sis, on the incidence in the sons and daughters of patients. We are in touch with over 500 such males and nearly 100 such females who were successfully treated by Rammstedt's operation at The Hospital for Sick Children between 1920 and 1939, and have visited the families of the 174 men and 48 women who have already had children. The information on the brothers and sisters and the sons and daughters of these index patients is summarized in Tables 1 and 2.

Table 1
Relatives of 174 male index patients

	Brothers	*Sons*	*Sisters*	*Daughters*
Affected	5	11	5	2
Total	156	162	165	161
% affected	3·2	6·8	3·0	1·2

Table 2
Relatives of 48 female index patients

	Brothers	*Sons*	*Sisters*	*Daughters*
Affected	5	9	1	4
Total	38	44	40	36
% affected	13·2	20·5	2·5	11·1

The diagnostic criteria for calling a relative 'affected' were strict; in most cases the presence of a pyloric tumour was confirmed at Rammstedt's operation, but a few cases, medically treated, were included where a pyloric tumour was felt by an expert.

With male index patients, the incidence of pyloric stenosis in brothers and sons is about ten times, and in sisters and daughters about twenty times, the incidence in the general population. With female index patients, the corresponding ratios are about thirty times and about sixty times the incidence in the general population.

These findings indicate neither recessive nor sex-linked inheritance, but several genetic models could be used to explain them. One of the simplest is to assume that a single main 'dominant' gene and a multifactorial background together provide the genotype underlying predisposition to pyloric stenosis. The multifactorial background is presumably for a character which is modified by sex, and the author and his colleagues have been impressed by the athletic ability of many of these patients, both men and, relative to their sex, women. At the moment this is only a clinical impression, and it is planned to investigate the matter further.

Meeting January 20 1961

Paper

The Epidemiology of Rheumatoid Arthritis in Northern Europe

by J S Lawrence MD MRCP, V A I Laine MD and R de Graaff MD[1]

Despite extensive investigation by clinicians, pathologists, biochemists and immunologists the causative factors in rheumatoid arthritis remain obscure. Recently epidemiological techniques have been brought to bear on the problem and are producing valuable pointers both on the environmental and the genetic factors involved.

Methods: In earlier studies, notably the survey by Newman in 1924, data were collected by general practitioners on insured patients seeking advice for rheumatic symptoms. This method has the advantage of economy but has the serious disadvantage that many patients are missed since they do not attend their doctor, often despite quite extensive disease. The disadvantage is overcome if the survey is based on home interviews made by social workers of a sample of the population, as in the survey undertaken by the Central Office of Information (Stocks 1949). This in turn has the disadvantage that diagnoses are based on statements by the respondent and the accuracy of the diagnosis is therefore open to doubt.

The method may be extended by including a subsequent visit by a physician to all those with rheumatic complaints, as in the original survey of rheumatic complaints in the town of Leigh in Lancashire, which was based on a 1 in 10 sample of households (Kellgren *et al.* 1953). This gives a useful indication of the size of the problem and of the relative importance of different rheumatic diseases as causes of incapacity. The method has been developed particularly in the Netherlands where a 2% sample of the entire population of the country has been investigated (de Graaff 1960).

Though useful from the economic standpoint, the method has rather limited value as a method of investigating causative factors. The reasons for this are twofold: (1) The data depend partly on

[1]From: The Empire Rheumatism Council Field Unit, Manchester University; The Rheumatism Foundation Hospital, Heinola, Finland; and the 'Gezondheidsorganisatie T.N.O.' The Hague. The Netherlands.

the complaint thresholds of the individuals, which may vary considerably in different areas and in different occupational groups in the same area. In Leigh, for example, it was found that rheumatic complaints were only half as frequent in miners' families as in the rest of the population, despite identical X-ray changes. (2) The diagnostic standards of physicians vary greatly one from another and in the same physician from time to time, so that no reliable comparison between different groups is possible.

Criteria: For these reasons it has been necessary to introduce more precise criteria into surveys of rheumatoid arthritis in population samples. In 1956 a committee of the American Rheumatism Association (A.R.A.) introduced criteria for rheumatoid arthritis based on a study of the symptoms and signs in 332 patients (Ropes *et al.* 1958). Points were given for morning stiffness, pain on movement of a joint, joint swelling or effusion, subcutaneous nodules, X-ray changes typical of rheumatoid arthritis, a positive sheep-cell agglutination test and certain changes in the synovial fluid and on biopsy of nodules or of the synovial membrane. It was decided that a score of 5 or more points should indicate definite disease, 3–4 points probable and 2 points possible disease. These criteria have now been used in a number of population surveys and have proved of great value but are not entirely free from inaccuracies due to observer difference. For this reason, reliance has tended to be placed more on the radiological and serological findings.

Radiology: The radiological diagnosis of rheumatoid arthritis depends mainly on the recognition of erosions of bone. These are found chiefly at the joint margin and can be seen most clearly in the metacarpal and metatarsal heads. They must be differentiated from bone cysts which are common and are usually associated with osteoarthrosis or trauma. Cartilage erosion is also of value, but can be recognized only when it is sufficiently diffuse to cause narrowing of the joint space and must be differentiated from cartilage wear due to osteoarthrosis. Osteoporosis is also a feature of rheumatoid arthritis but, except where it is confined to the immediate neighbourhood of the joints, is more often due in population samples to other causes. Other less common signs are the formation of periosteal new bone in the region of affected joints, and soft tissue swelling, but these are more usually found in the active stage and are thus less frequent in population samples. In the spine there is ankylosis of the apophyseal joints with subluxation at the disc above or below the immobile joint and sometimes diminished disc space. In surveys of rheumatoid arthritis these three sites should be X-rayed as a routine. The other joints are less important.

For survey purposes all X-ray changes have been graded 0–4 and each group of joints, e.g. the proximal interphalangeal joints of the fingers, is read not only for rheumatoid arthritis but also for osteoarthrosis, porosis, erosions and gout, the grading being based on the worst affected joint.

Unfortunately in reading X-rays also considerable observer differences arise. In a comparison of the readings of a series of radiographs for osteoporosis, erosions and rheumatoid arthritis by six experienced observers, wide disagreement both in grading and interpretation was noted (Kellgren 1956). Reassessment of the same films by one observer, after an interval of one year, showed a closer agreement and it was evident that if a comparison of two series of X-rays is to be of any value they must all be read by one observer. It was clear, however, that appreciable changes in grading by one individual could occur over a period of time and that if differences between populations are to be established their films must be read at the same time, preferably mixed so that the observer is unaware of their origin.

To establish international radiological criteria for rheumatoid arthritis, a series of hand X-rays were presented at the International Congress of Rheumatic Diseases in Toronto in 1957. Rheumatologists were asked to grade the films into 5 categories as follows:

0=Definite absence of rheumatoid arthritis
1=Doubtful rheumatoid arthritis
2=Definite but minimal rheumatoid arthritis
3=Moderate rheumatoid arthritis
4=Severe rheumatoid arthritis

On the answers to this questionnaire four films, giving modal values for each grade, were chosen for use as standards (Kellgren & Lawrence 1957). Standards have also been produced for spinal rheumatoid arthritis (Sharp *et al.* 1958), since the radiographic appearances differ from those in the peripheral joints. These standards are being made available in the form of an atlas together with those for other rheumatic diseases.

Serology: Two types of serological test have been used in rheumatoid arthritis: (1) The sheep-cell agglutination test (SCAT), which depends on the ability of certain rheumatoid sera to agglutinate sheep or human red cells sensitized by anti-sheep or human erythrocyte rabbit serum. (2) The latex (LFT) or bentonite flocculation test (BFT), which depends on flocculation by certain rheumatoid sera of latex or bentonite particles coated with modified human γ-globulin. The SCAT is positive in some 70% of patients attending hospital in

whom a diagnosis of rheumatoid arthritis has been confirmed, the LFT and BFT in 80%.

Surveys of Rheumatoid Arthritis in Northern Europe
The radiological surveys so far undertaken are shown in Table 1. The total sample is 4,536 of whom 3,999 have been examined, a completion rate of 88%. Those who had only a clinical examination have been excluded from the completion rate and from the subsequent assessment of results.

Dr R de Graaff: the Pneumoconiosis Research Unit has examined rural samples in Annandale in Scotland and in the Vale of Glamorgan in South Wales. There have also been a number of genetic studies which will be described later.

Age and sex distribution: The Leigh and Wensleydale samples have been used to study the age and sex distribution of rheumatoid arthritis (Table 2). In both sexes the prevalence of probable and definite disease, as determined by the A.R.A.

Table 1
X-ray surveys of population samples

Locations	*Age distribution*	*Method of sampling*	*Number available*	*Number examined*	*Completion rate*
Leigh	15+	Random 1 in 30	1,565	1,343	86%
Wensleydale	15+	Area	1,025	891	87%
Rhondda	Males 35–64	Stratified	586	522	89%
	Females 55–64	Random 1 in 7	295	261	88%
Heinola	55–64	Random 1 in 2	361	346	96%
Rotterdam	55–64	Random 1 in 47	305	275	90%
Annandale	55–64	Random 1 in 4	199	186	93%
Glamorgan	55–64	Random 1 in 3	200	175	88%
Total	15+		4,536	3,999	88%

The largest survey was undertaken in the town of Leigh in Lancashire in the years 1954–9 and was based on a 1 in 30 sample of the adult population. There was a total of 1,565 persons of whom 1,343 were examined giving a completion rate of 86%. Between the years 1958–60, an area sample was examined in a rural population in Wensleydale. This included the southern half of the town of Hawes and half the villages and farms in the area. In 1958 a survey was undertaken in the Rhondda in conjunction with the Pneumoconiosis Research Unit. In this survey the males were aged 35–64 and were stratified for occupation so that half were miners and half non-miners; the females were aged 55–64. The remaining surveys are all based on random samples of the 55–64 age group; a rural sample of 361 in the village of Heinola in Finland was undertaken by Dr V Laine, and an urban sample of 305 in Rotterdam in Holland by

Table 2
Prevalence of rheumatoid arthritis as defined by the A.R.A. criteria in combined urban-rural population

	Males			*Females*		
Age	*Total examined*	*Probable or definite rheumatoid arthritis Cases*	*%*	*Total examined*	*Probable or definite rheumatoid arthritis Cases*	*%*
15–24	174	1	0·6	178		0
–34	178	2	1	176		0
–44	185	2	1	214	4	2
–54	235	8	3	227	9	4
–64	143	7	5	179	26	15
65+	145	6	4	200	32	16
Total	1,060	26	2·5	1,174	71	6·0

criteria, increased with age, starting at the age of 20 in the males and reaching a maximum of 5% in the 55–64 age group. In the females there was none below the age of 35 but thereafter the increase was more rapid so that, of those over 65, 16% had probable or definite disease. Taking all ages, the disease was two and a half times as common in females.

Radiological evidence of erosive arthritis in the hands and feet showed a similar relationship to age (Table 3). There was an earlier onset in males of whom 12 had grade 2–4 change in the first three decades, compared with only 2 females. After the age of 65 the condition had a higher prevalence in females so that the prevalence in the population sample as a whole was identical in the two sexes, amounting to 3%. There was, however, rather more grade 4 disease in the females.

Table 3
Radiological evidence of erosive arthritis – hands and feet – Leigh and Wensleydale

	Males					*Females*				
		Grade					*Grade*			
Age	*Total X-rayed*	*2*	*3*	*4*	*2–4 %*	*Total X-rayed*	*2*	*3*	*4*	*2–4 %*
15–24	165				0	172				0
–34	177		1		0·6	174				0
–44	184	2			1	214			1	0·5
–54	234	8		1	4	226	1			0·4
–64	141	5	1	1	5	178	4	2	2	4
–74	94	6	2		9	137	14	1		11
75+	47	3	1		9	57	5	1	3	16
Total	1,042	24	5	2	3	1,158	24	4	6	3

In the cervical spine radiological evidence of rheumatoid arthritis was found in 5% of males and 5% of females (Table 4). This was the most frequent site of the disease as judged by X-ray. As in the peripheral joints it was related to age, occurring in 1% of those in the 15–24 group and reaching a maximum of 22% in the oldest age groups. Unlike the changes in the hands and feet the onset was not earlier in males, there being no significant difference between the sexes at any age group. The cervical changes were, however, more often minimal in the males. Other sites were much less often affected.

Table 4
Age and sex distribution of radiological evidence of erosive arthritis in the cervical spine in Leigh and Wensleydale

	Males				*Females*			
		Grade				*Grade*		
	Total	2	3–4	2–4	*Total*	2	3–4	2–4
Age	*X-rayed*	*Cases*		%	*X-rayed*	*Cases*		%
15–24	165			0	170	2		1
–34	176			0	172			0
–44	183	1		0·5	213		1	0·5
–54	233	6		3	224	7	1	4
–64	139	10	1	8	174	8	3	6
–74	93	15	3	19	137	21	6	20
75+	47	9	4	28	57	12		21
Total	1,036	41	8	5	1,147	50	11	5

Serum tests: The SCAT was positive in 3·7% of males and 4·4% of females, the BFT in 4% of either sex. Both the SCAT and the BFT show an increasing titre with age but neither shows a sex difference at any age group, the proportion of positive tests being identical in males and females. The age distribution of positives in the mixed urban-rural population shows a stepwise increase between the ages of 15 and 74, with peaks every twenty years to a maximum of 11% of positives in males and 9% in females in the older age groups (Lawrence 1960). The BFT has so far been tested on only 383 sera from population samples but shows a similar increase with age and a similar twenty-year periodicity. The reason for this periodicity in serum tests for rheumatoid factor is by no means clear nor is the increase with age understood. It does not appear to be due to enhanced survival of seropositive individuals since there were only 3 positive SCATs in the 15–24 age group in the population, whereas there were 20 in the 65–74 year age group. Nor have individuals as opposed to populations an increasing titre with age in the population samples. In a five-year follow-up of 57 persons from the population of Leigh, the SCA titre was found to have risen in only 5, but it had become less in 16. This of course requires follow-up over a longer period, but if it is confirmed some other theory will have to be evolved. One possibility is that the sheep-cell titre depends on past exposure to some antigen which has become less frequent over the last seventy years so that the older members of the population stand a greater chance of having acquired a positive test. This theory might also explain the twenty-year periodicity. Certain infections – tuberculosis, syphilis and gonorrhœa, for example – have shown an increase during each world war and would thus have had approximately a twenty-year periodicity. An association between the SCAT and infection has been demonstrated in experimental animals. Hæmagglutinating factor can be induced in, for example, a proportion of rabbits by immunization with streptococci of group A and by various anaerobic bacteria and in rats by infection with a strain of *Streptobacillus moniliformis*. This occurs, however, only if *S. moniliformis* has been grown in the presence of human proteins. The factor reacts both with human F II globulin and with rabbit anti-erythrocyte globulin (Eyquem *et al.* 1959, Lerner *et al.* 1960).

The relationship of the SCAT to the BFT is also complex. In a series of 383 persons from the Wensleydale sample studied by Burch, Ball & Block (personal communication) in which both tests were used, the BFT was positive and the SCAT negative in 10, the SCAT only was positive in 4 and both tests were positive in 6. There were more in whom both tests were positive in the population sample than would be expected by chance so that it is evident that some factor is shared in common. This factor is not rheumatoid arthritis since only 1 of the 6 in whom both tests were positive had clinical or radiological evidence of the disease. A similar degree of association has been found between the SCAT and LFT (Valkenburg & Ball 1961). The association may be chemical since both tests depend on the presence in the serum of a fast migrating macroglobulin, having a sedimentation constant of 19S which exists *in vivo* as a soluble combination with 7S γ-globulin (Franklin 1960).

The association between rheumatoid arthritis and the serum tests is similarly obscure. Only one person in 3 with a positive SCAT in the random samples of Leigh and Wensleydale had clinical or radiological evidence of rheumatoid arthritis, so it is unlikely that the serum factor is produced by the disease. There is evidence, however, that a positive SCAT predisposes to rheumatoid arthritis. Of 19 seropositives in Leigh who were followed up for five years, 8 had rheumatoid arthritis in 1954 but by 1959 2 more had developed evidence of the disease. Of 19 with negative SCATs, 3 had rheumatoid arthritis in 1954 but only 2 in 1959, and of 19 with doubtful titres, 2 had rheumatoid

arthritis in 1954, 1 in 1959. Thus, of those with a negative test, none had developed the disease but in 2 it had cleared up completely. The predisposition, if such there be, would seem to be quantitative. In the Leigh and Wensleydale samples all those with a titre of 1 in 512 had definite disease.

Geographical distribution: Information on geographical distribution is available mainly on the 55–64 year age group in Northern European countries (Table 5). Definite rheumatoid arthritis (by the A.R.A. criteria) showed much the same prevalence, between 2% and 3% in all surveys undertaken, but when 'probable' disease was included the disease was twice as common in Leigh as in any other area ($\chi^2=8{\cdot}2$, $P<0{\cdot}01$). It is difficult to be certain how much of this is due to observer difference in assessing physical signs. The difference was most striking in the females. Of the 30 females with probable disease in Leigh, 11 were given a confident diagnosis of rheumatoid arthritis at the time and 9 were considered doubtful. This may be compared with the Rhondda where there were only 13 females with probable disease. Only 3 of these were given a confident diagnosis of rheumatoid arthritis and 6 were considered doubtful. Observer differences may, however, have played a part in the clinical diagnosis of rheumatoid arthritis.

When observer difference is excluded by using only the X-rays, which were all read by the same observer, the prevalence in Leigh is seen not to be unduly high. Indeed rheumatoid arthritis of the cervical spine was less frequent in Leigh than in any of the other surveys. There was significantly less change in the hands in Rotterdam and the Vale of Glamorgan, the two most southerly areas to be surveyed, and it is of interest that the sheep farmers of Wensleydale and their families most often had X-ray changes in the hands. This may well be a climatic effect determining the site of the disease rather than its total prevalence. X-ray changes in the feet were not strikingly different in the areas studied.

The SCAT results are of some interest. Although the geographical differences in titre were not striking, they were significant ($P\simeq 0{\cdot}02$), the urban populations having 5% of positive tests, the rural areas 2–3%. Here observer difference can be excluded with some certainty since all tests were made by Dr J Ball of the Rheumatism Research Centre in Manchester.

Family studies: The occurrence of rheumatoid arthritis in families has been known for some time. Kroner (quoted Falls 1953) reported rheumatoid arthritis in four generations of one family and Papp & Tepperberg (1937) in another family recorded 11 persons in four generations. Numerous comparisons have been made between rheumatoid arthritic and control families (Lewis-Faning 1950, Short *et al.* 1952, Stecher *et al.* 1952, Barter 1952, Miall 1955, de Blécourt 1961). All have found a higher prevalence in the rheumatoid relatives.

In a survey carried out by the Empire Rheumatism Council Field Unit of families of persons with rheumatoid arthritis or a positive SCAT discovered in the population samples in Leigh (Lawrence & Ball 1958), 183 out of a total of 209 adult relatives (parents, siblings and offspring) living in the area were examined. The completion rate was thus 87% and was therefore similar to that in the random samples. They were compared with controls taken from the random samples and matched by age and sex with the relatives. These controls were stratified for clinical arthritis and sheep-cell test in each age group against the random sample.

The relatives of seropositive arthritics had four times as much clinical disease as the controls, the families of seronegative arthritics had only twice

Table 5

Prevalence of rheumatoid arthritis in 55–64 age group in Northern Europe

	Urban						*Rural*							
	Leigh		*Rhondda*		*Rotterdam*		*Heinola*		*Wensleydale*		*Glamorgan*		*Annandale*	
Total	394		360		275		346		117		175 (87)●		186	
A.R.A. criteria		%		%		%		%		%		%		%
Definite	13	(3)	9	(3)	9	(3)	7	(2)	3	(3)	2	(2)		—
Probable and definite	55	(14)	26	(7)	23	(8)	24	(7)	7	(6)	6	(7)		—
Radiological changes														
Cervical spine	30	(8)	28	(8)	24	(9)	33	(10)	11	(9)	13	(15)		—
Hands	8	(2)	11	(3)	1	(0·4)	11	(3)	6	(5)	1	(0·6)	2	(1)
Feet	13	(3)	18	(5)		—	11	(3)	3	(3)	3	(2)	3	(2)
Positive SCAT	19	(5)	18	(5)	12	(4)	7	(2)	3	(3)	6	(3)	3	(2)

● In Glamorgan only the 87 females were examined clinically and had a radiograph of the cervical spine.

Table 6
Rheumatoid arthritis in relatives of persons with arthritis or a positive SCAT

Propositi	*Total relatives*	*Clinical arthritis*	%	*Erosive arthritis (hands or feet)*	%	*Positive SCAT*	%	*Osteoarthrosis 5+ joints*	%
Seropositive arthritis	43	7	(16)	6	(14)	7	(16)	5	(12)
Seronegative arthritis	88	7	(8)	1	(1)	5	(6)	9	(10)
Positive SCAT without arthritis	52	2	(4)	5	(10)	12	(23)	3	(6)
Total relatives	183	16	(9)	12	(6)	24	(13)	17	(9)
Expected number●	183	7	(4)	6	(3)	9	(5)	13	(7)

●The expected number is derived from the random sample of the population of Leigh adjusted for age and sex to correspond with the total relatives.

as much and the seropositive non-arthritic families the same amount as the controls (Table 6). Only the seropositive arthritic families had *significantly* more than the controls and there was no significant difference between the families of seropositive and seronegative arthritics in this respect.

Radiological evidence of rheumatoid arthritis was more than four times as common in the seropositive arthritic families as in the controls. In the seronegative families it was found in only one case but in the seropositive non-arthritic families it was three times as common as in the controls. Here again only the seropositive arthritic families had significantly more than the controls.

The SCAT was positive four times as often in the seropositive families as in the controls and was just as often positive in the non-arthritic as in the arthritic families. In the seronegative families on the other hand, there was no excess of positives.

Bremner *et al.* (1959), who compared relatives of hospital patients with seropositive and seronegative rheumatoid arthritis, found rather more clinical arthritis in the seronegative group, but like us they found more radiological disease and positive serology in the other group. Though the differences in this survey were not significant, they indicate, when taken in conjunction with our own findings, that in both seronegative and seropositive families there is more clinical disease than in the population as a whole but that only in the seropositive relatives are there more erosive changes or positive serology.

Multiple osteoarthrosis was found in both seropositive and seronegative arthritic families about twice as often as in the controls but was not increased in the seropositive non-arthritic families. It thus resembled rheumatoid arthritis in its distribution. It is of interest in this connexion that siblings of persons with generalized osteoarthrosis frequently have inflammatory polyarthritis and that this is nearly always seronegative (Lawrence 1961).

What is the cause of this familial aggregation of rheumatoid arthritis and of the SCAT? If it were environmentally determined it would be expected that both husband and wife would be affected in a proportion of families. In fact in only two families were both husband and wife found to have a positive SCAT in Leigh and Wensleydale where some 1,200 married persons were examined in the random sample. The prevalence of positive tests was 4% or 1 in 25 in married persons in these samples, so that by chance both spouses would be expected to be positive once in 625 matings, a close approximation to what was found. In no instance did the sheep-cell-negative form of polyarthritis occur in both spouses in the population of Leigh and Wensleydale, though, since 1 person in 34 has this type of arthritis, it should have occurred once in this size of population sample. Thus it is unlikely that environment, at least during adult life, is responsible for this familial aggregation. Environmental factors in childhood offer a possible explanation and this is at present under investigation in a number of centres in the United Kingdom and the Netherlands, under a scheme devised by Dr A Dixon and supported by the Empire Rheumatism Council. To this end the prevalence of clinical and radiological arthritis and of positive serological tests will be assessed in a series of monozygotic and dizygotic twins. There have been several twin studies in the past, notably by Berglund (1940), Edström (1941), Grossman *et al.* (1956) and Thymann (1957). Most report concordance and Kaufmann & Scheerer (1928) reported that this was greater in monozygotic twins but there is little objective information. Edström reported concordance in 3 of 5 monozygous pairs but in only 1 of 9 dizygous pairs of twins.

If the familial aggregation is genetically determined it would seem likely that more than one locus is involved. There would appear, for example, to be one factor favouring the appearance of clinical arthritis with or without secondary osteoarthrosis. It is tempting to assume that this is sex-linked and is a dominant on the X-chromosome since both clinical arthritis and generalized non-nodal osteoarthrosis are more common in females. If this were so, it would be passed by affected mothers equally to their sons and daughters, but by affected fathers only to their daughters. Rare instances have been recorded in which father and son have had clinical disease and this would appear to negative this type of inheritance but it is of course possible that the disease is not homogeneous and that an acquired form also exists.

Table 7
Sheep-cell agglutination titres in first-degree relatives of persons in the population sample of Leigh

Propositi	*Relatives*		
Titre	*Total in sample*	*Total tested*	*Titre 32+*
<4	363	207	3%
4	99	87	
8	42	39	6%
16	31	23	
32	158	124	10%
64	60	32	
128	59	40	
256	33	26	12%
512	11	8	

If the sheep-cell factor is inherited, it is in all probability a multifactorial inheritance. The evidence for this is: (1) That the distribution of sheep-cell titres in the population presents as a continuous variable (Kellgren & Lawrence 1956). Some 60% of the population have no reactant by this test and there is a progressive diminution in the number of persons reacting as the titre is increased. (2) There is a direct and continuous relationship between the titre in the propositus and the relatives (Table 7), varying from 3% of positive tests in relatives of those without reactant in their serum to 12% in those with a titre of 128 or more.

Benign Polyarthritis

In random population samples, in addition to those who have obvious polyarthritis, there is a group who give a history of polyarthritis but in whom the symptoms have completely subsided. This group, though less amenable to direct epidemiological study, is of considerable importance to the community. In the population of Leigh it was responsible for more frequent incapacity than rheumatoid arthritis (Fig 1). Such a history of past polyarthritis was given by 84 persons (5% of males and 7% of females) in the Leigh population sample (Lawrence & Bennett 1960). Although many of these stated that their illness was rheumatic fever, only 4 had mitral stenosis. On the other hand, 15 had joint residua on clinical examination. The prevalence of these joint residua was five times as great in persons with a history of polyarthritis as in the rest of the population and moreover they were found at an earlier age. They included subluxation of the interphalangeal and metatarsophalangeal joints and pain or limitation of movement of the metacarpophalangeal joints, wrists, knees, tarsal joints and cervical spine. Only 3 of these 84 persons had frank rheumatoid arthritis. Erosive joint changes in the hands or feet were not common in persons with a past history of polyarthritis and none showed the residual

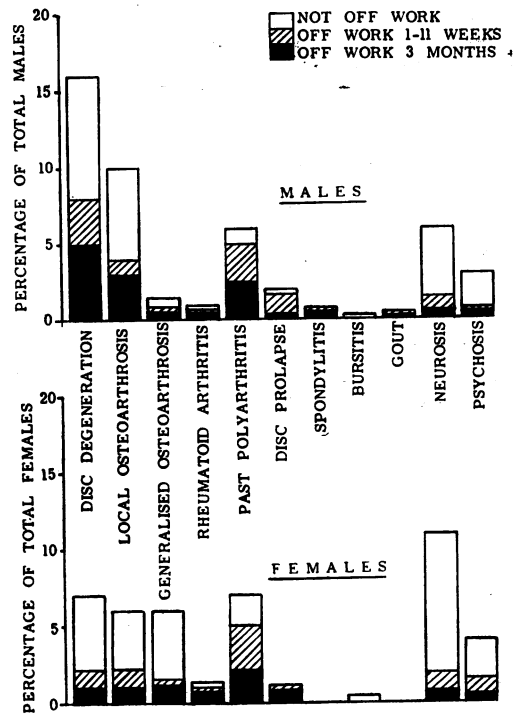

Fig 1 *Clinical diagnoses in population sample (grades 3–4)*

joint changes described by Jaccoud (1869) and by Bach (1935) and Bywaters (1950) as occurring after rheumatic fever. Altogether 9% of males and 10% of females had definite radiological changes in the cervical spine of the type usually associated with rheumatoid arthritis, compared with 3% and 4% respectively in the rest of the population. Thus the condition appeared to be related more to rheumatoid arthritis than to rheumatic fever. The SCAT, however, was positive in only 6% of males and 9% of females, little more than in the general population.

Ætiology: The onset of this transient type of polyarthritis in both sexes was mainly between the ages of 5 and 24. After the age of 24 the incidence fell sharply and in only 9 did the condition appear after the age of 45. This variation was partly but not wholly due to the smaller numbers at risk in the older age groups. Those with joint residua tended to have their attacks rather late in life. Those with cardiac residua, on the other hand, all had their attack between the ages of 5 and 24.

The season of onset, in those who could remember it, was mainly in the winter from January to March. The onset was rather earlier than in rheumatic fever but fitted closely the data given by Short *et al.* (1957) for exacerbations of rheumatoid arthritis. A study of the year of onset indi-

cated that the condition had existed at least since 1885. The greatest incidence was between 1905 and 1914 but there was no evidence that the condition ever attained epidemic proportions or that it was declining, though cardiac complications were less frequent since 1935. This is in conformity with known trends in rheumatic fever incidence. There was no definite evidence that joint residua were becoming less, except in the last ten-year period.

There is no evidence of any regional differences in prevalence, this being much the same in Wensleydale and South Wales as in Leigh.

Apart from inflammatory residua, there was found in persons with a past history of polyarthritis a greater prevalence of osteoarthrosis particularly in females. This tendency was not greater in those who had their attack late in life.

Clinical features: In its acute form this benign polyarthritis could not readily be distinguished from rheumatic fever. In the less acute type the joint symptoms persisted, many patients being off work for a year or more because of joint symptoms. A common sequence was pain which started in the feet and spread to the ankles and knees, sometimes to the hands. Severe pain in the back, neck and shoulders was often mentioned, suggesting that the spinal joints were affected. The attacks were usually single but up to 8 relapses have been recorded. Although minimal rheumatoid changes were common, only 3 of the 84 persons with a history of polyarthritis had moderate or severe rheumatoid disease at the time of examination. The prognosis is thus excellent.

Although this benign form of polyarthritis would appear to be more common than true rheumatic fever as judged by a comparison of cardiac and joint residua, it should be pointed out that those persons who had died from rheumatic heart disease would automatically be excluded from the population sample. From the *Report of the Ministry of Health* (1957) it would be expected that some 18 persons in a population sample of the size used in this study would die of rheumatic heart disease over the period of seventy years covered by our survey. Thus the original sample might have been 102 of whom 22 developed heart disease and 18 died. It would thus appear that at least as many of the original cases developed cardiac as arthritic residua and that rheumatic fever and benign polyarthritis have roughly the same prevalence.

The cause of this benign form of polyarthritis is uncertain. The seasonal incidence would suggest an infection. Benign forms of polyarthritis have been reported in virus infections such as rubella, measles and infective hepatitis (Geiger 1918, Hope Simpson 1940, Bennett & Copeman 1940, Loudon 1953, Lewis 1954, Lloyd 1960). It would thus seem possible that this is an abnormal immune response to some quite common infection.

The relationship of benign polyarthritis to rheumatoid arthritis is also uncertain. All those in the Leigh sample with a past history of polyarthritis and a positive SCAT had clinical evidence of persistent rheumatoid arthritis (grades 1–4) and it may well be that the possession of a positive SCAT or other predisposing factor such as psoriasis, for example, determines whether the arthritis clears after a time or persists. Until rheumatoid serum factors have been followed up for many years it will not be possible to determine whether this is the true explanation.

Summary

The prevalence of rheumatoid arthritis has been assessed clinically, radiologically and by means of the sheep-cell agglutination test (SCAT) in seven population samples in the United Kingdom, Finland and the Netherlands. Two of these surveys included all persons from age 15 onwards. In the remaining 5, complete radiological and serological data are available only on the 55–64 age group. The total number of persons in these samples was 4,536 of whom 3,999 were examined, a completion rate of 88%.

In the population samples in Leigh and Wensleydale, in which all age groups from 15 onwards were included, 2·5% of males and 6·0% of females had definite or probable rheumatoid arthritis as defined by the American Rheumatism Association criteria. Radiological evidence of erosive arthritis was encountered in the hands or feet in 3% of males and 3% of females but severe grades were more often encountered in the females. Radiological evidence of cervical rheumatoid arthritis was found in 5% of males and 5% of females. Other sites were much less frequently affected. The SCAT was positive in 3·7% of males and 4·4% of females. The proportion of positive tests rose with age, reaching a maximum of 11% positive in males and 9% in females in the older age groups. Only a third of those with a positive SCAT had clinical or radiological evidence of rheumatoid arthritis.

There was no difference in the prevalence of 'definite' rheumatoid arthritis in the 6 population samples in Northern Europe on which full clinical data are available. Radiological evidence of rheumatoid arthritis in the cervical spine also showed no significant geographical difference, but there was significantly more erosive arthritis in the hands in the Wensleydale sample than in the population samples in Rotterdam and the Vale of

Glamorgan. The SCAT was more often positive in the urban populations of Leigh, the Rhondda and Rotterdam than in the rural population samples.

Aggregation of rheumatoid arthritis and positive SCATs in families is discussed and the relationship of rheumatoid arthritis to the benign forms of polyarthritis commonly encountered in population samples is considered.

Acknowledgments: We are indebted to Dr J Ball of Manchester and Dr T A Burch and Dr K Bloch of Bethesda for permission to quote their serological findings on the population samples reviewed in this paper, also to Dr I T T Higgins of the Pneumoconiosis Research Unit and to Dr J B Cochran of Dumfries for clinical details of their Annandale survey and permission to use their X-rays and sera.

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