An attempt is here made to add to our knowledge of the aetiology of ankylosing spondylitis by marshalling what appear to be the relevant facts and by adding certain observations that have resulted from a detailed study of one hundred cases that have been under treatment or observation for from two to ten years.

Geographical Distribution

The geographical distribution appears to be worldwide. Reports of series of cases have come from all parts of Europe and America, from Syria, South Africa, India, Australia, Japan, the Argentine, Brazil, and Chile. Seventy-four cases living within the City of Bristol have been found to be evenly distributed between the various suburbs.

Incidence

Few attempts have been made to estimate the frequency of the disease in the general population. Clausen and Kober (1936) accepted an incidence of 1 in 1,000, based on the autopsy findings of Schmorl and Junghanns (1932), who found six or eight definite cases among 10,000 bodies coming to necropsy at the city hospital of Dresden. More than half the spines were only examined in situ by palpation. Other figures relate to highly selected material. Bachmann (1930) found sixty-six examples among 3,201 spines he had studied radiographically. Willis (1933) found smooth ankylosis of the sacro-iliac joints in 1.2 per cent. of 1,509 museum skeletons. Boland and Shebesta (1946) found 18 per cent. affected among 6,000 consecutive admissions to an American Army Rheumatism Centre. The ratio of cases of "rheumatoid spondylitis" to "peripheral rheumatoid arthritis" among U.S. Army patients was reported as 1 to 3 (Boland and Present, 1945). The ratio in civilian practice has been estimated by various workers as 1 : 11, 1 : 13, and 1 : 19 (Hare, 1940; Dunham and Kautz, 1941; Tyson, 1937), but the figures are of little value when an attempt is made to estimate the incidence of ankylosing spondylitis, owing to the selected nature of clinic material, the general misdiagnosis of mild cases in general practice, and the variable criteria of diagnosis adopted for both diseases.

In Bristol the orthopaedic work is centralized and there is reason to believe that almost all the cases diagnosed during the last five years have passed through the spondylitis clinic at the x-ray therapy department of the Royal Hospital. As only some 2 per cent. of the patients have been found to manifest the disease for the first time after the age of forty, it is possible to obtain a rough estimate of the number of cases in Bristol from a simple histogram (see Figure). An average age at death of 60 years is assumed.

The total of cases from the City, both known cases and those assumed missed, is 144. If one further assumes that 10 per cent. of the population of 420,000 are, or have been, "at risk," one arrives at an incidence of 1 in 2,000 of the general population "at risk." This figure will be used below when the expected incidence of multiple cases within sibships is estimated.

After each world war it was suggested that the incidence had increased. The segregation at those times of young adult males with "rheumatic" complaints is the likely explanation of this clinical impression. Such explanation was accepted by Schmorl and Junghanns after the first war. That the
disease is not of recent origin is shown by numerous
descriptions dating back to 1700, by a suggestive
clinical description from the Beloved Physician
(Luke xiii, verse 11), and by the study of skeletons
of Nubians who lived many thousands of years
before Christ.

Sex Distribution

Forestier (1940) thought the disease was rare in
women, but Scott (1942) found 30 per cent. of
women among his cases. The sex incidence reported
in most large series of patients has been approxi-
ately ten males to one female. At the Mayo
Clinic the figures were 931 men to 104 women
(Polley and Slocumb, 1947). Of 134 patients seen
here during the last ten years twelve were women,
a ratio of 1 to 10.

Type and Occupation of Person Affected

The type of individual affected has been the
subject of much comment. Two statements of
Scott (1942) warrant attention. He found that
90 per cent. of three hundred were swimmers and
divers, mostly well above the average. At Bristol
forty-five of one hundred were found to be swimmers,
not a high percentage for the district; and fifty-
three had indulged in organized field games after
leaving school. At least it may be said that the
disease is found more among the active than the
weaklings. Scott's other statement was that many
had a characteristic facies, "ferret face". Profile
photographs were taken of a series of patients,
but the practice was discontinued when it was
realized that there was no common feature.

No occupational predilection has been noted. Of
one hundred patients only thirty-three had been engaged
in heavy manual labour. There is no evidence to suggest
that economic factors are concerned.

Age and Mode of Onset

The onset occurs when growth has ceased, or is
ceasing, in bone, when the secondary epiphyses have
appeared, or are appearing, and when articular
cartilage is showing chemical change by beginning
to stain blue with haematoxylin. It does not
begin or flourish during the physical decline of the
body. The course is usually said to be one of
relentless progress with remissions and exacerb-
bations, but when case histories are examined
it is found that in most there have been three phases:
the first being of isolated attacks of pain and stiffness
occurring at increasingly frequent intervals; the
second a florid phase of continuous symptoms and
constitutional upset; and the third of declining
activity and minor relapses. In severe cases the
florid phase is prolonged, while in mild cases it
may never be reached. This pattern of progress
with the constant symmetrical anatomical sequence
of involved structures, occurring as it does at a
particular period in life, suggests a local defect in
metabolism rather than an infection.

This picture of the disease coupled with the
predominance of affected males and the work of
Batson (1940) on the spread of prostatic carcinoma
has suggested to Buckley (1945) the possibility that
a "morbidific agent" arising in the prostate may be
the cause. The occurrence in some severe cases of
prespondylitic lesions in the joints of the lower
limbs, as well as the evidence to be presented below,
detracts from this otherwise attractive theory.

The Connective-Tissue Ground Substance

Of the symptoms attention is directed to the
characteristic stiffness. This stiffness develops
during rest and can be "worked off", and though
not peculiar to ankylosing spondylitis is a striking,
persistent, and invariable symptom. Muscle spasm
occurs commonly when the back symptoms are
acute, but is quite different in nature from the
stiffness. There is no evidence that it is due to
abnormal tone and, so far, pathologists have been
unable to detect any abnormality in biopsy material
from affected muscles (Desmarais and others, 1948).
Any theory as to the aetiology of the disease must
account for this stiffness as well as for the lesions
in the spinal joints. As yet little attention has been
paid to the connective-tissue ground substance.
Hyaluronic acid would appear to be the lubricant of
the tissues as well as of the joints, which latter are,
embryologically, but clefts within connective tissue.
An undue increase in the viscosity of the connective
tissue lubricant might well occasion stiffness. There
is evidence to suggest that the viscosity of this
connective tissue ground substance is normally
increased by rest (Duran-Reynals, 1942) and that
age, sex, and heredity are factors in connective-
tissue permeability in animals. The viscosity of the
connective-tissue ground substance is not, of course,
the only factor governing permeability. The
secretion of synovial fluid is increased by exercise
and decreased by rest, and an analogous situation
may well obtain in the connective tissue. It is
suggested that a defect in the metabolism of hyalu-
ronic acid or related substances may play a part in the
aetiology of the disease. It would be interesting
to know what effect an intravenous infusion of
homologous hyaluronidase has upon the stiffness.
Salicylates appear to relieve the stiffness temporarily,
though by what mechanism is not known. Uncon-
firmed work of Gil and Guerra (1947) suggests
that salicylates interfere with the spreading effect.
AETIOLOGY OF ANKYLOSING SPONDYLITIS

of testicular hyaluronidase in human skin. Quinn (1948) has reported increased anti-hyaluronidase activity in the serum of patients with "active acute rheumatic fever", and Glick and Gollan (1948) have reported an increase of inhibitor to hyaluronidase in the serum of patients with spondylitis. Whether a specific anti-hyaluronidase was concerned, or whether there was simply an increase in the non-specific hyaluronidase inhibitor of the serum, was not known. One wonders whether this has any bearing on the fact that many patients with quiescent ankylosing spondylitis experience a fresh access of stiffness with a febrile illness such as influenza.

Iriritis.—The association of "diffuse" iritis is of great interest; it is not commonly associated with any other disease. Of one hundred patients, no less than fifteen had had iritis at least once, whereas Sorsby and Gormaz (1946) found only one patient with evidence of past iritis among 316 "non-rheumatic" hospital patients. This comparison is not quite true, since Sorsby and Gormaz recorded only objective evidence and did not accept "histories". The iritis of ankylosing spondylitis often recovers without leaving any objective evidence. Schley (1937), studying diffuse iritis, found that of seventy-three patients fifteen had ankylosing spondylitis. The particular interest lies in the fact that the ciliary body contains hyaluronic acid, and the aqueous and vitreous humours contain both hyaluronic acid and hyaluronidase (Meyer. 1947). Blair in 1942 drew attention to the chemical relations between cartilage and the ciliary body.

Effect of Pregnancy

Pregnancy made little difference to one patient, but to another it occasioned considerable relief and an absence of back stiffness (objective) lasting for two weeks into the puerperium in two pregnancies.

Laboratory Investigations

Laboratory investigations have so far failed to reveal any abnormality in the inorganic constituents of the blood (Hemphill and Reeves, 1945; and others). Spectrographic analysis of incinerated whole blood for trace elements at first suggested an excess of copper, but subsequent examination of some twenty further samples from active cases and controls failed to show any constant abnormality. (This work was kindly undertaken for the author by Dr. M. N. Thruston of I.C.I. Ltd.) There is no evidence that fluorine is concerned. The vertebral ankylosis that is seen occasionally among patients suffering from severe fluorosis, with or without renal disease, is quite unlike that seen in ankylosing spondylitis. Blood lipids and blood phosphatases have also been found to be present in normal quantities (Hemphill and Reeves, 1945), though a significant rise in alkaline phosphatase has been reported by Buckley (1945). No distinctive pattern of plasma proteins has been noted. It has been said that the increased erythrocyte sedimentation rate points to an infective aetiology, but a number of non-infective conditions, such as gout and closed injuries, occasion a similar rise. In the cerebrospinal fluid the only abnormality noted has been an increase in protein (Ludwig and others, 1943), most marked—up to 98 mg. per 100 ml.—in patients with active disease (Boland and others, 1947). It is suggested that this is due to hyperaemia of the spinal meninges secondary to the intense activity in the adjacent joints and vertebral bone. The excretion of 17-ketosteroids has been found to be well above the normal range (Davison and others, 1947). This work awaits confirmation. Steffens (1938) and others have postulated an underlying endocrine disturbance, and Ködderman (1939) treated his patients for an alleged hypofunction of the testes and pituitary, but the administration of androgenic and oestrogenic preparations by various workers has not resulted in any marked benefit.

No organisms have been isolated from affected joints. Gonorrhoea has been regarded by many as a factor in the aetiology. Sir Jonathan Hutchinson suggested that gonorrhoea was the cause of the case that Davies-Colley described so clearly in 1885. Recent studies in America have shown that a history of gonorrhoea is no more common among patients with ankylosing spondylitis than it is among the general army population. Scott (1942) tried to incriminate the tubercle bacillus. He found evidence of calcified mesenteric glands in 95 per cent. of four hundred radiographs. This finding has not been confirmed by others. The radiographs of a hundred patients seen here revealed only sixteen examples. Goldfain (1943) found raised agglutination titres against Brucella organisms in a considerable percentage of his patients, but the results were not controlled and the endemity of Brucellosis was not known. A local spondylitis that heals by ankylosis is not rare in Brucella infections, but it does not resemble the disease under discussion. No other abnormal agglutinins have been reported, and Perry (1940) did not find in the serum any abnormal resistance to fibrinolysis.

Pathological and Radiographic Studies

Pathological and x-ray studies reveal the following pertinent facts :

1. The joints affected are those that are most liable to continuous strain and movement, namely the sacro-iliac joints, the vertebral apophyseal joints and the rib articulations, and the disease progresses from the joints bearing the greatest
strain to those bearing less. It may be noted that these joints, perhaps more than any others, have had to adjust themselves recently in evolution to an alteration in the direction of the strain. (Fox (1939) attempted to relate arthritis to joint size and body weight.)

2. The calcification of the vertebral ligaments occurs where the strain upon the bone at their attachments is greatest. This calcification provides reinforcement at defective ligament-bone junctions; it is not a physiological response to faulty alignment. Spinal curvature from other causes, even when the vertebrae are markedly osteoporosed, does not call forth this response, except in the local ankylosis that may occur between two diseased vertebrae (as in tuberculosis, typhoid fever, and undulant fever).

Calcification in the ligamentous attachments about the pelvis, seen best between the alae of the sacrum and the ilium and at the attachment of the hamstring muscles to the tuber-ischii, is also proportional to the strain imposed. This was well shown in a severely affected patient who had had an amputation through one thigh in childhood. Buckley (1945) postulated a defect in the metabolism of bone alkaline phosphatase giving rise to a mobilization of calcium from the bone and its immediate deposition in the adjacent ligaments. From a study of many serial radiographs it is clear that the ligamentous calcification is often long delayed in the presence of marked osteoporosis of the vertebrae. The joint pathology so far described resembles microscopically that found in rheumatoid arthritis, but muscle biopsies have failed to reveal the extra-articular pathology of that disease (Desmaraës and others, 1948). Güntz (1933), who made one of the first thorough histological studies of the joint lesions, could find no abnormality in the vertebral bodies.

Effects of Treatment

The effect of treatment has not thrown any light on the nature of the disease, though Blair (1942) has speculated in this connexion on the disappearance of mast cells from the vicinity of tumours following irradiation. (Mast cells produce heparin—mucoitin polysulphuric acid—a substance chemically related to chondroitin sulphuric acid and hyaluronic acid.) Deep x-ray therapy, especially "intensive" treatment, does relieve severe pain and facilitate orthopaedic measures, but how it brings this about is not known. Whether x-ray therapy affects the course of the disease is as yet uncertain, for most reports of treatment have been couched in very similar terms for the last twenty years (Woldenberg, 1926; Krebs and Vontz, 1934; Swaim, 1939; Forestier, 1939; Smyth and others, 1941; Hilton, 1943; Wyatt, 1945; McWhirter, 1945; Williams, 1948).

Hereditary Factors

Though many reports have been made of families with more than one affected member (for example that of Campbell, 1947), statements to the effect that inheritance plays no part in the aetiology of the disease are still to be found in the most recent textbooks. In 1938 Clausen and Kober published a paper on the inheritance of "Becheterew's" disease. They pointed out the fact so often forgotten that "history taking" does not reveal nearly so much as a thorough investigation of the family. They investigated the families of ten cases from among eighty-one; the others, they said, were too difficult to get hold of. In these ten families they found nine secondary cases, four alive and five dead (three with medical evidence and two without). They found one secondary case in each of three families, two in one family, and four in one family. Although they mentioned no criteria for diagnosis, their evidence was certainly impressive. Rogoff and Freyberg (1948) studied 114 patients and found thirty-four with family histories of disabilities of the back. Of these thirty-four they investigated eighteen and found ten families with multiple cases. They estimated a family incidence of 9 to 13 per cent. Of the hundred patients studied in this series there were ten who knew so little of their families that the recording of their histories was worthless. The remaining ninety patients came from eighty-three families. In these there were ten secondary cases among brothers and sisters. Eight families contained two affected members, and one three. The incidence of multiple cases within sibships was thus nine in eighty-three, or approximately 11 per cent, which is more than a hundred times greater than would be expected assuming a random distribution.

Taking the incidence among those at risk as 1 in 2,000 and the fact that the average number of individuals per affected sibship was 4.45, and assuming a random (Poisson) distribution, one may estimate the expected incidence of multiple cases within sibships as follows:*

<table>
<thead>
<tr>
<th>No. of patients per family</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of families found</td>
<td>41,907</td>
<td>74</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>No. of families expected</td>
<td>41,907</td>
<td>74</td>
<td>0.065</td>
<td>0.00003</td>
</tr>
</tbody>
</table>

* I am indebted for the series to Dr. Munson, Physicist at the Bristol Royal Hospital.
AETIOLOGY OF ANKYLOSING SPONDYLITIS

These figures are likely to under-estimate the incidence of multiple cases within sibships, since a number of sibs with suggestive symptoms have so far remained inaccessible. The existence of the disease in other than siblings has not been recorded, since the material so far collected is as yet too incomplete.

Speculation as to the reason for the uneven sex incidence led to the question, "Why do nine out of every ten women, who presumably inherit the abnormal genetic material, fail to manifest the disease?" This in turn led to a further study of the families of those women who had manifested the disease, and it was found that of the ten women who had brothers no less than four had an affected brother.

The acceptance of these findings depends upon the acceptance of the fact that bilateral sacro-iliitis is "ankylosing spondylitis". It is here assumed that this is the case for three reasons. First, because most cases of bilateral sacro-iliitis do subsequently develop radiological evidence of involvement of the lumbar spine. Of forty-five patients who, when first seen, had only sacro-iliac involvement, thirty-two have already progressed to lumbar spine involvement. Secondly, because it is not possible to differentiate between those cases which will progress to spinal involvement and those which will not. Thirdly, because cases showing radiological evidence of sacro-iliitis alone may be found among the brothers and sisters of the severely affected (? forme fruste). The requirements for diagnosis were, in addition to a typical history of signs and symptoms, radiological evidence of bilateral sacro-iliitis which in its minimal form had to show at least multiple circumscribed areas of sclerosis or relative osteoporosis in the lower part of the joint. It has been said that the earliest radiological signs were "lack of definition", "ground-glass appearance", and "haziness". An x-ray study of the sacro-iliac joints of forty normal University students showed that such appearances could not be accepted as criteria of sacro-iliac involvement.

The facts reviewed are consistent with the finding that heredity plays a major role in the aetiology of the disease. Further study of the relatives of patients, other than siblings, is required to establish the type of inheritance involved. This study might well be coupled with a search for cases of rheumatic fever among both patients and relatives, since many workers suspect some relationship between acute rheumatism and ankylosing spondylitis (Polley, 1948). Several patients in this series had attacks of polyarthritis intermediate between acute rheumatic fever and rheumatoid arthritis, either before or at the onset of their spinal symptoms. Twelve gave a history of having had acute rheumatic fever, and five actually had mitral stenosis.

The mechanism of expression of the defective genetic material must now be sought. It is suggested that a histochemical study of biopsy material from normal and acutely affected structures may provide a first step.

Summary and Conclusions

1. The facts concerning the disease which might be expected to have a bearing on its aetiology are reviewed and some of the theories so far propounded are discussed.

2. Observations on the nature of the disease and of the affected joints are made, and emphasis is laid on the chemical relationship that exists between the affected structures (connective-tissue ground substance, synovial fluid, the chemical constituents of the eye, cartilage, and ligament).

3. The incidence of the disease in the general population is discussed, and evidence is produced which suggests that the inherited factor is sex influenced.

4. It is concluded that the facts so far known point to a local metabolic defect in articular structures subject to continuous stress and in bone-ligament attachments similarly subject, with heredity as a major aetiological factor.

For clinical facilities and for encouragement and advice I am greatly indebted to Prof. C. Bruce Perry.

References


ANNALS OF THE RHEUMATIC DISEASES


L’Etiologie de la Spondylite Ankylosante

RÉSUMÉ ET CONCLUSIONS

L’auteur passe en revue les faits concernant la spondylite ankylosante susceptibles d’avoir une importance au point de vue étiologique et discute quelques-unes des théories proposées jusqu’ici. Il relate ses observations sur la nature du processus pathologique et des articulations atteintes, et insiste sur la parenté chimique existant entre les tissus affectés (substance fondamentale du tissu conjonctif, liquide synovial, les constituants chimiques de l’œil, cartilage, et ligaments). Il discute la fréquence de la maladie dans la population en général, et donne des preuves qui suggèrent que la facteur heréditaire est lié avec la sexe. Il conclut que les faits connus jusqu’à présent indiquent l’existence d’un trouble local du métabolisme des structures articulaires et des insertions ligamentaires soumises à un effort continu, l’héritéit constituant un facteur étiologique important.
Aetiology of Ankylosing Spondylitis

H. F. West

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