the cause of death in 30 cases of rheumatoid arthritis (all necropsied cases seen at the Mayo Clinic in the preceding twenty-five years), found that there were cardiac lesions indistinguishable from those of rheumatic heart disease present in 16 cases (53%), and that these had proved fatal in 7 cases. There was a history of rheumatic fever in only 2 of the cases. In an earlier paper Baggenstross & Rosenberg (1941) had pointed out that clinical studies might not be sufficient for the accurate diagnosis of rheumatic heart disease, clinical investigations in rheumatoid arthritis having given an incidence of 4% to 40%. This may account for the lack of evidence of rheumatic heart disease occurring in ankylosing spondylarthritis, despite the fact that in some series up to 12% have a history of rheumatic fever.

Comroe (1944) thought it likely that rheumatic fever and rheumatoid arthritis were closely related. He pointed out that subcutaneous nodules occurred in both diseases and that they both tended to occur in the same
families, and in the temperate zones. However, he also noted that there were differences between the two diseases. He stated that the antistreptolysin titre was usually increased in rheumatic fever but was normal in rheumatoid arthritis, and the agglutination reaction to haemolytic streptococci was usually negative in rheumatic fever and positive in most cases of rheumatoid arthritis after the disease had been present for some months.

Gibson & Kersley (1949) stated that the nodules of rheumatoid arthritis could be clearly distinguished histologically from those of rheumatic fever, although they considered that the pathology might not be dissimilar.

More definite evidence of a close relationship between rheumatic fever and rheumatoid arthritis has been provided by the dramatic response to 17 - hydroxy - 11 - dehydrocorticosterone of both diseases. (Hench, Slocumb, Barnes, Smith, Polley & Kendall (1949); Hench, Kendall, Slocumb & Polley (1949)).

*Gibson & Kersley, cited by a Special Correspondent (1949), reporting on the 7th. International Congress on Rheumatic Diseases.
THE RELATIONSHIP OF VARIOUS CONDITIONS TO THE AETIOLOGY.
TOGETHER WITH DIFFERENT HYPOTHESES CONCERNING
THE CAUSATION OF ANKYLOSING SPONDYLOARTHRITIS.

INFECTIONS

In patients suffering from ankylosing spondylarthritis, many of the clinical symptoms and signs and the laboratory findings are similar to those found in patients suffering from a known chronic infective process. So far, however, nobody has been able to isolate a causative organism from the lesions. Scott (1942) made an attempt to culture organisms from material obtained from the sacro-iliac joints of early cases, but, in all the cases in which no contamination occurred, the material withdrawn was found to be sterile.

STREPTOCOCCAL INFECTION

Anti-fibrinolysin determinations were carried out forty-nine times with the plasma of 8 patients with ankylosing spondylarthritis by Perry (1940). He found a transient rise in the anti-fibrinolysin titre in 1 patient only. Thus from this work there is no evidence to suggest that β-haemolytic streptococci are the causative factor in ankylosing spondylarthritis, nor has any other work been found in the literature which suggests that this is so.

GONOCOCCAL INFECTION

Marie (1898) described a patient with symptoms
of spondylose rhizomélique (ankylosing spondylarthritis) who also had gonorrhoea, and he came to hold the belief that gonorrhoea could cause this disease.

Since that time various authors have considered gonorrhoea to be the aetiological factor in a varying proportion of their cases. It is evident that an unrelated history of gonorrhoeal infection is bound to be found in a certain percentage of cases, but a very close time relationship between the gonorrhoeal infection and the onset of symptoms has lead some workers to believe that in some cases the infection was of definite aetiological importance. Boland & Present (1945), in a series of 100 soldiers, found acute gonorrhoeal urethritis to be related to the onset of back symptoms in 5 cases, and Dunham & Kautz (1941) stated that in 1 out of 20 cases the disease definitely followed acute gonorrhoea, and in another case was associated with either a second attack of gonorrhoea, or a reactivation of an old gonorrhoeal infection. Parr & Shipton (1946) gave details of 4 cases with typical ankylosing spondylarthritis in which the disease started almost immediately following a gonorrhoeal infection. They stated that in other cases arthritis started in various joints following gonorrhoea, and that there was subsequent concentration of the process in the spine to the exclusion of the other joints. They thought that the antecedent history of gonorrhoea was of importance. Dekkers (1943) found that in 4 out of a series of 9 cases of ankylosing spondylarthritis the rheumatic complaint had either started during an attack of gonorrhoea, or was aggravated by it. He considered that the facts illustrated in these cases made a connection between gonorrhoea, rheumatic polyarthritis and spondylose rhizomélique (ankylosing spondylarthritis) seem very credible.

On the other hand Dawson (1935) and Tyson (1937) considered that the incidence of gonorrhoea was no higher in patients with ankylosing spondylarthrits than with other diseases, and Buckley (1945) stated that the view that ankylosing spondylarthrits was caused by gonorrhoea had been abandoned.
Thus from a review of the literature it is found that there is some rather unconvincing evidence that gonorrhoea may be an aetiiological factor in some cases, but there is no evidence at all to suggest that it is causally connected with more than a small percentage of cases.

GENITO-URINARY INFECTION

Forestier (1939) found that in 60% of 153 cases of ankylosing spondylarthritis there was a history of a previous genito-urinary ailment. On this he based a hypothesis that the primary focus of infection in ankylosing spondylarthritis was in the genito-urinary system or low bowel, and that toxic products were excreted and drained into the lymph system of the pelvis and from there were carried up alongside the spine. He pointed out that in the male the lymphatic vessels draining the prostate and seminal vesicles pass in front of each sacro-iliac joint, and extend upwards in the posterior part of the abdomen on both sides of the spinal column just in front of the apophyseal joints, with which they have many connections. He also pointed out that, although the lymph vessels of the uterus and vagina follow much the same course, those draining the tubes and ovaries lie much more laterally in the pelvis, while in the abdomen they are on the ventral aspect of the large blood vessels. Drainage to the exterior is much easier from the uterus and vagina than from the ovaries and tubes, and he considered that the above differences in the anatomy of the lymph vessels draining what he thought to be the likely sources of infection might account for the infrequent occurrence of spondylarthrosis in females. Buckley (1945) also pointed out that streptococci, staphylococci and colon bacilli might invade the prostate, and that the primary infection might be in the prostate.

Dunham & Kautz (1941) stated that 14 of their 20 cases had white blood cells present in their urine. These white cells varied from an occasional one to ten or fifteen per high power field. They
considered this to be evidence that a low-grade urinary tract infection was frequently present in ankylosing spondylarthritis. However, on referring to the detailed figures given by them it is found that in 8 cases an occasional white blood cell was seen in a high-power field of the urine, in 3 cases there were between one and three cells, in 1 between five and ten, in the 13th between ten and fifteen and in the 14th between ten and twenty cells. They did not state whether or not the urines were centrifuged before examination, but in any case an occasional white cell is not sufficient evidence on which to base a diagnosis of a low-grade urinary infection. They were probably justified in regarding the findings to be abnormal in 3 cases, and possibly in 6, but not in 14.

Thus, although it is a possible hypothesis that a genito-urinary infection is the primary source of infection in ankylosing spondylarthritis, there is not sufficient evidence to show that it is so.

TUBERCULOUS INFECTION

Some authors have considered tuberculosis to be the cause of ankylosing spondylarthritis.

Kienboch (cited by Dekkers, 1943) considered ankylosing spondylarthritis to be an exudative synostosing form of joint tuberculosis, but he gave no extensive casuistic documentation of his cases.

Scott (1942) was also convinced that tuberculosis would be found to be the cause of spondylitis ankylopoietica (ankylosing spondylarthritis) in a certain percentage of cases.

Weissenbach, Perles, Francon & Témine (1940) described a case in which Pott's Disease of the first and second lumbar vertebrae occurred in a man who also had spondylose ankylosante (ankylosing spondylarthritis). The sacro-iliac joints showed abnormalities, and there was ligamentous ossification extending from the fourth dorsal to the
fifth lumbar vertebra. They considered this to be important evidence in favour of the tuberculous origin of certain cases of spondylose ankylosante.

Buckley (1935) gave some reasons in favour of the hypothesis that tuberculosis was the cause of ankylosing spondylitis, among which he included the fact that he found the intradermal tuberculin test to be positive in 15 out of 18 cases. This, however, does not help in forming an opinion one way or the other, and in a later paper (1945) he himself said that it was difficult to determine the significance of this finding.

Robinson (1940) found the tuberculin sensitiveness of 45 patients with ankylosing spondylarthritis to be 30% higher than that of 90 rheumatic controls. This result is statistically significant, but he said that he could not explain it, although he thought it possible that a more intense tuberculous baptism than normal might predispose some cases to the inheritance of ankylosing spondylarthritis.

Different authors have recorded various figures showing an association between ankylosing spondylarthritis and pulmonary tuberculosis. The highest incidence recorded in the literature is that of Dunham & Kautz (1941) who found that pulmonary tuberculosis was present in 25% of 20 cases. However, they pointed out that the source of their cases, which was the Desert Sanatorium, Tucson, Arizona, was partly responsible for the high incidence. They said that they were in accord with the view of Assman and Fraenkel that pulmonary tuberculosis was not causally related to ankylosing spondylarthritis, and was either secondary to it or merely incidental.

The available evidence in the literature does not give any grounds for holding an opinion different from the latter.
BRUCELLOSIS

Goldfain (1943) stated that 5 out of a series of 18 cases of ankylosing spondylarthritis could be listed as being caused by chronic brucellosis. It is true that the general symptoms of chronic brucellosis resemble those of ankylosing spondylarthritis, and the course of the two diseases may also be similar. Until a few years ago chronic brucellosis was held by most clinicians to be a self-limiting disease, but Harris (1941) stated that the course was often one of a long drawn out disease with exacerbations and remissions and that it might continue and relapse indefinitely, often with a "flare-up" in the symptoms if the general resistance was lowered by any means, such as intercurrent infection, strain or exposure. The disease might run a chronic course from the start, with no acute phase occurring.

Bone and joint affections caused by brucellosis, although uncommon, have been described, and both arthritis and spondylitis have been ascribed to it. Although there is no doubt that arthralgia and other joint affections occur during the acute phase of brucellosis, unless a purulent lesion is produced from which the organism can be obtained in pure culture, it is difficult, if not impossible, to prove that the bone or joint lesions are really due to brucella infection. However, brucella organisms have been cultured from such lesions, Kulowski & Vinke (1932) apparently being the first to report a purulent lesion in the spine from which focus the brucella organisms were recovered on culture.

Hardy (1937) stated that arthritis in man was rather rare in infections with bovine strains, was common with porcine strains, but was most common with caprine strains. He also stated that eroding suppurative arthritis might be caused by brucella infection in men, and in cases seen by him in which the spine and wrist joints were affected the lesions clinically resembled tuberculous ones.
Goldfain quoted some of the findings of Bishop who wrote a paper in which he reviewed 56 cases of spondylitis due to undulant fever which he had collected from the literature. Bishop also described 1 further case of his own. Goldfain has picked out the points in which these cases resemble ankylosing spondylarthritis, but if the paper of Bishop (1939) is studied it is seen that neither the symptoms, nor the X-ray findings, nor the course of the disease in the cases described, present a picture which resembles that of ankylosing spondylarthritis.

It should be mentioned that among many other diseases of various systems that might be caused by brucellosis, Harris (1941) included a form of arthritis indistinguishable from atrophic rheumatoid arthritis. The diagnosis in these cases was said to be established either by strongly positive opsonocytophagic tests, together with the clinical findings, and also by the response to specific bacterin or vaccine therapy. Whether these are sufficient grounds for assuming the cause of the arthritis to be an infection with brucella organisms is open to question. Much the same objections can be raised as are discussed more fully below in relation to ankylosing spondylarthritis.

Concerning the paper of Goldfain (1943), it must be assumed from the information included in the article that the cases were true cases of ankylosing spondylarthritis. The inferences of the paper may be questioned on two grounds:

1) the uncertainty of the diagnosis of brucella infection, and
2) the doubt as to whether the brucella infection was the cause of the spondylarthritic process, or whether the two conditions were coincidental.

On the first question it may be said that the results given by Goldfain suggest that 3 cases (Nos. 1, 2 and 3) were suffering, or recovering, from infection with brucella, and that 2 cases (Nos. 4 and 5) were beginning, or had experienced in the past, brucella infection, despite the facts which follow. No details are given as to whether the antigens used in the agglutination tests were Br. abortus, Br. melitensis or Br. suis. This information would be of interest.
because, while there is a considerable antigenic relationship between these organisms, the titre to a heterologous organism would probably be lower than to a homologous one. Secondly no data are given as to the level regarded as diagnostic of active infection as compared with past infection, (although it is admittedly doubtful if any level can be so regarded). This might be of importance in the interpretation of cases No 4 and No 5 in which the titres were low. Goldfain attached significance to the opsonic indices and skin sensitivity tests, but there is no general agreement as to the correct interpretation of results in terms of past or present infection or susceptibility.

With regard to the second question, even if the five patients are all conceded to be suffering from active brucella infection, the causative relationship of this organism to the spondylarthritis is not proved. 5 (27%) of 18 patients had the infection. The area from which these patients were drawn, Texas and Oklahoma, is devoted largely to cattle rearing and pig farming and, although accurate statistics are difficult to obtain, it is known that infections with the brucella group of organisms (Br. abortus and Br. suis) are frequent in persons working on farms and in the slaughter yards. It is of interest that during the years 1938 and 1939 the reported number of cases of brucellosis was higher in states of Texas and Oklahoma than elsewhere in the U.S.A. (Harris, 1941). Gould & Huddleson (1938) estimated that 10% of the population of the U.S.A. became infected with brucella, and presumably the percentage would be higher in those exposed to special risk. The possibility of a coincidental occurrence of ankylosing spondylarthritis and brucella infection is therefore not unlikely, although, without figures of the incidence, it is impossible to say what the probability would be.

Lastly, it is of interest that in a different disease, namely lymphadenoma, workers in mid-western states, such as Poston & Parsons (1940) of the Duke University Medical School, Durham, North Carolina, have cultured brucella organisms from the tissues of a high proportion of patients suffering from lymphadenoma. This finding, unconfirmed elsewhere, again suggests that
a high degree of latent infection with brucella in these mid-western communities may lead to mistaken aetiological conclusions where in fact only coincidental infection exists.

Owing to these considerations it is maintained that it has not been proved that brucella infection can directly cause the condition of ankylosing spondylarthritis.

FOCAL INFECTION

The relationship that focal infection bears to atrophic arthritis in general is not clear, and even less facts concerning its relationship to ankylosing spondylarthritis have been published.

With regard to atrophic arthritis in general, Snyder, Fineman & Traegar (1932) in a paper on sinusitis in chronic arthritis, claimed to show that the arthritis responded favourably when rhinologic treatment was carried out. They took as their material 386 consecutive cases of chronic arthritis. 262 (69%) showed X-ray evidence suggestive or indicative of sinus disease. Only 126 of the 262 cases were examined clinically, and of those examined 93 (75%) showed corroborative clinical evidence of nasal disease sufficient to need treatment. The paper is really based on the course of these 93 cases. It is perhaps worth mentioning that only 16 of the 93 had a history suggesting sinus trouble.

For various reasons which they did not state 42 of the 93 cases were not treated, and in this group the arthritis became worse in 23 and improved in 19. In 5 cases treatment was incomplete. 28 cases were given conservative treatment, and in 27 the arthritis improved. A further 18 cases had radical treatment and 17 of these improved.

They thus showed a significant difference in the treated and untreated groups. It is however, unsatisfactory that no details of the method of selection of the
treated and untreated groups are given.

Since 1932, when the paper was published, other workers have obtained very different results, and the tendency at present is to regard focal sepsis in relationship to atrophic arthritis as of less importance than previously. Cecil (1940), after a study of 200 cases of rheumatoid arthritis, came to the conclusion that a much more conservative attitude to the removal of septic foci should be adopted. He thought that there was a type of infectious arthritis related to focal sepsis, but it was not rheumatoid in type.

Even if septic foci are found with greater frequency than usual in chronic rheumatic patients the question arises as to whether the foci are of aetiological significance, or whether they are due to a general debilitated state due to the chronic disease. Osgood (1940) thought that the focal infection might be the result rather than the cause of chronic rheumatic conditions, owing to the fact that there was frequently a spontaneous disappearance of foci of infection when recovery or remission of the underlying chronic disease occurred.

In regard to ankylosing spondylarthritis, Scott (1942) described a case which lends support to this theory. It was the case of a girl who had moderately advanced ankylosing spondylarthritis. She also had an infected right antrum, opaque to X-rays. Following widefield X-ray therapy she regained complete freedom of movement of the back, and the antrum cleared and became free of infection within two months without rhinological treatment.

Johnson (1945), considered that, although foci of infection did not cause ankylosing spondylarthritis, they could prevent a response to treatment.

The views of Oppenheimer (1938) on the relationship of focal infection to apophyseal joint disease were similar to the views of Cecil (1940) on its relationship to general arthritis. After studying 147 patients with various lesions of the apophyseal joints, together with 1,000 X-ray films, he concluded that there were two main types of
arthritis which affected the apophyseal joints, atrophic and hypertrophic. The atrophic occurred in the following three forms:–

1) an acute reparable form without cartilage involvement,
2) a localised chronic type marked by destruction of cartilage, and
3) a chronic, more or less systemic disease which he called ankylopoietic spondylarthritis.

In his view it was the first type, and not the last, which was chiefly associated with focal and general infections.

A further reason why septic foci are not considered of much importance as an aetiological factor is because after removal no benefit is found to occur in the patient's condition.

Thus Buckley (1945) stated that, although the constitutional symptoms pointed to an infective origin from a focus, the removal of septic foci rarely helped the patient's condition. Similarly Blair (1942) stated that his cases were searched for septic foci, but when these were treated there was no shortening in the course of the disease.

If no improvement occurs in the patient's condition this is certainly a reason for not removing the foci, but it is not necessarily true that the foci play no part in the aetiology of the condition, because chronic septic conditions, particularly of the sinuses, are difficult to treat satisfactorily. With conservative measures one cannot be sure that the offending organisms have been eliminated, and even with radical measures it may be impossible to clear up the condition completely. It may be that, although the septic focus has apparently been cured, there are still organisms present in quantities sufficient to allow antigens to escape into the general circulation, and to continue to cause allergic manifestations elsewhere. This leads on to a discussion of the possible role of allergy in the aetiology of ankylosing spondylarthritis.

It can be seen at this stage that there is no evidence in favour of focal sepsis being a factor
of importance in the aetiology of the condition.

**ALLERGY**

Freiberg (1929) showed that an experimental arthritis simulating the proliferative arthritis seen in man could be produced in rabbits by the repeated injection of a bacterial extract, and that this experimental arthritis appeared to be a local allergic manifestation of a generalised state of allergy to a specific bacterium or bacterial extract.

Angevine & Rothbard (1940) injected the right knee joints of rabbits with repeated small amounts of either heat-killed streptococci or a nucleo-protein fraction. They found that, if the animals were subsequently infected intravenously with living cultures of the same organisms, the previously injected joints were more susceptible to infection than were joints which had previously been injected with heat-killed staphylococci or horse-serum.

Klinge (quoted by Bruun, 1940), from his experiments, concluded that the aetiology of the rheumatic joint diseases might be explained as being the result of a bacterial influence in an allergically changed organism. It should be noted, however, that his experiments were carried out in animals with horse-serum.

Bruun (1940) carried out further work in animals to try to supplement Klinge's experiments. His results substantiated Klinge's work in that he found it possible to produce, by purely allergic non-bacterial means, articular changes very much resembling the rheumatic diseases known from human pathology. He showed a number of important points of resemblance in the pathological anatomy of sero-allergic tissue reactions in animals and rheumatic lesions in humans. He pointed out that Klinge's work was sometimes criticised because the allergic arthritis only appeared after direct injection into the joint concerned, and that it was not possible to produce it following intravenous or intra-peritoneal
injection. In his experiments Bruun produced an allergic polyarthritis in 4 cases in which changes were present in non-injected joints. He also showed that sufficiently sensitized rabbits would react not only to specific but also to non-specific factors, such as cold, with allergic manifestations in joints. From his work he deemed it warrantable to assert that the action of bacteria in an allergically changed organism should be considered to be the aetiological factor in rheumatic joint diseases, although he admitted that no conclusive proof was furnished.

Rich & Gregory (1943a, 1943b, 1944, 1946), in a series of articles, have produced extremely strong evidence that the various lesions of human rheumatic fever represent the results of focal hypersensitive reactions.

Levinthal (1943) considered that rheumatism, acute and chronic, was an anaphylactic disease with multiple lesions in the mesodermal system produced by continual antigen-antibody reactions in or on tissue cells. It was his view that the antigen, in most cases, consisted of dissolved bacterial substances derived from sub-acute or chronic infection. He thought that any foreign protein entering the body and producing hypersensitivity (i.e. the presence of cell-fixed antibodies in reticulo-endothelial cells without sufficient free antibody in the circulation) but no immunity (i.e. fully developed state of antibody equipment in cells and tissue fluids) would lead to rheumatism. He considered that rheumatic fever was produced when the first contact with the antigen caused a critical antibody distribution with suddenness, while rheumatoid arthritis was due to a gradual decline in antibody production, producing a critical antibody distribution gradually. In his view the hypersensitive, imperfectly immune state was due to partial debility of the antibody producing system, and this in turn might be due to constitutional causes, or be secondary to malnutrition, climate, strain, endocrine disorders, physical or mental trauma, bad housing conditions or any other cause producing general debility.
Maclean (cited by Levinthal, 1943) demonstrated that in their response to antigens 10% of the population were poor responders, 70% average and 20% good responders. If individuals made a poor response to one antigen, their response to others was also poor.

Levinthal attempted to demonstrate a poor antibody response in persons with chronic rheumatism. Courses of subcutaneous injections of a non-specific yeast vaccine were given to a small number of patients with chronic rheumatism. He did not show definitely whether or not the antibody response was poor, as no controls were used, but he showed that, although the skin tests became positive after a few injections of antigen, precipitin did not appear in the serum in some cases for several months. He also showed that precipitin and agglutinin appeared in the knee joint fluid before the serum, and the antibodies in the former exceeded in amount the antibodies in the latter.

Levinthal has put forward a plausible theory, but it has so far by no means been substantiated.

Thus up to the present the only rheumatic manifestations in humans which have been shown, almost without doubt, to be due to an allergic process are those of rheumatic fever. It may be that chronic rheumatism is due to the same process, but it has not been proved.

However, it has been shown above that it is probable that there is a relationship between rheumatic fever and rheumatoid arthritis, and also that there is probably a relationship between rheumatoid arthritis and ankylosing spondylarthritis. With these premises, it might be argued that ankylosing spondylarthritis is probably caused by an allergic mechanism, but no work with a direct bearing on the relationship between allergy and ankylosing spondylarthritis has been published.

There are two other grounds on which it might be argued that ankylosing spondylarthritis is related to allergy. The first is the frequent occurrence of iritis in ankylosing spondylarthritis, and the second is the response to wide-field X-ray therapy.
The incidence of iritis in ankylosing spondylarthritis has been discussed above (Page 25). The cause or causes of irido-cyclitis are not known, but in some cases it is considered to be an allergic manifestation. Gill (1945) considered the commonest cause of uveitis to be focal sepsis. He offered no explanation of how the focal sepsis caused the uveitis, but it is conceivable that it is through an allergic mechanism. He stated that uveitis was sometimes due to food allergy.

Berens, Angevine, Guy & Rothbard (1938) carried out some work which suggested that irido-cyclitis might be caused allergically. They produced acute and chronic inflammatory lesions in the eyes of rabbits by the intravenous injections of small doses of various organisms. They pointed out, however, that the lesions were not similar to those found clinically in humans, and also that few eye lesions were produced when foci of infection were artificially established in various sites.

With regard to the response to wide-field X-ray therapy, Scott (1942) obtained good results by treating cases of ankylosing spondylarthritis by this method. In a previous paper (1939) he also stated that beneficial results were obtained in asthmatic patients to whom X-ray treatment was given, and that in purely allergic asthma it was exceptional for cases not to become and to remain symptom free. However, no figures of details of the investigation are given. He treated various chronic infective conditions with wide-field X-ray therapy and he came to the conclusion that the therapeutic effects were due to the general resistance of the patient being raised, probably by some stimulating or balancing action on the ductless gland system as a unit. He admitted that the evidence for the therapy was scanty.

Taking Levinthal's views (see Page 48) into consideration it is possible that Scott's "raising of resistance" is due to the reticulo-endothelial system being stimulated, with a subsequent greater antibody production and therefore an increase in the amount of circulating antibodies. This would produce a state of immunity rather than one of hypersensitivity. This is admittedly pure speculation.
Seth - Smith (1947) also considered that the action of wide-field X-ray therapy was one of desensitization, and that it was effective only in certain stages when desensitization was indicated.

Further scanty evidence of the possible allergic nature of ankylosing spondylarthritis is provided by the work of Campbell. In his series of 25 cases he found an association between ankylosing spondylarthritis and the following diseases: asthma, erythema nodosum, purpura, chronic lupus erythematosus, psoriasis and nephritis. He reported that in 2 of his cases there was an eosinophilia of over 5%, but as he gave no absolute figures this finding as it stands is valueless.

It is seen that there is no direct evidence in the literature to support the view that ankylosing spondylarthritis is due to an allergic reaction to infection, and that such evidence that it has been possible to collect is extremely indirect and unconvincing.

**DIETARY DEFICIENCIES**

Baker, Rinehart, Mettier & Bruckman (1939), presented observations on a series of patients with rheumatoid spondylitis (ankylosing spondylitis) pertaining to their vitamin C nutrition and metabolism. They found almost uniformly low plasma vitamin C levels, indicating a significant undersaturation. Their conviction was that this deficiency contributed to the onset and continuance of the disease.

These findings were given at a meeting of the American Rheumatism Association, and the evidence has to be studied as published in a report of the Association proceedings. According to this, in the preliminary paper, no mention was made of any findings in a control group.
In the following discussion Rinehart is reported as having said that over 90% of the spondylitic patients had a severely lowered vitamin C concentration in the blood, and that lowered values had been found in approximately 40% of non-arthritic persons. In these persons the levels had not been so uniformly and strikingly low as in the patients with rheumatoid spondylitis. However, he said that the findings in the non-arthritic group had not been analysed for inclusion in the paper under discussion. Without further details of the control group, the evidence cannot be regarded as acceptable.

No other evidence of vitamin C nutrition in ankylosing spondylarthritis has been found in the literature, but Freyberg (1942) determined the vitamin C content of the blood in a series of normal adults, in patients with rheumatoid arthritis, and in patients with non-arthritic diseases. Compared with normal adults, 38% of cases with rheumatoid arthritis had a normal vitamin C level and 62% had a low level. The distribution in non-arthritic hospital patients was of the same order, 42% having a normal level and 59% a low vitamin C level. It was thus obvious that there was no special incidence of low vitamin C levels in the rheumatic group. The vitamin C levels appeared to follow the social status.

In the same paper, on the treatment of arthritis with vitamin and endocrine preparations, Freyberg (1942) concluded that it had not been clearly shown that any vitamin had any direct relationship to any rheumatic disease, although deficiency existed not infrequently in patients with chronic arthritis.

Nothing has appeared in the literature which makes this view untenable in the case of ankylosing spondylarthritis.

**FLUOROSIS**

It has been suggested that ankylosing spondylarthritis may be caused by fluorine poisoning.
Ockerse (cited by Lloyd, 1947) found an association between ankylosing spondylitis and chronic endemic dental fluorosis in areas in South Africa. Unfortunately the publication was unobtainable.

Lyth (1946) described 4 cases of spondylitis which occurred in Kweichow, China, in an area where chronic endemic fluorosis occurred. Four clinical reports were given, together with a description of an exhumed skeleton. Unfortunately no mention was made of any X-ray findings in these cases, but, although the histories and clinical findings described are similar to those of patients with ankylosing spondylarthritis, the description and photograph of the skeleton do not illustrate changes which correspond to those which occur in that condition.

Kemp, Murray & Wilson (1942) quote Roholm's work in which he reported on bony changes occurring in fluorine workers and showed that fluorine was responsible for the changes. The X-ray appearances of the bones do not correspond to the changes which are found in ankylosing spondylarthritis, but represent changes similar to those present in the skeleton described by Lyth.

Kemp, Murray & Wilson (1942) noted the frequency of "round back" in children and adults in areas where mottled enamel was prevalent, and they carried out an investigation to see whether any changes could be detected radiologically in the bones of persons with dental fluorosis. They examined 5 adults and 22 children, none of whom had symptoms. They found evidence of disturbance of ossification, with X-ray appearances similar to those described by Scheuermann in cases of adolescent kyphosis. They did not, however, find changes suggestive of ankylosing spondylarthritis. From a study of these papers it can be seen that, inspite of some apparent similarities between the changes in fluorosis and ankylosing spondylarthritis

such as the stiffness of the back, the ligamentous ossification about the intervertebral and costovertebral joints, and the ossification of other spinal ligaments, the findings taken as a whole present pictures of two quite distinct processes. In fluorosis there is often gross thickening and irregularity of the long bones, and the ribs. On X-ray examination both the cortical bone and the cancellous trabeculations are seen to become thicker until ultimately the osseous pattern is completely effaced and the bones appear marble white and structureless. The muscle attachments become thickened and ossified so that the bones appear to be covered with excrescences and the bony contours are almost everywhere irregular. These are all changes which are not seen in ankylosing spondylarthritis.

Hart (1947) on investigation of 15 cases of ankylosing spondylarthritis stated that he was unable to find anything in their histories, or on examination, which suggested that they might be suffering from fluorosis.

Thus a study of the evidence leads to the conclusion that the aetiology of ankylosing spondylarthritis is not connected with an excessive intake of fluorine.

PHOSPHATASE ACTIVITY

McWhirter (1945) thought it possible that ankylosing spondylitis might be due to the leakage of acid phosphatase into the prostatic veins. He noted that the areas affected in ankylosing spondylitis corresponded closely to the areas of distribution of prostatic secondaries in the spine and pelvis, and therefore considered it possible that the prostatic phosphatase might be spread to the
sacro-iliac region and spine by the same route as secondary deposits from the prostate; that is to say, by the pelvic venous plexuses and the paravertebral veins, as previously described by Batson (cited by McWhirter).

McWhirter reported that the acid phosphatase was investigated in 7 cases of ankylosing spondylitis, and in some cases, when the disease was in an early stage, the blood level was raised.

Race (in a personal communication to Buckley, quoted by Buckley, 1945) found that the average blood level of acid phosphatase, in a series of 13 cases of ankylosing spondylarthritis, was 2.2 units; by the method used the normal maximum was 4 units. The highest individual figure found was 3.8, so that in no case was the acid phosphatase above the normal maximum.

Campbell (1947) stated that in his series of cases the blood acid phosphatase was never more than twice the normal level.

Parr & Shipton (1946) also stated that the blood phosphatase level was not raised to any great extent, but they gave no figures, and they did not state to what type of phosphatase they were referring.

Buckley (1935) also investigated the level of phosphoric esterase in the blood of 13 cases. In that paper he did not specify what type of phosphatase was estimated, or the method used, but he referred to this work in a later article (1945) when he said it was the alkaline phosphatase that was estimated. He stated that by the method used 0.20 was the normal figure, but did not state the upper limit which should be regarded as normal. He gave the figure found in each of the 13 cases; the lowest was 0.14, the highest 0.56, and the average value was 0.29.

Desmarais (1948) investigated the phosphatase activity in 26 cases of spondylitis ankylopoietica (ankylosing spondylarthritis). By the method he used
the normal level for the acid phosphatase was between 1 and 3 units. He found the average value for the cases was 1.75 units. 2 cases gave a high normal reading. The normal levels for the alkaline phosphatase by the method used was between 5 and 10 units, and he found the average value for the cases was 6.2 units, 3 cases giving high normal readings.

Simpson & Stevenson (1949) reported that in 27 cases of ankylosing spondylitis they found that the acid phosphatase was raised only in 2 cases and that the alkaline phosphatase was also raised only in 2 cases.

It thus appears that in the majority of cases the acid and alkaline phosphatase levels in the plasma are within normal limits, and that if the levels are raised it is never to any great extent.

SULPHUR METABOLISM

It has been suggested that there is an upset of sulphur metabolism in rheumatoid arthritis. According to Freyberg, Block & Fromer (1940) previous claims that this was so based on the findings of a lowered content of cystine in the finger nails and a reduced sulphur content of articular cartilage. The occurrence of free indole in the urine of arthritics has also often been reported and from this it was inferred that there was insufficient sulphur available for the detoxication of indole to be carried out. They pointed out that a low cystine content of the nails, apart from occurring in arthritics, had also been observed in patients chronically ill with other diseases, and might be accounted for by malnutrition. They also noted that in many arthritics the cystine content of the nails was normal.

They investigated the sulphur metabolism of 4 cases of rheumatoid arthritis, 2 cases of hypertrophic arthritis, 3 cases of ankylosing spondylarthritis and 4 normal controls. Their investigation showed that
there was no important difference in the amount of sulphur eliminated by patients with arthritis, as compared with normals. They stated that their study revealed no biochemical or metabolic indication of need for, or benefit from, sulphur medication in the treatment of arthritis, and they found no evidence of sulphur deficiency, or abnormality of sulphur metabolism, in patients with arthritis.

Block & Murrill (1941) carried out determinations of several amino-acids in the serum, as well as an elemental analysis of the total proteins, in 11 patients with rheumatoid arthritis, and compared the results with the findings in 6 normal controls. No essential difference in values between the two groups was found, and this, in their opinion, invalidated any suggestion that an altered composition of the total serum protein of arthritic patients reflected a disturbed sulphur metabolism.

Blair (1942) formulated a hypothesis that ankylosing spondylarthritis was caused primarily by an absorption of cartilage from the involved joints due to a metabolic change, and was not caused by an infectious process. He considered, if this was so, that the absorption would start, and be most marked, in areas of low relative vitality, and that in areas such as the sacro-iliac joints in which there was normally little movement, the vitality of the cartilage would be relatively low. He pointed out that movements which were used least often were lost first, and he thought that immobilisation, although relieving pain, lead to the absorption of the cartilage and eventual ankylosis. He based his hypothesis on the fact that he found that irradiation caused mast cells to give up their sulphuric ester granules, and, as cartilage consists of chondroitin-sulphuric acid, he argued that the beneficial results of X-ray therapy were brought about by the liberation of sulphur within the body in a usable form. He also considered that iritis might be caused by the same metabolic disturbance. In support of this assumption he pointed out that there was an increase of mast cells in the eye when iritis occurred, and that the aqueous and vitreous humours consisted of mucoitin-sulphuric acid, which was closely related to chondroitin-sulphuric acid.
The previous work on sulphur metabolism in arthritis, reviewed above, does not necessarily invalidate Blair's hypothesis, for the following reasons. The investigation of Block & Murrill was carried out on the amino-acids in the serum, and need not necessarily reflect changes taking place in the chondroitin-sulphuric acid content of cartilage and the sulphuric ester content of mast cells. Freyberg, Block & Fromer, in their investigation, administered colloidal sulphur by intramuscular or intravenous injection, or gave colloidal sulphur or sodium thiosulphate by mouth, and analysed the sulphur elimination in the urine. They concluded that there was no biochemical evidence that elemental sulphur or inorganic sulphate, injected or ingested, could be utilised by the human in the synthesis of sulphur containing amino-acids. Despite the fact that this work does not necessarily invalidate Blair's hypothesis, the latter is no more than a hypothesis, for which the available evidence provides no proof.

From this sub-section it can be seen that no association between the aetiology of ankylosing spondylarthritis and sulphur metabolism has been proved to exist.

THE DUCTLESS GLANDS

Pemberton & Scull (1943) discussed the role of central factors in the pathogenesis of rheumatic disorders. They considered that the symmetrical distribution of the lesions, as well as other factors, suggested that a central mechanism was involved, and in their view the factors comprising the mechanism were the great systems of the body, interrelated through the central nervous and endocrine chains. They also presented other arguments, which, however, are no more than suggestive, that there is some linkage between endocrine functions and arthritis.
Osgood (1940) considered that the aetiologic factor in arthritis was probably a biochemical rather than a bacterial one, and he thought, like Hench (1949), that the relief obtained by rheumatoid arthritis cases during pregnancy and jaundice pointed to this conception.

The Pituitary Gland

Pemberton & Scull (1943) gave some evidence supporting the view that arthritis was connected with the functions of the pituitary gland, and that both hypo- and hyperfunction might cause arthritic and related symptoms. They mentioned the occurrence of remissions during pregnancy and of exacerbations premenstrually. They also pointed out that menopausal arthritis was a definite entity. Another fact to which they drew attention was that following hypophysectomy in adult rats there was a lowering of the serum albumen level and an increase in the globulin, and that these changes also occurred in rheumatoid arthritis.

Chester & Chester (1940) presented the radiological findings in the vertebrae in 8 cases of acromegaly. In 5 of these cases there was a symmetrical spondylitis. The illustrations of the vertebrae, however, show no resemblance to ankylosing spondylarthritis, the appearances being more like those of osteoarthritis of the spine except that changes are more symmetrical.

In acromegaly, besides the bony changes, which are not similar to those of ankylosing spondylarthritis, changes in many other organs occur which are not seen in ankylosing spondylarthritis.
Adrenal Cortical Hormones and Sex Hormones

There is abundant evidence that the sex hormones influence the ossification of bones and the fusion of epiphyses. Albright, Bloomberg & Smith (1940) showed that oestrin therapy had a very marked ability to put patients with post-menopausal osteoporosis into a positive calcium and phosphorous balance.

There is also some evidence that the sex hormones may be connected with some forms of arthritis.

Selye, Sylvester, Hall & Leblond (1944) produced experimental evidence which they considered indicated that the adrenal cortex might play an important role in rheumatic and rheumatoid conditions in man. They showed that in rats overdosage with desoxy-corticoesterone acetate elicited a polyarthritis which histologically resembled that seen in rheumatic fever in man. As has been mentioned, it is known that remissions during pregnancy are common in women suffering from rheumatoid arthritis, and that in post-menopausal arthritis a definite response can be expected to the administration of oestrogenic hormones. However, until the recent work of Hench, Kendall, Slocumb & Polley (1949) the latter seemed to be the only form of arthritis in which a consistent effect could be produced by the administration of a hormonal like substance.

These workers showed that there is a definite connection between rheumatoid arthritis and the adrenal cortex in humans by giving 17-hydroxy-11-dehydrocorticoesterone (Compound E) to 14 patients with severe or moderately severe rheumatoid arthritis. Improvement in the clinical features and in the sedimentation rates began to occur within a few days of giving of the drug, and when its administration was discontinued there was usually a prompt relapse.

With regard to ankylosing spondylarthritis, until this year, the only evidence which it had been
possible to collect to show that it might be connected
with the sex hormones was scanty.

Freyberg (1942) tried the effect of giving
oestrogens to 8 cases of ankylosing spondylarthritis,
7 males and 1 female, but no effect was produced in
any case.

Davison, Koets & Kuzell (1947), as has been
mentioned previously (Page 28), had shown that there
was an increased urinary excretion of 17-ketosteroids
in males with ankylosing spondylarthritis as
compared with normal males. 17-ketosteroids are the
metabolic end products of steroids originating in
the adrenal cortex and gonads of the male.

Of the 14 cases of rheumatoid arthritis treated
by Hench et. al. (1949) with Compound E, one of
these cases had polyarthritis and rheumatoid spondylitis.
The response in this case was the same as that shown
by the other cases.

The Parathyroid Glands

Between 1928 and 1933 several authors concluded
that ankylosing polyarthritis was associated with
hyperparathyroidism, and in a fair number of cases
parathyroidectomies were carried out, with reported
improvement.

Funsten (1933), out of 95 cases of arthritis,
chiefly of the ankylosing type, found evidence of
"parathyroidism" in 26 cases. In 14 of these parathyroidecto-
was carried out, and only one failed to show improvement.
However, the details of the investigations given are
inadequate for forming an opinion either of the
correctness of the diagnosis of hyperparathyroidism, or
of the degree of improvement obtained.

Compere (1933), reviewing the literature for
the preceding few years on the subject, quoted several
authors, who had reported clinical improvement in cases of
ankylosing polyarthritis following parathyroidectomy. He pointed out that the reports of microscopical examinations of the glands, which had been published, failed to demonstrate true adenomata, and that the cell picture was that of hyperplasia. He stated that enlargement and benign hyperplasia of the gland might be caused by deficiency of calcium absorption from the gut. He also pointed out that no reports had been published by the authors to show the results of studies of the metabolism of calcium and phosphorous in the cases. He said that in true hyperparathyroidism the patient was in negative calcium balance, but Bauer and his associates, in a personal communication to him, stated that every case of ankylosing polyarthritis in their series was in positive calcium balance. For these and other reasons Compere concluded that ankylosing polyarthritis was probably not caused by hyperparathyroidism.

Nachlas (1933) found that the serum calcium levels were normal in 37 cases of arthritis, and concluded that at that time one had no right to assume that arthritis was the result of a calcium - phosphorous dyscrasia.

Dunham & Kautz (1941), from a review of the literature and the findings in their series of 20 cases, discovered no convincing evidence to show that the parathyroid glands played a role in ordinary cases of ankylosing spondylitis.

Parr & Shipton (1946) stated that they checked the serum calcium content of a large number of patients with ankylosing spondylarthritis and rheumatoid arthritis, and found no great variation from the normal.

There is no evidence that abnormal function of the parathyroid glands is responsible for ankylosing spondylarthritis. In fact the evidence supports the view that in most cases there is no such abnormal function present.
The Thyroid Gland

Parr & Shipton (1946) stated that in cases of ankylosing spondylarthritis the thyroid gland might be enlarged and toxic. Their grounds for stating this appear to be scanty. They found that in a small number of cases in their series there was prominence of the thyroid gland. They thought, however, that this prominence might be due to the position of the head and neck. In one case they found that there was a Basal Metabolic Rate of +22, a rapid pulse rate after resting, a raised evening temperature (1°F.), and excessive sweating. They considered this case to be thyrotoxic, but no other evidence supporting this is presented and the gland was not enlarged. Without further details this cannot be accepted as a case of thyrotoxicosis.

While a possible connection between the functions of the thyroid gland and ankylosing spondylarthritis is being considered the work of Felix Mandl (1943) will be mentioned briefly. He tried to influence ankylosing spondylarthritis by means of implantations of toxic goitre. 3 advanced cases were given implants; 2 improved markedly and 1 had signs of bony decalcification. In 2 other cases thyroidin was given internally, with improvement for the duration of the treatment. He did not, however, consider that ankylosing spondylarthritis was due to thyroid deficiency, but that the results were symptomatic, possibly due to an increased blood flow, larger circulating blood volume and an increased heart output.

No other evidence has been found in the literature which suggests that abnormalities of the function of the thyroid gland are connected with ankylosing spondylarthritis.

From this sub-section it can be seen that there is some indirect evidence which suggests that arthritis may be connected with the functioning of the endocrine glands, and in particular with that
of the pituitary gland. The work of Hench et. al. (1949) shows that there is some connection between rheumatoid arthritis and adrenal cortical hormones.

It can also be seen that ankylosing spondylarthritis does not appear to be associated with any recognised syndrome which is due to endocrine dysfunction. However, the work of Davison, Koets & Kuzell (1947) suggests a relationship between ankylosing spondylarthritis and the adrenal cortex. The case of rheumatoid spondylitis (ankylosing spondylarthritis) treated by Hench et. al. (1949) in the series of rheumatoid arthritis cases reinforces this conception. If other cases of ankylosing spondylarthritis treated with 17-hydroxy-11-dehydrocorticosterone respond in the same way, a relationship will be definitely proved.
SECTION II

In the following section the findings from an investigation of 26 cases of ankylosing spondylarthritideselected.

All the cases attended the Leicester Royal Infirmary for treatment as out-patients. The area served by the hospital included the city of Leicester and also the surrounding villages and country areas.

39 cases, all of whom had been diagnosed as cases of ankylosing spondylarthritis by physicians or surgeons at the hospital, were seen, but in 13 of them the evidence in favour of the diagnosis was not sufficiently definite for their inclusion in this series.

Of the 26 cases which have been included, there was evidence of ankylosis of both sacro-iliac joints in 13 cases, and in a further 4 cases the appearances were such that ankylosis of both joints was probably present. In 3 cases the sacro-iliac joints on one side were considered to be ankylosed, with marked abnormality present in the opposite joint. In the remaining 6 cases there were abnormal appearances in both sacro-iliac joints consisting of erosion, irregularity and indistinctness of the joint margins, together with irregular sclerosis in the neighbourhood of the joint spaces. In all these latter 6 cases there was other confirmatory evidence of ankylosing spondylarthritis; in 3, signs of early bridging between the vertebral bodies were present; in the other 3, besides a typical history and clinical picture, there were abnormal X-ray appearances in the lumbar intervertebral joints, as well as either roughening of the ischia or changes in the upper costo-transverse joints, together with "squaring" of the vertebral bodies.

Thus the present series contains no very early cases, but it is considered that in the 26 cases which have been included there was conclusive evidence that they were suffering from ankylosing spondylarthritis.
3 additional cases have been included in the sub-section on familial incidence (No. 27, No. 28 and No. 29). It was not possible to investigate cases No. 27 and No. 28 fully enough for their inclusion in the other sub-sections, but sufficient evidence was collected to show that they were cases of ankylosing spondylarthritis.

Thus the sub-section on familial incidence contains the findings from an investigation of 29 cases. All the remaining sub-sections contain the findings from an investigation of 26 cases (No. 1 to No. 26), unless a special note to the contrary has been made.

**INCIDENCE**

**SEX INCIDENCE**

In this series there were 25 males and 1 female.

**FAMILIAL INCIDENCE**

The disease occurred in persons showing the following family relationship:-

a) **Two Brothers** (Cases No. 21 and No. 22)

They were the sixth and seventh in a family of eight children. They had four older sisters, one older brother and one younger brother.

There was no other significant family history of ankylosing spondylarthritis or rheumatism.

b) **Brother and Sister** (Cases No. 8 and No. 29)
The sister (Case No. 29) had one sacro-iliac joint that appeared to be within normal limits, except for slight increase in density around the upper part of the joint. Ligamentous calcification was present in the lower dorsal and lumbar region, and there were marked changes in both hip joints with bony ankylosis of the right one.

From these and other findings in this case (see appendix, Page 155) it was felt that there were sufficient grounds for making a diagnosis of ankylosing spondylarthritis, but as the case was atypical the case findings have not been included in the other analyses. There were four other siblings. The father had a history of "old man's rheumatism" and died at the age of 73. The mother had rheumatic fever three times, and died of heart trouble.

There was nothing else significant in the family history.

c) Two Brothers (Cases No. 11 and No. 27)

There was one other brother in the family and he had no history of ankylosing spondylarthritis.

There was nothing else significant in the family history.

d) Father and Daughter (Cases No. 28 and No. 14)

There was one other child, who was healthy, nine years younger than the affected daughter.

There was no history of ankylosing spondylarthritis or rheumatism in any other member of the family.

e) Uncle and Nephew (Cases No. 3 and No. 4)

The uncle was the sixth of eleven siblings. The nephew's father suffered from rheumatism in his leg during his "teens", but had had no disability since. The nephew had one other brother.

There was nothing else significant in the family history.
Thus, out of 29 cases, ankylosing spondylarthritis was present in the following relations:

1) Two Brothers
2) Brother and Sister
3) Two Brothers
4) Father and Daughter
5) Uncle and Nephew

In this series there is shown a greater familial incidence than has been found in any published report, although the series of Campbell (1947) (see Page 6) showed almost as high an incidence.

**OCCUPATIONAL INCIDENCE**

The 26 persons in this series were engaged in various occupations at the time of the onset of symptoms in the back. 16 were in civilian employment and 10 were serving in the armed forces. Of the 16 civilians, 11 had indoor and 5 outdoor employment; 2 were mental workers, 6 were light manual and 8 heavy manual workers.

Thus no special class of worker was found to be particularly liable to develop ankylosing spondylarthritis.

**SOCIAL HARDSHIP AND ABNORMAL MENTAL STRESS**

An endeavour was made to see if the above factors were connected with the development of ankylosing spondylarthritis.
In response to direct questioning 14 patients stated that their symptoms were aggravated during periods of mental stress and worry, whereas 12 said that they had noticed no such connection.

The main events from each patient's social history, together with any outstanding occurrence likely to cause mental stress, were charted in time sequence. The times of the onset and exacerbations of symptoms were than charted, and the two lists were compared to see if there was any close relationship in time between the two. No such connection was found in the majority of cases.

It was concluded that adverse social situations and periods of mental stress bore no more than a chance relationship to the onset or exacerbation of the symptoms of ankylosing spondylarthritis.

**HOUSING CONDITIONS**

The housing conditions of this series of patients prior to and at the onset of symptoms of ankylosing spondylarthritis were as shown in Table 2.
TABLE 2

Housing conditions of 26 cases of ankylosing spondylarthritis at the onset of symptoms

<table>
<thead>
<tr>
<th>Housing conditions at onset</th>
<th>No of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory</td>
<td>11</td>
</tr>
<tr>
<td>Fairly satisfactory (occasionally damp)</td>
<td>2</td>
</tr>
<tr>
<td>Unsatisfactory (damp, no overcrowding)</td>
<td>1</td>
</tr>
<tr>
<td>Very unsatisfactory (damp, overcrowded, badly built)</td>
<td>2</td>
</tr>
<tr>
<td>In Armed Forces</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

It can be seen that in the majority of those not in the Armed Forces the housing conditions were satisfactory at the time of onset.

SPORT

The findings of Scott (1942) and Parr & Shipton (1946) concerning the liability of keen athletes and especially swimmers to develop ankylosing spondylarthritis have already been reviewed (Page 9).
Of the patients in this series 10 were assessed as being keener than the average on organised outdoor games. Of these, all had played games since leaving school, and seven had given up playing owing to their disability. 11 were classed as average in their liking for games, and 5 disliked games. Only 2 in the series had done more than average amount of swimming.

These findings confirm those of Parr & Shipton that ankylosing spondylarthritis occurs both in athletic and non-athletic individuals, and are in disagreement with those of Scott who found that 95% of his cases were exceptionally keen on sport and were originally keen athletes.

Scott also stated that he found a higher proportion of swimmers and divers in patients than in the general population. Without knowing what is the proportion in the general population all that can be said is that swimmers and divers did not form a large proportion of this series.

**TRAUMA**

In 23 out of the 26 cases there was no history of trauma related to the onset of symptoms. In 1 case of the remaining 3 the onset of symptoms followed a fall from a bycicle; the 2nd had severely twisted his back just prior to the onset of back symptoms; the 3rd at the time of the onset of his symptoms was frequently engaged in "ceremonial" riding in a cavalry regiment, and he considered that the repeated jogging movements might have started his symptoms.

This series of cases therefore supports the view that in the great majority of cases trauma is not an aetiological or precipitating factor in ankylosing spondylarthritis.
EXPOSURE

1 case out of the 26 dated the onset of his symptoms to a time when he was constantly wet with oil at his work, and 2 others gave a history of exposure being the cause of an exacerbation of symptoms, one ascribing it to severe wetting and chilling at a harvest camp, and one to exposed conditions while camping when serving in the Army.

In the other 23 cases there was no evidence in the histories that exposure either caused or precipitated exacerbations of ankylosing spondylarthritis.

AGE INCIDENCE

From a consideration of the history of any particular case it was sometimes difficult to decide when the onset of ankylosing spondylarthritis occurred. For this reason the age at which the first rheumatic symptoms occurred, and the age at the onset of symptoms in the back, are presented in Table 3.

TABLE 3

The age at onset of rheumatic and back symptoms in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Age in years</th>
<th>0-15</th>
<th>-20</th>
<th>-25</th>
<th>-30</th>
<th>-35</th>
<th>-40</th>
<th>-45</th>
<th>-50</th>
<th>-55</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of rheumatic symptoms</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Onset of back symptoms</td>
<td>0</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>
The ages at onset shown in Table 3 correspond closely to the average findings of other workers.

LABORATORY DATA

SERUM PROTEINS

Estimations of the levels of total protein, albumen and globulin in the serum were made in 22 of the 26 cases. The method used was that of Hawk & Bergein (1938).

Total Serum Proteins

8.6 g.% and 5.6 g.% were regarded as the upper and lower limits of normal for the total serum protein. In 1 case the total protein level was above the upper limit of normal, and in 5 cases it was below the lower limit of normal. The distribution is shown in Table 4.

TABLE 4

<table>
<thead>
<tr>
<th>Total protein in g.%</th>
<th>below 4.6</th>
<th>4.6 to 5.0</th>
<th>5.1 to 5.5</th>
<th>5.6 to 6.0</th>
<th>6.1 to 6.5</th>
<th>6.6 to 7.0</th>
<th>7.1 to 7.5</th>
<th>7.6 to 8.0</th>
<th>above 8.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>22</td>
</tr>
</tbody>
</table>

The total serum protein levels in 22 cases of ankylosing spondylarthriti
Serum Albumen

6.7 g.% and 3.4 g.% were regarded as the upper and lower limits of normal for the serum albumen. In no case was the level above the upper limit of normal, whereas in 4 cases the levels were below the lower limit of normal.

The mean albumen level was 4.2 g.%.
The distribution is shown in Table 5.

TABLE 5

The serum albumen levels in 22 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Serum Albumen in g.%</th>
<th>below 2.6</th>
<th>2.6 to 3.0</th>
<th>3.1 to 3.5</th>
<th>3.6 to 4.0</th>
<th>4.1 to 4.5</th>
<th>4.6 to 5.0</th>
<th>5.1 to 5.5</th>
<th>5.6 to 6.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>22</td>
</tr>
</tbody>
</table>

Serum Globulin

2.9 g.% and 1.2 g.% were regarded as the upper and lower limits of normal for the serum globulin. In 4 cases the levels were above the upper limit of normal, whereas in no case was the level below the lower limit of normal.

The mean globulin level was 2.4 g.%.
The distribution is shown in Table 6.
TABLE 6

The serum globulin levels in 22 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Serum Globulin in g.%</th>
<th>below 1.1</th>
<th>1.1 to 1.5</th>
<th>1.6 to 2.0</th>
<th>2.1 to 2.5</th>
<th>2.6 to 3.0</th>
<th>3.1 to 3.5</th>
<th>3.6 to 4.0</th>
<th>4.1 to 4.5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>22</td>
</tr>
</tbody>
</table>

The Albumen : Globulin Ratio

The normal range of the albumen : globulin ratio (A : G ratio) was considered to be from 4:1 to 1.2:1. In all cases except 1 the A : G ratio was within normal limits, and in this 1 case it was below the level regarded as the lower limit of normal.

The mean A : G ratio was 1.8:1. The distribution is shown in Table 7.

TABLE 7

The A : G ratio in 22 cases of ankylosing spondylarthritis.

<table>
<thead>
<tr>
<th>A:G ratio</th>
<th>below 1.1:1</th>
<th>1.1:1 to 1.5:1</th>
<th>1.6:1 to 2.0:1</th>
<th>2.1:1 to 2.5:1</th>
<th>2.6:1 to 3.0:1</th>
<th>3.1:1 to 3.5:1</th>
<th>3.6:1 to 4.0:1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td>0</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>22</td>
</tr>
</tbody>
</table>
Thus in these cases the total serum protein level tended to be low, with the albumen fraction low and the globulin fraction high. These findings confirm those of Pemberton & Scull (1943) and Parr & Shipton (1946), and are in disagreement with those of Simpson & Stevenson (1949).

**ERYTHROCYTE SEDIMENTATION RATE**

Westergren's method, as described by Whitby & Britton (1939), was used for estimating the erythrocyte sedimentation rate (E.S.R.).

The results are shown in Table 8.

**TABLE 8**

The erythrocyte sedimentation rates in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>ESR in mm/hr</th>
<th>0-10</th>
<th>-20</th>
<th>-30</th>
<th>-40</th>
<th>-50</th>
<th>-60</th>
<th>-70</th>
<th>-80</th>
<th>above 80</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>26</td>
</tr>
</tbody>
</table>

Below 7 mm. per hour was regarded as a normal rate, 7 to 15 mm. per hour as a doubtfully increased rate, and above 15 mm. per hour as a definitely increased rate of fall.

Out of 26 cases the rate of fall was normal in 2, possibly abnormal in 6 and definitely abnormal in 18 cases.

An estimation of the activity of the disease process was made in each case from an evaluation of the symptoms and signs. The disease process was classed as inactive in 1 case, as very slightly
active in 6 cases, as slightly active in 6 cases and as moderately active in 13 cases.

The relationship between the estimated degree of activity and the E.S.R. is shown in Table 9.

**TABLE 9**

The degree of activity and the E.S.R. in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Degree of activity</th>
<th>E.S.R. in mm. per hr.</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Doubtfully increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>None, or very slight</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Slight</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>1</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>26</td>
</tr>
</tbody>
</table>

This total shows that the more active cases tended to have an increased sedimentation rate, but there were some exceptions.

The results of Table 9, reduced to a two by two contingency table, are shown in Table 10.
TABLE 10

Results of Table 9 shown as a two by two contingency table

<table>
<thead>
<tr>
<th>Degree of activity</th>
<th>E.S.R. in mm. per hr.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal or doubtfully increased</td>
<td>Increased</td>
</tr>
<tr>
<td>None, or very slight</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Slight or moderate</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8</strong></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>

\[ \chi^2 = 5.0 \quad \text{P.is} > 0.02 \quad \text{and} \quad < 0.05 \]

Thus the relationship shown between the degree of activity and the E.S.R. would occur by chance alone less often than one in twenty times and more often than one in fifty times. These figures can be regarded as showing that there is a significant relationship between the two.

SERUM COLLOIDAL GOLD REACTION

The tests were carried out by Maclagan's modification of the technique of Gray as described in "Recent Advances in Clinical Pathology" (1947).

The results are shown in Table 11.
### TABLE 11

Results of the Serum Colloidal Gold Reaction in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Colloidal Gold Reaction</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>14</td>
</tr>
<tr>
<td>1+ Flocculation</td>
<td>5</td>
</tr>
<tr>
<td>3+ Flocculation</td>
<td>3</td>
</tr>
<tr>
<td>5+ Flocculation</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
</tr>
</tbody>
</table>

The results of the serum colloidal gold reaction and the degree of activity of the disease process were correlated. Reduced to a two by two contingency table, they are shown in Table 12.
TABLE 12

Relationship between the results of the Colloidal Gold Reaction and the clinical activity of the disease process in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Clinical Activity</th>
<th>Colloidal Gold</th>
<th>Flocculation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to +</td>
<td>++ to ++++++</td>
<td></td>
</tr>
<tr>
<td>Inactive, or very slight, or slight activity</td>
<td>12</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Moderate activity</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>7</td>
<td>26</td>
</tr>
</tbody>
</table>

$\chi^2 = 3.15$  \hspace{1cm} P. is $< 0.1$ and $> 0.05$.

The relationship shown between the results of the serum colloidal gold reaction and the clinical assessment of the activity of the disease process would occur by chance alone between one in ten and one in twenty times. The relationship, therefore, cannot be regarded as significant.

Thus from this series it appears that the colloidal gold is not of use to assist either in the diagnosis or in the assessment of activity of cases of ankylosing spondylarthritis.
BLOOD CELLS

Haemoglobin and Red Blood Corpuscles

In some cases a degree of anaemia was present. The haemoglobin varied from 10.2 g.% to 15.7 g.%, with an average value of 12.8 g.% (Table 13).

The red cell count varied from 3,800,000 per c.mm. to 5,400,000 per c.mm., with an average value of 4,700,000 per c.mm. (Table 14).

The mean corpuscular haemoglobin varied from 25.5 g.\% to 30.6 g.\% , with an average of 27.7 g.\%.

TABLE 13

The haemoglobin values in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Haemoglobin Values in g.%</th>
<th>10.1 to 11.0</th>
<th>12.0</th>
<th>13.0</th>
<th>14.0</th>
<th>15.0</th>
<th>over 15.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>26</td>
</tr>
</tbody>
</table>
TABLE 14

The red cell count in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Red Cell Count in millions per c.mm.</th>
<th>3.6 to 4.0</th>
<th>-4.5</th>
<th>-5.0</th>
<th>-5.5</th>
<th>-6.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>

No haemtocrit readings were carried out, but from the mean corpuscular haemoglobin values and the appearances of stained films the anaemia was seen to be of a hypochromic normocytic or microcytic type. This is in agreement with the findings of others.

White Cells

The Total White Cell Count

The total white cell counts varied from 3,700 per c.mm. to 16,900 per c.mm., with a count over 11,000 per c.mm. in 7 out of the 26 cases. This is in agreement with the findings of Dunham & Kautz (1941) and of Comroe (1944).

The Differential White Cell Count

In 6 of the 7 cases with counts over 11,000 per c.mm. the leucocytosis was caused by an absolute increase in the neutrophils, the lymphocytes remaining within
normal limits. In the 7th case there was an absolute increase in both neutrophils and lymphocytes. In no other case was there a lymphocytosis above 4,500 per c.mm. but in 4 cases there was a decrease in the lymphocytes to less than 1,000 per c.mm. The significance of the latter finding is not apparent.

There was a slight monocytosis in 2 cases (1,000 per c.mm. and 676 per c.mm.) in both of which the disease process was moderately active.

A slight eosinophilia occurred in 2 cases, the highest being 1,089 per c.mm. Campbell (1947) reported an eosinophilia of 5% in 2 out of 25 cases, and he attached significance to this finding as indicating an allergic basis for the disease process. It is not considered that the findings in this series can be given any such significance, and it is doubtful if he was justified in doing so.

The Cooke Count

The Cooke count, carried out as described by Cooke & Ponder (1927), was normal in 8 cases. There was a "shift to the left" in 17 cases (66%) and "a shift to the right" in 1 case. There was a larger percentage showing a "left shift" in this series than in that of Parr & Shipton (1946), who found it to be present in 50% of their cases.

The presence or absence of a "shift to the left" was correlated with the clinical assessment of the degree of activity, and the results expressed as a two by two contingency table, as shown in Table 15.
TABLE 15

Correlation of a "shift to the left" with the activity of the disease in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Clinical Activity</th>
<th>&quot;Shift to left&quot;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>None, very slight or slight</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Moderate</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

\[
\chi^2 = 4.18 \quad \text{N}=1 \quad \text{P. is } < 0.05 \text{ and } > 0.02
\]

The relationship shown between the presence or absence of a "shift to the left" and the degree of activity of the disease would occur by chance alone less than one in twenty times and the relationship may therefore be regarded as significant.

The figure for the relationship between the E.S.R. and the activity of the disease is higher than that for the relationship between the presence or absence of a "left shift" and the activity of the disease. Thus in this series an increased E.S.R. bears a closer relationship to the activity of the disease than the presence or absence of a "shift to the left" in the neutrophil cells.

THE SERUM PHOSPHATASES

The phosphatase activity was estimated by the method of King, as described in "Recent Advances in Clinical Pathology" (1947). The normal values
are stated to be from 0.5 units to 2.0 units (occasionally up to 4.0 units) for the acid phosphatase, and from 3.0 units to 10.0 units (occasionally up to 13.0 units) for the alkaline phosphatase.

The Serum Acid Phosphatase

The results of the estimation of the serum acid phosphatase activity in this series are set out in Table 16.

**TABLE 16**

The serum acid phosphatase activity in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Serum Acid Phosphatase Activity in Units</th>
<th>0 to 1.0</th>
<th>-2.0</th>
<th>-3.0</th>
<th>-4.0</th>
<th>-5.0</th>
<th>-6.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>

In this series the serum acid phosphatase activity was 2.0 units or less in 13 cases. It was between 2.1 and 4.0 units in 11 cases, and in 2 cases it was over 4.0 units.

The Serum Alkaline Phosphatase

The results of the serum alkaline phosphatase activity are set out in Table 17.
TABLE 17

The serum alkaline phosphatase activity in 26 cases of ankylosing spondylarthritis

<table>
<thead>
<tr>
<th>Serum Alkaline Phosphatase Activity in Units</th>
<th>3.1 to 5.0</th>
<th>-7.0</th>
<th>-9.0</th>
<th>-11.0</th>
<th>-13.0</th>
<th>-15.0</th>
<th>-17.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>

In 18 cases the serum alkaline phosphatase activity was 10.0 units or below, in 4 cases it was between 10.0 units and 13.0 units and in 4 cases it was over 13.0 units.

Thus both the serum acid phosphatase and the alkaline phosphatase activity tended to be a little high, but were never greatly raised.

**X - RAY CHANGES**

Nothing relevant to the consideration of the aetiology of ankylosing spondylarthritis emerged from a study of the X - ray appearances in the spine and pelvis in this series of cases, and therefore a description of these appearances has not been included.

It is thought that involvement of the hip and shoulder joints, and of the peripheral joints, is of some importance, and the findings concerning these joints are therefore given.
HIP JOINT AND SHOULDER JOINT INVOLVEMENT

On clinical examination, there was no movement possible at the hip joints in 3 cases, and in all these there was X-ray evidence of bony ankylosis of both hips. There was moderate or marked limitation of movement in a further 4 cases, and in all these there was X-ray evidence of changes in the joints. In a further 14 cases there was very slight limitation of one or more hip movements (flexion in 8, internal rotation in 7, extension in 6 and external rotation in 5). Only 5 of these 14 cases showed X-ray evidence of hip joint involvement.

Thus hip movements were full in only 5 cases, whereas there was no X-ray evidence of abnormality in 14 cases.

Apart from complete bony ankylosis the X-ray appearances consisted of irregularity and erosion of the articular surfaces of the acetabulum and head of the femur, slight pseudocysts as seen in very early osteo-arthritis, narrowing of the joint space and lipping. Apart from the cases in which complete bony ankylosis had occurred the changes resembled those of osteo-arthritis more than atrophic arthritis. This tends to confirm the findings of Miller (1936) rather than those of Dunham & Kautz (1941).

The movements at the shoulder joints were full in 16 cases. In the remaining 10 cases there was very slight limitation of internal rotation, external rotation or abduction. There was no X-ray evidence of abnormality in any case. Polley & Slocumb (1947) found evidence of hip joint involvement in 28% of their large series of cases and in a quarter of these (7% of the series) there was also shoulder involvement.

In the present series, if slight limitation of one movement is considered to be evidence of joint involvement, there was clinical evidence of hip joint involvement in 81% and of shoulder joint involvement in 38% of cases. There was X-ray evidence of hip joint abnormality in 46% of cases, but no X-ray evidence of shoulder joint abnormality in any case.
KNEE JOINT INVOLVEMENT

In 2 of the 26 cases there was no movement possible at the knee joints; in one of them the X-ray films showed bony ankylosis and in the other there were marked changes in the joints, with great narrowing of the joint spaces and also minor lipping of the bones. In 1 case there was a flexion deformity at the hip and knee joint in one leg with limitation of extension in the knee. X-ray films of the knee showed no abnormality. In 1 further case knee flexion was about 50% limited, the only change shown on X-ray being marked osteoporosis. There was slight limitation of flexion of one or both knees in 3 further cases; in only 2 of them were there abnormal X-ray appearances, and these consisted of very slight lipping as seen in osteo-arthritis. In the remaining 19 cases there was no clinical or X-ray evidence of abnormality in the knee joints.

Thus there was some limitation of movement of one or both knee joints in 7 cases, and abnormal X-ray appearances were present in 5 cases.

IN Volvement of OTHER JOINTS

There was no clinical or X-ray evidence of involvement of any other joints except that in one case there was some limitation of ankle movements. There was no evidence of involvement of the elbows, wrists or small joints of the hands or fingers in any case.

This is in agreement with the findings of Buckley (1945) and McWhirter (1945), but it is in conflict with the main weight of evidence available in the literature.

As already discussed, it is possible that the method of selection of cases accounts for the conflicting findings in the literature, and also for the findings in this series. All the cases
in this series had been diagnosed as cases of ankylosing spondylarthritis by physicians or surgeons in the Leicester Royal Infirmary, and had been referred to the radio-therapy department. It is possible that if cases classified in the hospital records as rheumatoid arthritis had been examined there might have been cases among them in which, besides typical rheumatoid changes in the peripheral joints, there were also X-ray changes in the sacro-iliac joints and spine which fulfilled the criteria necessary for making a diagnosis of ankylosing spondylarthritis.

ASSOCIATED DISEASES

RHEUMATIC FEVER

As was pointed out in Section 1 (Page 34), from an analysis of the cases of several authors, it was found that about 12% of cases had previously suffered from rheumatic fever. There was a history of rheumatic fever in 2 (8%) of the 26 cases in this series. In one case the disease started with an attack of acute rheumatism in the feet, hands and knees, the history being consistent with that of rheumatic fever; following this the patient began to get pains in the back. The other patient had an attack of acute rheumatism affecting the hands, knees, feet and shoulders, and four years later developed pains in the back.

CARDIO - VASCULAR DISEASE

There was no clinical evidence of rheumatic heart disease in any case. In 2 cases there was a systolic murmur at the apex, but in neither was there any clinical or X-ray evidence of cardiac disease. It was noted before (Page 34), that Baggenstross & Rosenberg (1941) thought that
clinical studies were not sufficient for the accurate diagnosis of rheumatic heart disease, and that a higher incidence of rheumatic heart disease was found in post-mortem examinations of 30 cases of rheumatoid arthritis (Rosenberg, Baggenstross & Hench, 1943) than had been shown in any clinical investigation.

In this series no other abnormality of the cardio-vascular system was recognised except, in one case, extra systoles for which no cause was found, and in another, a mild degree of hypertension with no evidence of cardiac enlargement or kidney disease.

GONORRHOEA

In no case was a history of gonorrhoea or any clinical evidence of a gonorrhoeal infection obtained. The gonorrhoeal complement fixation test gave negative results in 24 cases; in 1 case the result was doubtful, but on repetition was negative; in 1 case there was a low positive result confirmed on repetition, but further questioning and examination of the patient produced no evidence of a past or present gonorrhoeal infection. This supports the view of Dawson (1935), Tyson (1937) and Buckley (1945) that there is no special relationship between ankylosing spondylarthritis and gonorrhoea.

SYPHILIS

There was no history of syphilis in any case, nor was any evidence of a healed or active syphilitic lesion found. The Kahn test and Wassermann reaction were both negative in 23 cases. In 3 cases the Wassermann reaction was classed as doubtful but the Kahn test was negative, and on repetition of the Wassermann reaction a negative result was obtained.
**TUBERCULOSIS**

One case developed hyperplastic tuberculosis of the ileo-caecal region six years after the onset of ankylosing spondylarthritis. This was successfully treated by surgery and he has developed no evidence of any further tuberculous lesion. Apart from this no case had a history or clinical evidence of active tuberculous disease.

In all cases the chest was X-rayed and in none was there any radiological evidence of pulmonary tuberculosis.

Thus there is no evidence that tuberculosis is related to ankylosing spondylarthritis. This was also the view formed from a study of the available evidence in the literature (Page 40).

**NON-TUBERCULOUS PULMONARY DISEASE**

Only 2 cases had a history or symptoms of pulmonary disease. One had had pneumonia four years before the onset of ankylosing spondylarthritis, and had had cough and morning sputum from that time. The other had had a cough and sputum in the winter for the preceding five years. The cough started one year before the onset of back symptoms. In neither case were there any physical signs or X-ray evidence of pulmonary disease.

**GENITOURINARY DISEASE**

The theory of Forestier (1939) about the causation of ankylosing spondylarthritis, and the opinion of Dunham & Kautz (1941) that a chronic urinary tract infection was often present have been reviewed above (Page 38).
In this series in only 2 cases was there a history of any genito-urinary disease. One had a history of having had an attack of renal colic lasting for three weeks. This had occurred eleven years previously and he had had no recurrence. The other had had acute orchitis three years before the onset of symptoms of ankylosing spondylarthritis.

The urine was examined in all cases and in none was there any albumen, sugar, pus cells or other pathological deposit, and no organisms were seen in direct smears in any case.

**BRUCELLOSIS**

As was seen previously (Page 41), it was Goldfain's (1943) opinion that chronic brucellosis was a cause of ankylosing spondylarthritis in some cases, although, after considering the evidence put forward by him together with other available evidence, it was concluded that the point had not been proved.

In 16 cases of the present series, agglutination tests were performed, using Dreyer's Standard Agglutination Method, as described by Mackie & McCartney (1949), using strains of Br. abortus and Br. melitensis. In no case was there any agglutination. It is realised that brucella infection may be present without the serum agglutination test being positive. However, in the present series there was no clinical evidence suggestive of brucellosis in any case.

**FOCAL SEPSIS**

**Oral Sepsis**

Six cases were edentulous. Of the remaining 20 cases 2 had signs of gross periodontal infection and 3 others
evidence of a mild degree of periodontitis.

**Middle Ear Disease**

One case had chronic otitis media; evidence of ear disease started three years after the onset of his first rheumatic symptoms and two years before the onset of his back symptoms. Another case had chronic otitis media for seven years which cleared up following mastoidectomy; the operation was performed two years before the onset of symptoms of ankylosing spondylarthritis.

**Nasal Infection**

Seven of the 26 cases gave a history of chronic nasal catarrh. In 1 of these no abnormality was found on clinical examination, but in 6 of them clinical evidence of chronic rhinitis or sinusitis was present. Similar evidence was also present in 3 further cases who did not complain of symptoms. Thus there was clinical evidence of the presence of chronic rhinitis or sinusitis in a total of 9 cases.

The sinuses of 23 cases were X-rayed. (These included all those mentioned above, but the reasons why 3 cases were not X-rayed were fortuitous and the history of chronic nasal catarrh was not a factor influencing the selection of cases which were to be X-rayed). In 6 cases there was evidence of mucosal swelling at the base of one or both antra, but no other abnormality. In 2 cases the appearances were those of encysted fluid or a polyp in one antrum, and in 1 of these cases there was also the appearance of mucosal swelling in the opposite antrum. In 6 cases there was increased opacity of the whole of one antrum, and in 4 of these there was evidence of abnormality in the opposite antrum. In 1 case both antra and both frontal sinuses were opaque and there was increased
density in the right ethmoid region.

Thus out of 23 cases there were symptoms of nasal disease in 7 cases (30%). There was clinical evidence of chronic rhinitis or sinusitis in 9 cases (39%). There was X-ray evidence of a pathological process of the sinuses in 15 cases (65%) and in 9 of these (or in 39% of the total series) this was more than mucosal thickening alone. Taking the clinical and X-ray evidence in combination chronic nasal infection was considered to be present in 10 cases (43%).

A control series of 25 males, in which the age distribution was comparable to that in the spondylarthritic series, was questioned and examined. The two series were not strictly comparable in that the control group was composed of British personnel in Berlin in the summer. For comparison the findings in the two series are set out in Table 18.

It was felt that the interpretation of the X-ray appearances of mucosal thickening were so dependent on the individual observer that these appearances should not be regarded as evidence of sinus pathology and therefore, in the absence of other clinical evidence of nasal disease, they have been disregarded.
TABLE 18

The findings from rhinological examination of 23 cases of ankylosing spondylarthritis and of 25 controls

<table>
<thead>
<tr>
<th>Findings</th>
<th>Percentage number of cases of ankylosing spondylarthritis</th>
<th>Percentage number of control series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of nasal disease</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>Clinical evidence of chronic rhinitis or sinusitis</td>
<td>39%</td>
<td>20%</td>
</tr>
<tr>
<td>X-ray evidence of sinus pathology, excluding mucosal thickening</td>
<td>39%</td>
<td>12%</td>
</tr>
<tr>
<td>Evidence of chronic nasal infection</td>
<td>43%</td>
<td>28%</td>
</tr>
</tbody>
</table>

In order to see whether the finding of evidence of chronic nasal infection in the apparently high proportion of 43% of cases of ankylosing spondylarthritis was significant the number of cases with and without evidence of chronic nasal infection in both the spondylarthritic and the control group were arranged as a two by two contingency table. (Table 19.)
TABLE 19

The presence or absence of chronic nasal infection in 23 cases of ankylosing spondylarthritis and 25 controls

<table>
<thead>
<tr>
<th></th>
<th>Nasal Infection Present</th>
<th>Nasal Infection Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases of Spondylarthritis Group</td>
<td>10</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>No. of cases of Control Group</td>
<td>7</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>31</td>
<td>48</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.67 \quad P. \text{ is } < 0.5 \text{ and } > 0.3 \]

It can be seen from Table 19 that the figures found would have occurred by chance alone more often than three in ten times but less often than one in two times. No significance can therefore be attached to the finding of evidence of chronic nasal infection in 43% of cases of ankylosing spondylarthritis.

Including all forms of septic foci, there was evidence of focal sepsis present in 16 (62%) of the 26 cases.
IRITIS

There was a history of iritis in 5 (19%) of the 26 cases.

4 cases had had only one attack. This occurred in 1 case four years, in 2 cases five years and in the other case fourteen years after the onset of symptoms in the back. In only 1 of the 4 cases has any residual damage been left, causing the vision in one eye to be hazy. The 5th case had four attacks of iritis, each lasting about a month; three of the attacks occurred from one to seven years prior to the onset, and the last attack occurred one year after the onset of ankylosing spondylarthritis.

In no case was there any close time relationship shown between an attack of iritis and an exacerbation of the symptoms of ankylosing spondylarthritis.

ALLERGIC DISEASES

The fact that irido-cyclitis may be an allergic manifestation has already been discussed above (Page 50).

Excluding irido-cyclitis, and also chronic rhinitis and sinusitis, only 4 of the 26 cases had suffered from diseases in the causation of which allergy may play a part. 1 case had suffered from asthma since childhood, 1 suffered from migraine, and 2 had had skin diseases; one of the latter 2 cases had had flexural eczema, and the other contact dermatitis.

As has already been seen, a slight eosinophilia occurred in 2 cases.

Thus, scarcely anything is added to the scanty evidence put forward by Campbell (1947) (see Page 51) concerning the possible allergic nature of ankylosing spondylarthritis.
DEFICIENCY DISEASES

No patient gave a history of abnormal dietary habits, and no clinical evidence of any deficiency disease was found in any case.

FLUOROSIS

The fluorine content of the four main water supplies of the region from which the cases were drawn was stated by the Leicester City Health Department to be between 0.20 p.p.m. and 0.07 p.p.m. Water containing this amount of fluorine is not known to produce pathological changes in the teeth and bones.

The teeth of all the cases were examined to see if there was any evidence of chronic endemic fluorosis. This was the only investigation concerning the possible presence of chronic fluorine poisoning that was made in these cases.

6 cases were edentulous. Of the other 20 cases only 5 cases showed appearances suggestive of endemic fluorosis. These cases had small white opaque areas on the labial surfaces of the incisors, but in all cases these areas covered less than 25% of the tooth surface. This appearance, according to Dean & Arnold (cited by Stones, 1948) is due to a very mild form of endemic fluorosis. In no case did the teeth show changes suggesting a more advanced degree of fluorosis, and it is not certain that the appearances described in these cases were due to fluorine.

Thus, from the fluorine content of the local water supplies and from an examination of the teeth of the cases, there occurred no evidence to suggest that an excessive intake of fluorine was connected with the development of ankylosing spondylarthritis in this series of cases.
DISEASES OF OTHER SYSTEMS

There was no history or clinical evidence of any disease of the ductless glands, or of the nervous system in any case.

Diseases of the digestive system occurred in 3 cases. 2 cases suffered from duodenal ulceration, but in both of these the symptoms started after the onset of ankylosing spondylarthritis. In 1 case there was a history of ulcerative colitis. The symptoms started three years before the onset of symptoms of ankylosing spondylarthritis, and bleeding from the rectum continued intermittently for four years.

Thus there was no evidence suggesting an association between ankylosing spondylarthritis and diseases of the ductless glands, the nervous system or the digestive system in these cases, nor was there any evidence suggesting that any other disease might have such an association.
SECTION III

SUMMARY OF THE EVIDENCE FROM THE LITERATURE AND THE PRESENT SERIES

INCIDENCE

Sex Incidence

Literature. Male : Female = 6 : 1
Present series. Male : Female = 25 : 1

Familial Incidence

Literature. The disease has been reported in three siblings by one author, in twins by three authors, and in other family relationships by many authors.
Present series. Out of 29 cases, 5 pairs showed a close family relationship.

Occupational Incidence

Literature

& No special occupational incidence has been shown.
Present series.
Exposure and Trauma

Literature
There is no evidence that exposure and trauma have a connection with the onset or exacerbations of ankylosing spondylarthritis in any significant number of cases.

Present series. No particular physical type was recognised with special frequency.

Type of Individual Affected

Literature. The evidence is conflicting.

Present series. No particular physical type was recognised with special frequency.

Social Hardship and Abnormal Mental Stress

Literature. No references were found.

Present series. It was concluded that adverse social situations and periods of mental stress bear no more than a chance relationship to the onset or exacerbation of symptoms of ankylosing spondylarthritis.

Housing Conditions

Literature. No references were found.

Present series. In the majority of cases these were satisfactory.
Age Incidence

Literature & The onset most commonly occurs during the third decade.
Present series.

LABORATORY INVESTIGATIONS

Serum Proteins

Literature. The evidence is conflicting.
Present series. The total serum protein level tended to be low, the albumen level being slightly lowered and the globulin level being slightly raised.

Erythrocyte Sedimentation Rate (E.S.R.)

Literature. The E.S.R. is raised in the majority of active cases.
Present series. In 69% of cases the E.S.R. was over 15 mm. per hr. A significant relationship was shown between the E.S.R. and the activity of the disease process.

Colloidal Gold Reaction

Literature. No references were found.
Present series. No flocculation occurred in 54% of cases.
No significant relationship was shown between the results of this test and the activity of the disease.

**Blood Cells**

**Literature** & Present series:

There is frequently a mild anaemia, and a mild leucocytosis is found in some cases.

**The Cooke Count**

**Literature.** Parr & Shipton found a "shift to the left" in 50% of their cases.

**Present series.** There was a "shift to the left" in 66% of cases. A significant relationship was shown between a "shift to the left" and the activity of the disease, but this was not so close as that shown between the E.S.R. and the activity of the disease.

**The Serum Phosphatases**

**Literature.** In the majority of cases the serum acid and alkaline phosphatase levels are within normal limits. The levels are certainly never increased to any great extent.

**Present series.** The activity of both the acid and alkaline phosphatase tended to be a little increased, but never to any great extent.
PATHOLOGY

Literature. Histological changes similar to those which occur in chronic inflammatory processes are found in the apophyseal joints. No evidence of an inflammatory process has been found in the discs.

Present series. No material for pathological examination was available.

X - RAY APPEARANCES

Sacro - Iliac and Apophyseal Joint Changes

Literature & The changes that occur in the sacro - iliac and apophyseal joints are essentially similar and occur almost invariably bilaterally.

Present series.

Hip Joint Changes

Literature. These changes sometimes resemble those of atrophic arthritis and sometimes those of osteo - arthritis.

Present series. The changes resembled osteo - arthritis rather than atrophic arthritis.
RELATIONSHIP to RHEUMATOID ARTHRITIS

Literature. Despite some points of difference the evidence suggests that ankylosing spondylarthritis and rheumatoid arthritis are essentially similar processes.

Present series. No additional evidence was forthcoming.

RELATIONSHIP to RHEUMATIC FEVER

Literature. The average number of cases, in different series, in which there was a history of rheumatic fever was 12%.

Present series. There was a history of rheumatic fever in 8% of cases. There was no clinical evidence of rheumatic heart disease in any case.

INFECTIONS

Streptococcal Infection

Literature. There is no direct evidence to suggest that infection with \( \beta \)-haem. streptococci is related to ankylosing spondylarthritis.

Present series. No relevant evidence was provided.
Gonococcal Infection

Literature. There is no evidence to suggest that gonococcal infection is related to the aetiology of ankylosing spondylarthritis in more than a small percentage of cases.

Present series. There was no evidence of gonococcal infection in any case.

Genito-Urinary Infection

Literature. There is not sufficient evidence to show that the hypothesis of a genito-urinary infection being the primary source of infection in ankylosing spondylarthritis is true.

Present series. There was no evidence of the presence of a urinary infection in any case.

Tuberculosis

Literature

There is no evidence to support the view that tuberculosis is related to ankylosing spondylarthritis.

Present series.
**Brucellosis**

**Literature.** Goldfain (1943) thought that brucellosis was the cause in some cases, but from the evidence in his paper it was not considered that this had been proved.

**Present series.** There was no evidence of a brucella infection in any case.

**Focal Sepsis**

**Literature.** There is no evidence to show that focal infection is a factor of importance in the aetiology of ankylosing spondylarthrosis.

**Present series.** There was evidence of the presence of some form of focal sepsis in 62% of cases. When one form, chronic nasal infection, was investigated with a control series, it was found that it was not present in a significantly high proportion of cases of ankylosing spondylarthrosis.

**ALLERGY**

**Literature** & **Present series.** There is no direct, only scanty indirect, evidence to support the view that ankylosing spondylarthrosis is due to an allergic reaction to infection.
DIETARY DEFICIENCY

Literature

There is no evidence to show that a deficiency of any specific factor causes ankylosing spondylarthritis.

Present series.

FLUOROSIS

Literature. A study of the evidence leads to the conclusion that the aetiology of ankylosing spondylarthritis is not connected with the intake of an excess of fluorine.

Present series. There were no changes suggestive of fluorosis in the teeth of the cases, and the water supplies in the locality did not contain an excessive quantity of fluorine.

SULPHUR METABOLISM

Literature. No association between the aetiology of ankylosing spondylarthritis and sulphur metabolism has been proved to exist.

Present series. There was no applicable evidence.
THE DUCTLESS GLANDS

An increased excretion of 17-ketosteroids (see Page 28) in males with ankylosing spondylarthritis has been found. This suggests a relationship between ankylosing spondylarthritis and the functions of the adrenal cortex.

Recent work has shown that there is some connection between rheumatoid arthritis and adrenal cortex hormones (see Page 60).

Present series. There were no relevant findings.
DISCUSSION

There are certain facts which suggest that ankylosing spondylarthritis is due to a chronic infective process. The constitutional effects are consistent with this hypothesis, and so are the blood changes. There is frequently a mild microcytic hypochromic anaemia, and also a slight polymorph increase with a "shift to the left" in some cases. The evidence in the literature concerning the serum proteins is conflicting, but in the present series the serum albumen tended to be lowered, and the serum globulin raised. Other workers have recorded similar findings. The increase in the globulin fraction could be due to the presence of an infective process leading to an increase in the amount of circulating antibodies, and the lowered albumen level could be caused by interference with albumen production in the liver due to chronic infective factors. However, the changes in the serum proteins could also be accounted for as being due to metabolic changes; it has been shown that in animals a lowered serum albumen and a raised serum globulin follow hypophysectomy (Pemberton & Scull, 1943) and adrenalectomy (Levin & Leathem, cited by Forsham, Thorn, Prunty & Hills, 1948). There is an increased erythrocyte sedimentation rate in the majority of active cases of ankylosing spondylarthritis. It is often assumed that an increase in the sedimentation rate indicates the presence of an active infective process. However, an alteration in rate depends on a modification of the colloidal medium suspending the cells, and anything which causes an alteration in the protein composition of this fluid may cause alterations in the sedimentation rate. Lastly, the observed histological changes in the apophyseal joints in ankylosing spondylarthritis are similar to those found in a chronic infective process. However, there is no evidence to prove that ankylosing spondylarthritis is due to an infective process, and none to show that any one known organism is the infecting agent.
An argument supporting the view that ankylosing spondylarthritis is due to an allergic reaction to infection can be put forward, built up on the following way. It is known that arthritis, simulating proliferative arthritis in man, can be produced in animals by an allergic mechanism, and several workers consider that rheumatic joint diseases are due to an allergic reaction to bacterial infection. As has been pointed out, (see Page 33), there are some facts to support the opinion that rheumatic fever and rheumatoid arthritis are due to a similar process, and the main weight of the evidence in the literature supports the view that rheumatoid arthritis and ankylosing spondylarthritis are related. Following the work of Rich & Gregory (1943a, 1943b, 1944, 1946), it is generally accepted that rheumatic fever is caused by an allergic mechanism. Therefore it may be assumed that ankylosing spondylarthritis is due to allergy. As can be seen, this argument is based on very indirect evidence. The role that focal sepsis plays in ankylosing spondylarthritis is doubtful, but the facts suggest that it is not an important factor. When all the evidence suggesting that ankylosing spondylarthritis is due to an allergic reaction to infection has been collected, it is found to be very far from conclusive.

Some authors consider that arthritis has a biochemical rather than a bacterial cause and the relief which is obtained by patients with rheumatoid arthritis during jaundice and pregnancy points to this conception. Arguments, based on scanty evidence, suggesting that there is some linkage between endocrine functions and arthritis in man, have been put forward by Pemberton & Scull (1943). The evidence in the paper suggests that the pituitary gland, in particular, plays a part in the relationship. The recent work of Hench, Kendall, Slocumb & Polley (1949) shows that there is a connection between rheumatoid arthritis and a hormone of the adrenal cortex.

In ankylosing spondylarthritis, there is no clinical evidence of the presence of any syndrome which is due to abnormal function of any particular ductless gland. However, it has been shown that there is an increased excretion of 17-ketosteroids in males with ankylosing
spondylarthritis as compared with normal males ( see Page 28 ), which suggests that the disease may be connected in some way with the adrenal cortex. It has also been shown that 1 case of rheumatoid spondylitis ( ankylosing spondylarthritis ) responded to treatment with an adrenal cortical hormone in the same way as cases of rheumatoid arthritis ( Page 31 ). In view of the fact that the available evidence suggests that rheumatoid arthritis and ankylosing spondylarthritis are similar processes ( Page 33 ) it is considered likely that further cases of ankylosing spondylarthritis will be found to respond in the same way, in which case a connection between ankylosing spondylarthritis and the adrenal cortex would be proved. It has already been mentioned that the changes in the serum proteins and the erythrocyte sedimentation rate could be accounted for as being due to metabolic changes ( Page 110 ).

The occurrence of ankylosing spondylarthritis in three siblings, and in identical twins, has been reported, and in the present series a high familial incidence was shown. The most feasible explanation of this finding seems to be that there is some inborn condition of metabolism which causes the disease process to develop. It could be argued that the inherited factor is a lowered resistance to infection, but this seems less likely. It might also be argued that the inborn factor is one which makes the subject liable to develop allergic reactions, but the case histories in the present series did not show that the other members of the families concerned were particularly liable to suffer from allergic manifestations.

One further possible speculation will be mentioned. The findings of various workers suggest that there is a connection between antibody formation and adrenal cortical activity ( Hadfield & Garrod, 1947 ). It seems probable that ankylosing spondylarthritis will be shown to be connected with a metabolic change dependent on pituitary and adrenal function. The manner in which this is brought about by the pituitary and adrenal glands may be by the production of a state of hypersensitivity; the latter state in turn causing the development of the rheumatic manifestations.
CONCLUSION

The aetiology of ankylosing spondylarthritis is still unknown. The paucity of positive evidence which has resulted from the considerable volume of research suggests that the various hypotheses concerning the aetiology of ankylosing spondylarthritis which have so far been put forward are probably not true. It has been possible to discount some of these hypotheses, and to show that others are unlikely. For reasons given in the discussion it is felt that the results of the recent work on the effect of 17-hydroxy-11-dehydrocorticosterone on rheumatoid arthritis and rheumatic fever are likely to be applicable to ankylosing spondylarthritis, and that this work, together with that on 17-ketosteroid excretion in ankylosing spondylarthritis, has indicated a field of research from which will be drawn facts that will eventually lead to a knowledge of the aetiology of ankylosing spondylarthritis.
APPENDIX

It is considered that no useful purpose would be served by including the full case sheets of all the patients, but it is felt that some evidence on which the diagnoses are based should be presented. Therefore for each case the following findings are set out in this appendix:-

a) A brief history of the main rheumatic and spondylarthritic symptoms.

b) The main physical signs of back and joint disease, and

c) a photograph of one X-ray film for each case.

(The figure, given in parentheses, recording the measurement of lumbar and thoracic back movement in each case, was obtained by measuring the distance from the seventh cervical spine to the coccyx, firstly with the back extended as far as possible and secondly flexed as far as possible, and subtracting the former from the latter. The figure given is the difference between the two measurements expressed in inches. The average value for normal controls is 6 in.).
CASE No. 1

Male, aged 39 years.

History

There was a sudden onset of pain and weakness in the right leg at the age of sixteen. He was in bed for four weeks. The pain then improved, but did not go completely. At the age of twenty-two he began to get pain, stiffness and tenderness in the back. This occurred in all parts of the back from the neck to the sacral region. It continued, with exacerbations and remissions, until, at the age of thirty-six, he got very wet at a harvest camp. Following this the pain and stiffness in the back became very much more severe, and he began to develop a thoracic kyphosis. The symptoms continued to be severe for the next two years, but since that time they have improved.

Condition on Examination

There is slight thoracic kyphosis.

There is slight limitation of movement of the lumbar and thoracic regions of the spine (4 in.). Movements of the cervical region are full.

The movements of all the other joints are full. Chest expansion 1 3/4 in. Vital Capacity 3,100 cc.
CASE No. 2

Male, aged 37 years.

History

He developed some swelling and weakness in the left knee at the age of twenty-six. This recurred at intervals for three years and then cleared up. At the age of thirty he began to get aching pains in the lower part of the spine. He was stiff on getting up in the mornings, but this became less with exercise.
He suffered from gradually increasing pain and stiffness in the back, with exacerbations and remissions, until the age of thirty-five. He has gradually improved for the past two years. His back is now stiff and he gets a little aching in the back at times.

**Condition on Examination**

There is thoracic scoliosis and kyphosis.

There is very marked limitation of movement of the lumbar spine and no movement of the thoracic spine can be demonstrated (1 1/8 in.). There is marked limitation of movement of the cervical spine.

Flexion of both hip joints is a little limited, and there is slight limitation of the movements of both shoulder joints. The movements of all other joints are full.

Chest expansion 1/2 in. Vital Capacity 2,000 cc.
CASE No. 3

Male, aged 63 years.

History

He has had periodic attacks of sciatica occurring approximately every ten years since the age of twenty. He has noticed an increasing thoracic kyphosis and stiffness of the back for the past ten years. He has had pain in the back for the past five years. This started in the lumbar region and has since spread up to the neck. The pain is worst on getting out of bed in the mornings, and improves with movement. There has been some improvement in the pain in the past few months, although he still gets some in the neck and the upper thoracic region of his back.

Condition on Examination

There is thoracic kyphosis and loss of lumbar lordosis.

The movements in the lumbar and thoracic region of the back are very limited (1 1/4 in.), and there is moderate limitation of neck movements.

Flexion of the left hip joint is a little limited, and there is slight limitation of external rotation of the right shoulder joint. The movements of all the remaining joints are full.

CASE No. 4

Male, aged 30 years.

History

He had some aching pain in the lumbar region of his back for two months at the age of eighteen. This cleared up with physiotherapy. It recurred at the age of twenty-three and he began to notice some stiffness of his back. (The pain was an aching one and was severe in bed at night. He had difficulty in getting out of bed and improved after he had been...
up for about an hour. He also had some pain spreading down the right thigh.

**Condition on Examination**

There is very little movement in the thoracic and lumbar region of the back (1 1/2 in.), and cervical movements are a little limited.

All movements of the right hip joint are markedly limited, and flexion of the left hip is a little limited. The movements of the left shoulder joint are a little limited. The movements of the remaining joints are full.

Chest expansion 1 in. Vital Capacity 3,000 cc.
CASE No. 5

Male, aged 37 years.

History

He developed an acute attack of lumbago at the age of twenty-nine. This cleared completely after ten days. Two years later he began to get an aching pain in the front of the left thigh and a few months later pain and stiffness started in the lumbar region of his back. The pain prevented him from sleeping. He was very stiff on getting up in the mornings, but this improved in an hour or so. His back has become progressively stiffer since that time. He now sometimes gets pain in the back between the shoulder blades, his neck, and the back of his right thigh and leg.

Condition on Examination

There is moderate limitation of movement of the lumbar and thoracic spine (3 in.), and slight limitation of neck movements.

There is slight limitation of flexion, internal and external rotation of the right hip joint and slight limitation of external rotation of the left hip joint. The movements of the shoulder and remaining joints are full.

CASE No. 6

Male, aged 28 years.

History

He developed stiffness and pain in the lumbar region of the back when aged twenty-six. The pain was worse on lifting. The symptoms were at their worst on getting out of bed in the mornings. He also developed slight pain and stiffness in the knees. The pain has since spread up the back to the upper thoracic region, and at present he gets some pain
and stiffness in the shoulders, back and knees.

**Condition on Examination**

There is definite limitation of the lumbar and thoracic region of the back (2 1/2 in.), with slight limitation of neck movements.

The movements of the other joints are full. Chest expansion 1 in. Vital Capacity 2,800 cc.

**CASE No. 7**

Male, aged 47 years.

**History**

He began to get pain in the sacral region of the back
at the age of thirty-seven. Three years later the pain began to move up the back and has continued to spread since. About eighteen months ago it began to affect his neck, and he now has pain from the sacrum to the neck. This is worst on getting up in the mornings and becomes better after he has been up for half an hour, but he is never free of pain. His back has become increasingly stiff for the past five years.

Condition on Examination

The spine is kyphotic.

There is no movement in the lumbar and thoracic spine (1 1/4 in.), and only slight movements are possible in the neck.

Extension and internal rotation of the hip joints are a little limited. There is slight limitation of shoulder joint movements. The movements of the remaining joints are full.

Chest expansion 1 1/8 in. Vital Capacity 3,800 cc.
CASE No. 8

Male, aged 47 years.

History

He had an attack of acute rheumatism affecting the hands, feet and knees at the age of thirty. He was unable to work for four months. Following this he developed pain in the mid-thoracic region of the back, and this continued with variable intensity until about two years ago. He had most pain at the
age of forty, at which time he first noticed that his back was becoming stiff. At present he only gets occasional discomfort in the lower thoracic region on movement.

Condition on Examination

There is gross limitation of movement of the lumbar and thoracic spine (1 1/4 in.) and moderate limitation of the cervical region.

There is no limitation of movements of the hips or shoulders, or other joints. Chest expansion 1 1/4 in. Vital Capacity 2,350 cc.
CASE No. 9

Male, aged 46 years.

History

He began to get pains in the hips at the age of thirty-four. These were made worse by exercise such as bicycling and climbing. They have continued intermittently since. At the age of forty-three he began to get pain in the upper lumbar region of the back, and his back became stiff. The stiffness was worse through the day. The pain has gradually spread up the back and for the past year he has had most pain in the neck.

Condition on Examination

Movement is absent in the thoracic and lumbar region (1 in.) and neck movements are very limited.

There is limitation of extension, internal and external rotation of the hip joints. There is slight limitation of abduction and external rotation at the shoulder joints. The movements of the remaining joints are full.

Chest expansion 1 in. Vital Capacity 2,300 cc.
CASE No. 10

Male, aged 30 years.

History

Pain started in the lumbar region of the back at the age of twenty-five. His back was stiff and painful in the mornings and improved after he had been up for a short while. He also had pain when he moved in bed at night. There has been some improvement in the past year, although he still gets some pain in the right hip and in the right thigh anteriorly.
Condition on Examination

There is no movement in the lumbar and thoracic region of the spine (1/2 in.). Very little movement is possible in the neck.

There is a flexion deformity of the right hip joint, and all movements of this joint are limited. Extension of the right knee joint is limited. Movements of the other joints are full. Chest expansion 1 in. Vital Capacity 2,500 cc.
CASE No. 11

Male, aged 34 years.

History

He developed aching pains in the left thigh at the age of twenty-one. These continued at intervals until he was twenty-six. At that time he began to get pain in the lower thoracic region of the back, and three years later he developed pain in both hips and groins. He noticed that his back was becoming stiff, especially on getting up in the mornings, and the pain in his back was at its worst at this time. It caused him to get out of bed at night and walk about. He now gets very little pain in the back. Most pain now occurs in the left hip.

Condition on Examination

There is some thoracic kyphosis.

There is no movement in the lumbar or thoracic spine (3/4 in.), and the cervical movements are very limited.

All movements of both hips are limited; those of all other joints are full. Chest expansion 1 1/4 in. Vital Capacity 2,000 cc.
CASE No. 12

Male, aged 52 years.

History

At the age of thirty - three he developed acute rheumatism affecting the hands, feet, shoulders and knees. He was unable to work for eighteen months. He continued to get slight pains in the joints for two years.

At the age of thirty - seven he had pain in the lumbar region of the back. He has had intermittent pains
in the back since that time, and his back has become gradually stiffer. The pain and stiffness are worst on getting out of bed, but the pain wears off with exercise. He has improved during the past three years. He now gets pain in the neck at times, and also sometimes in one or the other hip.

Condition on Examination

There is no movement in the lumbar and thoracic spine (7/8 in.), and cervical movements are very limited.

There is slight limitation of flexion and internal rotation of the right hip joint, and slight limitation of shoulder joint movements. Movements of the other joints are full. Chest expansion 1 in. Vital Capacity 2,100 cc.
CASE No. 13

Male, aged 24 years.

History

At the age of twenty-one he developed pain in the right hip and in the back of the right thigh. In a few months he developed similar pains in the left hip. He began to get pain and stiffness in the lower thoracic and lumbar region of the back at the age of twenty-two. The pain kept him awake at night and he had to roll out of bed in the mornings. The stiffness wore off through the day. These symptoms have continued to get worse since that time.

Condition on Examination

The movements of the thoracic and lumbar region of the spine are a little limited (3 1/2 in.).

The movements of other joints are full. Chest expansion 2 in. Vital Capacity 2,900 cc.
CASE No. 14

Female, aged 22 years.

History

This patient developed pain in the left thigh and leg at the age of sixteen. This continued for six weeks. Next, at the age of seventeen, she began to get pains in the left hip and groin, worse at the end of the day. These symptoms continued for a year. She was then put in a plaster spica for six months, and this was followed by a period of four months lying in a plaster shell. She developed pain in the right hip at this time and while she was in the shell the right leg was on extension. When the use of the plaster was discontinued her hips and back were very stiff. She was in bed for the next nine months and then began to get up, but had to use crutches. For the past year she has had some pain in the neck.

Condition on Examination

The thoracic and lumbar spine are fixed (1/8 in.). Practically no movement of the neck is possible.

Both hip joints are fixed; flexion of both knees is limited. The movements of other joints are full. Chest expansion 1 in. Vital Capacity 1,400 cc.
CASE No. 15

Male, aged 22 years.

History

He began to get pain in the right hip during exercise at the age of nineteen. Six months later pain started in the left hip and also in the lumbar region of the back. These pains were worse in bed at night, and after sitting in one position for some time. His back began to get stiff at about the same time. The pains in the back and hips have continued since.

Condition on Examination

There is no movement in the lumbar region and thoracic spinal movements are very limited (2 in.). Neck movements are full.
There is slight limitation of extension of both hips. The movements of the remaining joints are full.

CASE No. 16

Male, aged 27 years.

History

At the age of twenty-one he began to get pain in the left hip and lumbar region of the back. This gradually increased over the next two years, and some stiffness developed in the back. The pain and stiffness were most severe after resting and improved with exercise. When aged twenty-four he was treated in a plaster shell for ten months. After six months the pain improved,
but when he was taken out of the plaster his neck, back, hips and knees were fixed, and have remained so. He has got up for some hours daily since that time. He now gets no severe pain, but has some aching in the back, shoulders, hips and ankles at times.

**Condition on Examination**

There is no movement in the thoracic or lumbar region of his back (3/8 in.). The cervical movements are limited. The movements of the remaining joints are full. Chest expansion 7/8 in. Vital Capacity 2,400 cc.
CASE No. 17

Male, aged 22 years.

History

Pain and stiffness in his whole back started at the age of twenty-one. The pains were worst on getting up in the mornings, and were also made worse by jarring. They have continued since, but have improved during the past year.

Condition on Examination

There is very little movement in the thoracic and lumbar spine (2 in.). Cervical movements are full.

Movements of the right hip are markedly limited and those of the left hip limited to a lesser extent. The movements of other joints are full.

Chest expansion 1 in. Vital Capacity 1,850 cc.
CASE No. 18

Male, aged 47 years.

History

At the age of twenty-five had some pain and weakness in the right leg on exercise, which lasted a few months.

At the age of forty-three he noticed pain and stiffness in his neck when he got up in the mornings. After a few months his neck became very stiff and has remained so since.

His whole back has been becoming increasingly stiff for the past four years.

Condition on Examination

There is scoliosis of the spine in the lower thoracic region.

There is some limitation of movement of the thoracic and lumbar region of his back (2 1/2 in.). Movements of the neck are very limited.

There is slight limitation of extension at the hip joints, and a little limitation of external rotation of the left shoulder joint. The movements of the remaining joints are full. Chest expansion 1/8 in. Vital Capacity 1,850 cc.
CASE No. 19

Male, aged 24 years.

History

He first began to get pain and stiffness in the hips, knees and sacral region at the age of ten. This occurred on getting up in the mornings and wore off through the day. This continued on and off, but was not severe, until the age of nineteen. He then developed pain and stiffness in the thoracic region of
his back, which spread up to his neck. He now gets little pain in the back, but gets some in the hips, knees, shoulders and neck at times.

**Condition on Examination**

There is some thoracic kyphosis.

The movements of the lumbar and thoracic regions of the back are very limited (1 1/8 in.) and neck movements are moderately limited.

There is slight limitation of the movements of the right hip and right shoulder. The movements of the other joints are full. Chest expansion 1 1/2 in. Vital Capacity 2,650 cc.
CASE No. 20

Male, aged 29 years.

History

He had sharp pains in the thighs on movement for two weeks, at the age of eighteen. He then had no symptoms until the age of twenty-three when he had pains in the lumbar region of the back. These lasted for nine weeks and then cleared. Two years later he again got pains in the lower back and he also noticed some stiffness of his back. He has had pain and stiffness on and off since that time, made worse by movement after resting and by severe exertion. At the age of twenty-eight the pain and stiffness increased, and the pain spread to his hips and thighs and neck. The symptoms have continued since.

Condition on Examination

There is no movement in the lumbar region and practically none in the thoracic region of his back (1/2 in.). Cervical movements are markedly limited.

There is slight limitation of movement at both hip joints. The movements of the remaining joints are full. Chest expansion 1 1/4 in. Vital Capacity 2,300 cc.
CASE No. 21

Male, aged 31 years.

History

At the age of ten he had aching pain in the right thigh which lasted for two weeks. Next, when aged twenty-six, he developed pain in the lumbar region of his back which spread to the back of his thighs. It was usually most severe in bed at night. A few months later he began to get pain in the thoracic region of his back and in the lower part
of his neck. His back began to get stiff. The symptoms have continued since, with exacerbations and remissions.

Condition on Examination

There is scoliosis and kyphosis of the thoracic spine.

The lumbar and thoracic spine are fixed (3/8 in). Neck movements are markedly limited.

Extension at the hip joints is limited. The movements of the other joints are full. Chest expansion 3/4 in. Vital Capacity 2,270 cc.
CASE No. 22

Male, aged 34 years.

History

He began to get pain in the left knee at the age of twenty-six, and a few months later he developed pain and stiffness in the left hip. At the age of thirty he developed aching pains in the lumbar region of the back. These gradually spread to the thoracic region, and also to the neck. He has had pain and stiffness in his back, with exacerbations and remissions, since that time.

Condition on Examination

There is a moderate degree of thoracic kyphosis.

There is limitation of movement of the lumbar and thoracic spine (3 1/4 in.), and also of the cervical spine.

Flexion and external rotation of the left hip joint are limited and there is slight limitation of flexion of the right hip. Flexion of the left knee is a little limited. The movements of the other joints are full.

Chest expansion 2 in. Vital Capacity 2,350 cc.
CASE No. 23

Male, aged 29 years.

History

At the age of twenty-four he began to get pains in the lumbar region of the back. He was stiff on getting up in the mornings but improved after he had been up for a few hours. A few months later the pains began to spread up his back, and within a year had reached his neck. The symptoms have continued since, with exacerbations and remissions. During the past year he has had some pain and stiffness in the shoulders.

Condition on Examination

There is no movement in the lumbar and thoracic
region (1/2 in.), and very little in the cervical region of the spine.

There is limitation of extension at the hip joints and slight limitation of left shoulder movements. The movements of other joints are full. Chest expansion 1 1/4 in. Vital Capacity 2,700 cc.

CASE No. 24

Male, aged 30 years.
History

At the age of twenty-three he began to get pain, which was difficult to localise, in the lower part of his chest posteriorly, worse on movement and deep breathing. During the next year the pains became localised in the lumbar region of the back. When he was aged twenty-five the pains spread to his hips and thighs, and his back became stiff. The stiffness was worst on getting up in the mornings and wore off through the day. For the past two years the pains have not been so severe, although he still gets some pain and stiffness, mainly in the upper lumbar region of his back.

Condition on Examination

There is limitation of movement of the lumbar and thoracic region of the back (2 1/4 in). Neck movements are not limited.

Flexion and external rotation of the hips are very limited. The movements of the other joints are full.

Chest expansion 1 in. Vital Capacity 3,100 cc.
CASE No. 25

Male, aged 35 years.

History

He noticed some pain in the back of his left thigh on exertion for a few months at the age of twenty-seven. He then developed pain in the left buttock on exercise, especially after resting. About a year later he had pains across the front of the chest, and began to get pain and stiffness in the lumbar region of the back. At the age of thirty he was given a plaster
jacket for five months. It relieved the pain, but his back was stiffer when it was removed. Since that time he has had pains in the back, neck, hips, knees, shoulders and arms at times. For the past six months his back has been becoming increasingly stiff.

Condition on Examination

There is no movement in the lumbar or thoracic region of the back (1 1/4 in.). Neck movements are limited.

There is slight limitation of hip and shoulder joint movements and slight limitation of flexion of the left knee. The movements of the other joints are full. Chest expansion 1/4 in. Vital Capacity 1,500 cc.
CASE No. 26

Male, aged 25 years.

History

When aged seventeen he developed pains in the left hip, thigh and knee. These continued on and off, and two years later he began to get similar pains on the right side, and also developed pain and stiffness in the lumbar region of his back. These pains continued with exacerbations and remissions until he was twenty-two. At that time he was confined to bed for two or three weeks because of suggested pleurisy, and while in bed his hips and knees became completely stiff. He has had very little pain since that time.

Condition on Examination

There is no movement in the lumbar region, and very little in the thoracic region of his back (1 in.). There is some limitation of neck movements.

His hip joints and knee joints are fixed. There is very slight limitation of shoulder joint movements. The movements of the remaining joints are full. Chest expansion 3/4 in. Vital Capacity 2,300 cc.
CASE No. 27

Male, aged 41 years.

History

At the age of twenty he developed an aching pain in the right hip region. The pain was aching in character and sometimes spread down the back of the right thigh to the knee. A tuberculous infection of the hip joint was suspected and a plaster spica was applied. While in plaster of Paris he had some pain in the lumbar and thoracic region of his back. When the plaster
was removed his right hip was fixed, and his left hip was very stiff; so was his back. He continued to get slight pains in the back, and at the age of twenty-three he began to get pain in the neck, and this began to get stiff. His back and hips have remained stiff since that time.

**Condition on Examination**

There is no movement in the lumbar and thoracic region of the spine (5/8 in.). Neck movements are markedly limited.

The right hip joint is fixed, and little movement is possible at the left hip joint. Flexion of both knees is limited. The movements of the other joints are full. Chest expansion 1 1/2 in. Vital Capacity 2,100 cc.
CASE No. 28

Male, aged 45 years.

History

At the age of twenty-three he started to get mild aching pain in the lumbar region of the back. This has recurred at intervals since, but has never inconvenienced him greatly. At the age of thirty-seven he began to get pains in the neck and he noticed that his neck was becoming stiff. These pains have continued since that time. They are most severe in bed at night, and sometimes cause him to wake. His neck has become progressively stiffer since that time.

Condition on Examination

There is practically no movement in the lumbar or thoracic region of his back. The movements of his neck are severely limited.

Flexion and abduction movements at the hip joints are a little limited. The movements of other joints are full.
CASE No. 29

Female, aged 49 years.

History

At the age of twenty-three she had rheumatic fever with pain and swelling in most of her joints. She was in bed for six months. She recovered satisfactorily. At the age of twenty-eight she had an attack of "influenza", and following this she developed pain in the right hip region, and her right hip began to get
"drawn up", so that she was unable to straighten it. She also had slight pain in the lower part of her back, and slight intermittent aching in the back has continued since that time.

At the age of twenty-nine she had a baby, and following this the pains in the right hip region became more severe. Her right hip was manipulated under anaesthesia without improvement. At that time she also developed some pain in the left hip and groin. The pains in the hips have continued since, but have been improving for the past two years.

Condition on Examination

There is kyphosis of the thoracic region of the back.

There is very little movement in the lumbar or thoracic region of the spine (1 3/4 in.). Neck movements are very slightly limited.

There is a flexion deformity of the right hip, and all movements are lost. The movements of the left hip joint are very markedly limited. There is slight limitation of flexion of the knees, and very slight limitation of shoulder joint movements on both sides. The movements of the other joints are full. Chest expansion 3/4 in. Vital Capacity 1,600 cc.
REFERENCES


Rich, A.R. & Gregory, J.E. (1943 a). Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. Bull. John Hopkins Hosp. 73, 239


