Family surveys have been used to study etiological factors in rheumatoid arthritis, Still’s disease, and osteoarthrosis. It is suggested that certain genetically determined factors in the population acting alone or in conjunction lead to the clinical conditions mentioned above.

GENETIC STUDIES ON RHEUMATOID ARTHRITIS

J. S. Lawrence, M.D., M.R.C.P.

Evidence of familial aggregation of rheumatoid arthritis has been sought in a number of studies. All have shown a higher prevalence of rheumatoid arthritis in the relatives of rheumatoid patients than of control families. Of recent years the discovery of serological changes and the development of standards for grading radiological abnormalities have enabled a more objective analysis to be made of possible genetic factors in rheumatoid arthritis. The rheumatoid serum factors or antigamma globulins, as they should preferably be called, are of three main types — those reacting with rabbit gamma globulin, those which precipitate aggregated FII human gamma globulin, and those which react with incomplete anti-D human gamma globulin. All are macroglobulins with a Svedberg coefficient of 19 or more, and for each an inhibitor is known to occur. Any one of these antiglobulin factors may be present in the serum of a patient with rheumatoid arthritis, or a combination of them, but often none may be detectable in an apparently quite typical case. The reason for their association with rheumatoid arthritis is unknown, but it has been repeatedly shown that, where they are present, the disease carries a less favorable prognosis, and is more likely to be associated with severe erosions of articular cartilage and subchondral bone and with the presence of subcutaneous nodules.

Sheep-Cell Agglutination Test (SCAT) in Population Samples

The antigamma globulin, which reacts with rabbit globulin, has so far been studied most extensively. It was discovered by Waaler and Rose independently in 1940 and is tested by coating sheep red cells with antisheep-cell rabbit globulin, the red cells being agglutinated by the patient’s serum in dilutions up to 1 in 1,000 in some instances. When sera from a random population sample in the town of Leigh in northwest England were examined by this test, it was found that some 60 per cent of persons showed no agglutination, 20 per cent showed agglutination at a dilution of one in four, and so on in a continuous curve. It would thus appear that in this random population sample, the sheep-cell titer is a continuous variable.

Rheumatoid arthritis as defined by the American Rheumatism Association criteria is not related directly to the sheep-cell titer. Only when the titer rose above 1 in 32 was there an increased likelihood of rheumatoid arthritis being found; and the probability rose with further increase of titer so that 9 out of 13 of those with a titer of 1 in 256 or...
more had three or more criteria of rheumatoid arthritis. When those with a titer of 1 in 32 or over who showed no evidence of rheumatoid arthritis were re-examined after a period of five years, it was found that one in three had developed clinical or radiological evidence of the disease, whereas this occurred in only 1 in 13 of those with titers of less than 1 in 32. It would thus appear that these macroglobulins are associated in some way with a predisposition to develop rheumatoid arthritis. This does not, of course, exclude the possibility that a positive test may sometimes result from the disease process. So far only the occurrence of the serum factor in random samples has been considered.

Family Studies

Method

Two main methods have been employed in the investigation of genetic factors in rheumatoid arthritis. In one, probands have been chosen from a random population sample because of some characteristic, e.g., the sheep-cell titer, or the presence of rheumatoid arthritis. Details are obtained from the proband of all first-degree relatives, and those aged 15 or over, living within a predetermined radius of the x-ray center constitute the sample to be surveyed. These relatives are asked to come to the center for a clinical examination, for certain routine x-rays, and for a blood test. Those who cannot do so are examined at home. When the results are analyzed, comparison is made with a group of persons of the same age and sex distribution from the random sample, except when, as in sheep-cell titer studies, the survey has its own internal controls. In the second method, probands are chosen from hospital patients, all those suffering from the disease under study who have attended within a certain period, usually two years, being included. The families are examined in the same way, those living within a predetermined distance of the hospital being included; but where a comparatively rare disease is being investigated, it is necessary to make use of more than one center and to include relatives living within a predetermined radius of each center. Comparison is made with relatives of patients suffering from other diseases or preferably with random samples, but these should, if possible, be taken from the local population.

Where relatives are very widely scattered it may be impracticable to bring them to x-ray centers and examinations must then be carried out entirely in the home, using portable equipment. This type of survey has been developed particularly by Dr. Burch of the National Institutes of Health Field Survey Unit. The control groups for such surveys may be chosen by selecting from among the neighbors persons of the same age and sex as the proband and by examining them and their relatives. Between the neighbors and the neighbors’ relatives, Dr. Burch has so far found no significant difference. Alternatively, a neighbor of the proband’s relatives may be used as a control.

Genetic Studies on the SCAT

When persons taken from a random population sample are used as probands and their first-degree relatives examined, it is found that, with increasing sheep-cell titer in probands, there is an increasing chance of “positive” titers being found in the relatives. Of the relatives of probands with no agglutination in the town of Leigh, where extensive family surveys have been carried out, only 3 per cent had a positive test, whereas, if the proband were positive at a titer of 1/128 or over, 12 per cent of his relatives had a positive SCAT (P approximately 0.001). It is not known whether this familial aggrega-
tion is genetically determined or due to environmental factors. Environment during adult life did not seem to be important, since, of 1,200 married persons in random samples in northwest England, a positive test in both husband and wife was found in only two instances. Since 1 person in 25 had a positive test among married persons in this population, it would be expected that once in 625 both spouses would be affected. Thus the frequency in both spouses was only double the expected rate and was not significant. An environmental factor acting mainly in childhood and only slightly in adult life could explain our findings. Whether or not the familial aggregation of the sheep-cell titers can be entirely explained by environment is uncertain, but it would seem likely that a genetic factor is also involved. A final decision, however, must rest on twin studies. Such a survey is at present in progress as a multicenter study in rheumatic centers in the United Kingdom and the Netherlands.

So far, I have considered the sheep-cell factor only as it occurs in random samples of the population and in their first-degree relatives. When the titer distribution is examined in patients with inflammatory polyarthritis, a quite different type of curve is obtained. Instead of a smooth curve with its highest point at zero, there is a bimodal curve with a second peak at 1 in 128 to 512

Figure 1—Sheep-Cell Titer Distribution in Inflammatory Polyarthritis and in a Random Population Sample
Table 1—Clinical and Radiological Evidence of Rheumatoid Arthritis and Osteoarthritis in Male and Female Relatives of Rheumatoid Probands in Leigh

<table>
<thead>
<tr>
<th>Probands</th>
<th>Total Male</th>
<th>Total Female</th>
<th>Clinical Rheumatoid Arthritis Male</th>
<th>Clinical Rheumatoid Arthritis Female</th>
<th>Radiological Hands and Feet Male</th>
<th>Radiological Hands and Feet Female</th>
<th>Positive SCAT Male</th>
<th>Positive SCAT Female</th>
<th>Osteoarthritis in Five or More Joints Male</th>
<th>Osteoarthritis in Five or More Joints Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive Arthritis</td>
<td>22</td>
<td>21</td>
<td>0</td>
<td>33</td>
<td>5</td>
<td>25</td>
<td>9</td>
<td>29</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Seronegative Arthritis</td>
<td>38</td>
<td>50</td>
<td>3</td>
<td>12</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Positive SCAT without Arthritis</td>
<td>27</td>
<td>25</td>
<td>0</td>
<td>8</td>
<td>12</td>
<td>8</td>
<td>30</td>
<td>16</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>96</td>
<td>1</td>
<td>16</td>
<td>5</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Expected</td>
<td>87</td>
<td>96</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

dilution (Figure 1). This suggests that in this disease two factors are influencing the sheep-cell titer. To investigate this possibility, three groups of probands were selected from the random population samples in Leigh. These were persons with (1) rheumatoid arthritis and a negative SCAT, (2) rheumatoid arthritis with a positive SCAT, and (3) a positive SCAT without evidence of rheumatoid arthritis. When the first-degree relatives of these probands living within 15 miles of the center of Leigh were examined, it became clear that the familial aggregation of sheep-cell positivity was completely independent of the presence or absence of rheumatoid arthritis. Clinical evidence of arthritis, on the other hand, was found more often than expected in the relatives of both seropositive and seronegative arthritic probands. The relatives of healthy persons with a positive SCAT had exactly the expected amount of clinical disease as estimated from the random sample. Erosive changes, as seen on x-ray, followed much the same distribution as the SCAT. Multiple osteoarthrosis, on the other hand, was found slightly more frequently in the families of the seropositive and seronegative arthritic probands, but not in the relatives of probands without arthritis. When the relatives were divided into males and females it was found that clinical and radiological evidence of arthritis and multiple osteoarthritis was present in excess only in female relatives, but the serum factor was equally present in the two sexes (Table 1). There were more positive tests among female than male relatives of both seropositive and seronegative arthritic probands, but this was not significant and was reversed in the relatives of non-arthritic probands. When hospital patients are used as probands, the differences between seropositive and seronegative families are less striking. Ziff and his colleagues, who were the first to investigate rheumatoid factors in families, found no significant difference with the SCAT between rheumatoid and control families; but when an inhibition test was used, significant differences emerged. It is unlikely that this indi-
cates an inherited lack of the inhibitor, but, rather, that the inhibitor serves as a more sensitive measure of the presence of sheep-cell factor. Bremner and her colleagues failed to find any significant difference between seropositive and seronegative arthritic families, though there was actually three times as much positive serology and twice as much erosive change in the seropositive arthritic families. Clinical disease was slightly more common in their seronegative arthritic group. Thus, on an average, it would seem that clinical arthritis is just as frequent in seronegative as in seropositive arthritic families. If this is the case, two inherited factors would appear to be involved in rheumatoid arthritis—one concerned with the sheep-cell factor, the other with joint manifestations. If the sheep-cell factor may be either inherited and predispose to the disease or acquired and result from the disease, much that at first sight appears contradictory can be explained. Hospital probands, having more severe disease, would be more likely to have the acquired form of the sheep-cell factor and would thus have fewer relatives with a positive test. Moreover, the bi-modal curve previously cited could be explained as resulting from a combination of inherited and acquired serum factors.

On this view, the sheep-cell factor may be described as a biological palindrome, in that it not only predisposes to rheumatoid arthritis, but also results from it. This concept of a biological palindrome is not new. One example is the role of renal arterial disease in hypertension.

**Still's Disease**

Further evidence of a dual causation of the serological changes in arthritis and also of the complex genetic factors involved is forthcoming from a family study of Still's disease made by Ansell, Bywaters, and the present author at the Canadian Red Cross Hospital at Taplow and at the Hammersmith Hospital in London.

There has been much discussion in the past as to whether or not this is a separate disease or simply rheumatoid arthritis occurring in young persons. Certain differences, however, have emerged in recent years. The sheep-cell test for example is positive on admission in only some 13 per cent of cases compared with 70 per cent of cases of the adult disease. Moreover, sacroiliitis is present in some 25 per cent of cases of Still's disease, but is rare in the adult form.

When the first-degree relatives and grandparents of 93 patients with Still's disease were examined, it was found that the male relatives had more spondylitis and sacroiliitis and the females more peripheral polyarthritis than a random sample of the same age and sex. The sheep-cell titer on the other hand did not differ from that in the random sample, and none of the relatives of the probands with a positive sheep-cell test were themselves seropositive. It would thus appear that the positive sheep-cell test, when it occurs in Still's disease, does not depend on an inherited trait and may well result from the disease process. Two inherited factors, however, would appear to play a role in Still's disease—one associated with spondylitis and sacroiliitis, the other with peripheral polyarthritis. This latter may well be identical with the arthritic factor encountered in the adult form of rheumatoid arthritis. The partly hereditary nature of these familial associations is supported by findings in twins. Of four pairs of homozygous twins, two were concordant as regards Still's disease, whereas no concordance was noted in three heterozygous pairs.

Further light is thrown on genetic factors in arthritis by a family study made in Leigh on multiple osteoarthritis. Probands for this study were selected from random samples and were defined as those below the age of 65 who showed
radiological evidence of osteoarthrosis in six or more types of joint.

Probands were divided into two groups, those with and those without Heberden's nodes, and their first-degree relatives will be referred to as the nodal and nonnodal families. There was an excess of multiple osteoarthrosis in both the nodal and nonnodal families (Table 2), but clinical polyarthritis was encountered in excess only in the nonnodal families, and the excess was restricted to females (Table 3). Similarly, radiological evidence of erosive arthritis was found in excess only in females of the nonnodal families. Neither the nodal nor the nonnodal families had an abnormal titer distribution by the sheep-cell test. Heberden's nodes, on the other hand, were found in excess only in females of the nodal families.

Thus there is evidence of two genetic factors in generalized osteoarthrosis, not combining to produce a single disease entity as in rheumatoid arthritis and Still's disease, but producing two distinctive forms of the disease—one associated with Heberden's nodes, the other without.

The arthritic factor, evidence of which was found in the nonnodal families, may well be identical with the arthritic factor which we have already encountered in association with the sheep-cell factor in rheumatoid arthritis and with the sacroiliitis factor in Still's disease. Thus it would appear that where the arthritic factor is present alone, either a seronegative arthritis or multiple osteoarthrosis develops. These two, indeed, may simply be stages in a single disease process. The nature of this factor cannot as yet be considered proved, but is likely to be genetically determined, since in no instance in the random population samples were both husband and wife found to have seronegative polyarthritis, nor has multiple osteoarthrosis been found in both spouses more often than would be expected by chance.

Discussion

So far only one of the serum factors involved in rheumatoid arthritis has been considered in detail. The antihuman gamma globulin (latex or bentonite fac-
RHEUMATOID ARTHRITIS

Table—3 Clinical Inflammatory Polyarthritis, in First-Degree Relatives of Persons with Osteoarthritis in Six or More Types of Joint

<table>
<thead>
<tr>
<th>Heberden’s Nodes</th>
<th>Relatives</th>
<th>Total</th>
<th>Per cent with Polyarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>in Probands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>34</td>
<td>69</td>
<td>3</td>
</tr>
<tr>
<td>Present</td>
<td>52</td>
<td>173</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>252</td>
<td>3</td>
</tr>
<tr>
<td>Controls</td>
<td>86</td>
<td>646</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>40</td>
<td>144</td>
<td>22</td>
</tr>
<tr>
<td>Present</td>
<td>56</td>
<td>274</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>418</td>
<td>15</td>
</tr>
<tr>
<td>Controls</td>
<td>96</td>
<td>524</td>
<td>6</td>
</tr>
</tbody>
</table>

The factor has not shown the same familial aggregation as the sheep-cell factor. Ziff and his colleagues found more positive latex tests in relatives, but as the controls were chosen because they had no arthritis, this may have biased the result. Goldenberg and his colleagues found no evidence of familial aggregation using the latex test. The anti-D gamma globulin, anti-Gm (a), is found less frequently in the population and has not to the author’s knowledge been studied in families; but an inhibitor, the Grubb factor or Gm (a+), is found in 60 per cent of certain populations and appears to be genetically determined. It has shown no direct relationship to rheumatoid arthritis or to the antihuman gamma globulin titer. It is not known whether these other antigamma globulins bear the same palindromic relationship to rheumatoid arthritis as the sheep-cell factor, but if so they must between them weave such a web that it will not easily be disentangled.

How these factors act is quite unknown. Do they interfere with the immune properties of the gamma globulin and so prevent the body dealing adequately with infections? In support of this is the occurrence of rheumatoid-like polyarthritis in children with agamma-globulinemia. But the relatives of such children often have rheumatoid arthritis or a positive SCAT so that the agamma-globulinemia may simply be an alternative expression of the SCAT inheritance and not directly related to the rheumatoid process. Moreover, SCAT positive individuals are not in my experience more liable to infectious disease.

Summary

Family surveys have been used to investigate etiological factors in rheumatoid arthritis, Still’s disease, and osteoarthritis. Familial aggregation of the sheep-cell factor has been found to occur independently of clinical evidence of rheumatoid arthritis. A second “arthritic” factor must be postulated to explain the occurrence of clinical rheumatoid arthritis in families. It is believed that both these factors may be genetically determined.

In Still’s disease no familial aggregation of the sheep-cell factor was discovered, but a seronegative form of polyarthritis was found in excess in females and spondylitis in males.

In the female relatives of persons with multiple osteoarthritis, there was more seronegative polyarthritis than expected from comparison with random samples of the population.

It is suggested that a genetically determined arthritic factor is present in a proportion of the population. If the arthritic factor alone is present, either a mild polyarthritis or multiple osteoarthritis develops; if genetic factors of the type associated with spondylitis are also present, Still’s disease is likely to develop; and if antigamma globulins are present,
the adult type of rheumatoid arthritis is more likely to occur.

ACKNOWLEDGMENTS—I wish to thank Dr. J. Ball, Dr. T. A. Burch, and Professor J. H. Kellgren for permission to use their data on the sheep-cell titer in patients with polyarthritis.

REFERENCES


3. (a) Stecher, R. M.; Solomon, W.; and Wolpaw, R. Ibid., p. 66.


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