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THE EPIDEMIOLOGY OF RHEUMATIC DISEASES

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Epidemiology is the study of disease in populations as opposed to patients. Its objectives are to determine the causes of disease and by their definition to enable us to introduce preventive measures designed to eliminate disease from populations rather than to cure or relieve established cases. In the time of William Heberden Epidemiology had not emerged as a separate discipline and Preventive Medicine was practically non-existent. Nevertheless Heberden made some very penetrating observations in his "Commentaries on the History and Cure of Diseases", and he recognized that disease could result from both heredity and environment.

When either heredity or environment is the predominant cause of disease the problem is relatively simple, but if disease results from the interaction of several genetically-determined characteristics and a variety of environmental conditions all of which may be of equal importance, the problem becomes very complex and the limited success so far achieved in Rheumatology may well be due to the fact that most of our problems are of this kind.

Predominance of either heredity or environment are well illustrated by two rare diseases—familial osteochondrodystrophy and Urovskaia Bolezin or Kashin-Beck's disease (Kotrchov, 1953).

An example of the former is the family shown in Fig. 1. The father was of short stature and developed an awkward gait in adolescence, followed by osteo-

arthritis of the hips and spine when aged 40 years. His wife was normal and unrelated and no similar disability nor any consanguinity could be traced in the pedigree of either family. This union produced two daughters and one son. All three children are of short stature and all developed a waddling gait in childhood. The deformities of hips and spine are similar in all (Fig. 2, overleaf). Following medical advice all three have decided not to produce any offspring. This disorder presumably arose in the father from some mutation, but since such a gene is clearly disadvantageous it can be rapidly eliminated by genetic counselling.

Kashin-Beck's disease resembles the osteochondrodystrophies in that disorders of articular cartilage and epiphyses commence in childhood and lead to deformity of the joints with predilection for the hips and spine. This curious disease was observed only in certain river valleys in the trans-baikal region of Siberia where a high proportion of the indigenous population were affected. No familial aggregation was noted, but there was temporal variation in incidence which was greater in years following wet harvests. Furthermore adults who moved into the endemic area developed a modified form of the disease. It has therefore the characteristics of disease due to environment. The environmental factor responsible is said to be infestation of the locally-grown cereals with toxic strains of *Fusaria* due to the very unusual climatic conditions of this area, and it is said that the disease is being eliminated by importing grain from outside the endemic area.

The point which I wish to make is that both these rare but fascinating diseases can be eliminated without detailed knowledge of the mechanisms of pathogenesis and it is this particular short-cut to the elimination of disease provided by the epidemiological approach which is its special attraction.

Most of the common rheumatic diseases show some degree of familial aggregation, which suggests

Fig. 1.—Family with osteochondrodystrophy affecting all three offspring of initial case.

* Delivered on December 6, 1963.

Fig. 2.—Radiographs of right hips and spine of daughter (*a*) and son (*b*) from family shown in Fig. 1. The second daughter has similar changes of intermediate severity. Both hips were affected in all three siblings.

that genetically-determined predisposition is important. Environment, however, may determine whether the disease becomes manifest, so that there should be scope for preventive measures directed against their environment if we were able to define the factors involved. To study these we need to know the proportion of our population which is genetically predisposed and if possible to find the individuals concerned. Furthermore, preventive measures which may be necessary for the predisposed may be irksome and even disadvantageous to those who are not predisposed to that particular disease.

It is current dogma that all genes produce their effects by controlling the synthesis of enzymes or proteins. Such primary biochemical defects have not so far been found in rheumatic disease, with the exception of ochronosis in which the single enzyme homogentisic acid oxidase has been shown to be absent (La Du, Zannoni, Laster, and Seegmiller, 1958). The nearest approach is perhaps the secretor state in relation to rheumatic fever (Glynn, Glynn, and Holborow, 1959).

Hyperuricaemia is a necessary condition for the development of gout, but only a proportion of individuals with hyperuricaemia develop the disease. Hyperuricaemia also shows familial aggregation, but elevation of the serum uric acid level results from the interaction of many factors of which only some are genetically determined, so that a raised serum uric acid can at best be regarded as a rather unreliable and indirect index of genetic predisposition. A high titre of rheumatoid factor also shows satisfactory familial aggregation (Lawrence and Ball, 1958; Ball and Lawrence, 1961; Ziff, Schmid, Lewis, and Tanner, 1958), and would seem to predispose to

rheumatoid disease (Ball and Lawrence, 1963), but rheumatoid factor itself is currently considered to be an antibody to abnormal or altered 7S globulins, and does not appear to be directly concerned with the pathogenesis of the arthritis, so that it is even less satisfactory as a genetic marker. We have therefore to use some indirect method of estimating the proportion of individuals in a given population who are genetically predisposed to the various rheumatic diseases. Harris (1962) has recently discussed how this may be done by the method of Penrose (1953), using the calculation shown in Table I, provided we have data on the function K , which is the incidence of the disease in relatives divided by the incidence of the disease in the general population, and what I have to say is largely based upon Professor Harris's excellent paper.

Extensive data on the incidence of rheumatic disease in the general population is difficult to obtain so that most workers have used appropriately selected control groups instead. Although these should theoretically give a slightly higher value for K , the difference for our purposes is at this stage immaterial. Nor are we certain that the rheumatic diseases as at present defined are all homogeneous entities and some may be made up of several separate conditions with different causation but similar clinical end results. In spite of these difficulties it seems desirable to examine available data in this way, since even a very rough estimate of the proportion of susceptible individuals in the population would be invaluable in planning surveys designed to study environmental factors.

Amongst the common rheumatic diseases the most marked difference between the prevalence in relatives and controls has been observed in ankylosing

TABLE I
COMMON DISEASES
PREDISPOSITION FREQUENCY, F , FOR DIFFERENT VALUES OF K , THE INCIDENCE IN RELATIVES AS COMPARED WITH POPULATION INCIDENCE

(Reproduced from Maynard-Smith, Penrose, and Smith (1961))

K	Recessive		Intermediate	Dominant	
	Parent or Child	Sib	Parent, Child, or Sib	Parent or Child	Sib
1.0	1.000	1.000	1.000	1.000	1.000
1.5	0.444	0.476	0.333	0.455	0.483
2.0	0.250	0.299	0.200	0.311	0.324
3.0	0.111	0.165	0.111	0.190	0.195
5.0	0.040	0.083	0.059	0.109	0.109
10.0	0.010	0.035	0.027	0.052	0.052
Indefinitely large	$1/K^2$	$1/4K$	$1/4K$	$1/2K$	$1/2K$
General Formula	$FK^2 = 1$	$F(2K^{1/2} - 1)^2 = 1$	$F(4K - 3) = 1$	$FK[1 + (1 - F)^{1/2}] = F + (1 - F)^{1/2}$	$4FK[1 + (1 - F)^{1/2}] = 1 + 3F + 3(1 - F)^{1/2} + F(1 - F)^{1/2}$

spondylitis, and data contributed by various authors are set out in Table II. Their differing findings are not surprising since there was no uniformity in methods of survey or diagnostic criteria, but it is clear that their results are all of the same order. The data for siblings is most complete and reliable and if we take a rough mean prevalence of 0.1 per cent. in controls and 4 per cent. in relatives, we obtain a *K* value of 40. A higher prevalence among siblings is in favour of a recessive trait but family pedigrees (Riecker, Neel, and Test, 1950; Graham and Uchida, 1957) are in favour of a single autosomal dominant. Of the ten pairs of monozygotic twins recorded (Moesmann, 1960; Julkunen, 1962) only three were discordant. If we therefore assume the dominant hypothesis as proposed by Stecher (1957), the predisposition frequency would be approximately $\frac{1}{80}$ or 1.3 per cent. Since the observed prevalence is nearer 0.1 per cent., only about one in thirteen predisposed individuals actually manifest the disease. Owing to the sex difference in incidence the manifestation rate would be higher in men and lower in women. If this interpretation is correct, environment should play an important role in the causation of spondylitis and some additional factor such as genital infection (Romanus, 1953; Mason, Murray, Oates, and Young, 1958) or other concurrent disease such as colitis, ileitis, or psoriasis, may be a necessary condition for the development of manifest spondylitis in predisposed individuals.

Hersh, Stecher, Solomon, Wolpaw, and Hauser, 1950; Stecher and Hersh, 1955) proposed a frequency of 6 per 10,000 for heterozygotes with 71 per cent.

penetrance in males and 17 per cent. penetrance in females. This would give a prevalence of approximately 0.03 per cent. for genetically-determined spondylitis, which suggests that more than half of the actual cases encountered should be something different determined entirely by environment. Some support for this comes from studies of the incidence of spondylitis and sacro-iliitis in patients with colitis and regional ileitis (Table III, opposite). Some form of spondylitis is reported in from 2.3 to 6 per cent. of patients with this type of bowel disease, but since the highest calculated frequency of predisposition for spondylitis is only 1.3 per cent. some of these cases of spinal disease must represent some other process, unless the bowel and spinal lesions are both part of the same disease process, in which case there should be marked familial aggregation of colitis and spondylitis. On the other hand, the incidence of Reiter's arthritis in patients with urethritis is only 0.8 per cent. (Csonka, 1958) to 2.2 per cent. (Laird, 1958), the higher incidence being for patients who only had non-gonorrhoeal urethritis. Since only about one-tenth of the patients with Reiter's arthritis show sacro-iliitis or spondylitis, this could be accounted for by genetic predisposition to spondylitis. Although atypical forms of spondylitis (Sharp, 1957) are not always easily recognizable as such, it seems likely that ankylosing disease of the sacro-iliac joints and spine is not a homogeneous entity but results from a variety of causes which produce a rather similar clinical picture. If this interpretation is correct the manifestation ratio for typical genetically-determined spondylitis could be quite high,

TABLE II
ANKYLOSING SPONDYLITIS IN RELATIVES AND CONTROLS

Author	Date	Relatives of Both Sexes Examined	Relatives			Controls		
			Total No.	With A.S.		Total No.	With A.S.	
				No.	per cent.		No.	per cent.
West	1949	Sibs only ..	286	10	3.5	Estimate		0.05
Stecher and Hersh	1955	Total	281	7	2.5	3,315	6	0.18
		Sibs only ..	158	6	3.8			
de Blécourt, Polman, and de Blécourt-Meindersma	1961	Total	2,478	45	1.8	2,441	2	0.08
		Sibs only ..	401	24	6.0			
Julkunen	1962	Total	821	16	1.9	539	1	0.19
Whittinghill and others	1959, 1963	Total	324	4	1.2	1,766	2	0.11
		Sibs only ..	42	2	4.8			
O'Connell	1959	Total	428	16	3.7	—	—	—
		Sibs only ..	294	9	3.0			
Karten, Di Tata, McEwen, and Tanner	1962	Total	289	4	1.4	—	—	—
		Sibs only ..	169	3	1.8			
Schmorl and Junghanns	1932		—			10,000 (Autopsies)	8	0.08
Lawrence	1963a		—			2,233	4	0.18

TABLE III

ANKYLOSING SPONDYLITIS IN ULCERATIVE COLITIS AND REGIONAL ENTERITIS

Author	Date	Total Number with Ulcerative Colitis or Regional Enteritis	Those with Ankylosing Spondylitis	
			No.	per cent.
Bywaters and Ansell	1958	109	6	5.5
Fernandez-Herlihy	1959	555	28	5.0
Acheson	1960	2,320	54	2.3
Zvaifler and Martel	1960	100	6	6.0
Rotstein, Entel, and Zeviner	1963	333	9	2.7
McBride, King, Baikie, Crean, and Circus	1963	170	4	2.4
Ansell and Wigley	1964	114	5	4.4

approaching the figure proposed by Hersh and others (1950).

A further complication is the familial aggregation of cases of ankylosing spondylitis and Still's disease reported by Whittinghill, Hendricks, Taylor, and Thorp (1959) and Ansell, Bywaters, and Lawrence (1962). Although this could be due to the interaction of two separate genes, these findings could equally result from a more peripheral presentation of spondylitis in children and women. The whole position is therefore still obscure and further investigation is clearly required. The recent finding of spondylitis in 4.2 per cent. of Haida Indians (Robinson, Gofton, and Price, 1963) indicates that the frequency of the spondylitic gene may be much greater amongst them either because of race or because of inbreeding in an isolated community. Alternatively, their environment may have been particularly favourable to the development of non-hereditary forms of spondylitis. The absence of notable familial aggregation would be consistent with either interpretation, but further data about the prevalence of spondylitis amongst other American Indians and amongst Asians would be informative.

Gout was considered a common distemper by William Heberden (1806), who stated:

"The gout is derived from gouty ancestors, or is created by intemperance, or arises from some unknown causes, which are sometimes found in the sober and abstemious, none of whose family had previously been afflicted with this distemper. Women are less subject to it than men; yet examples of gouty women are by no means rare" (p. 35).

Since Heberden's time it has become fashionable to attribute greater importance to heredity than environment in the causation of gout but this may have been due to neglect until recent years of environmental factors influencing urate excretion.

There have been many studies of the prevalence of hyperuricaemia in the relatives of gouty probands but there is little information about the prevalence of gout, and what I have been able to assemble is shown in Table IV (overleaf). The data are scanty but it would seem that the average prevalence of gout in the European and North-American populations studied by these authors is less than 0.3 per cent., whereas that in the relatives of gouty probands ranges from 0 per cent. to 9 per cent; if one takes a rough mean of 6 per cent. this would give a *K* value of 20. Both overproduction and underexcretion of uric acid may be operative (Gutman, 1960; Seegmiller and Grayzel, 1961) and there is the further complication of gout secondary to haematological disorders. Furthermore, if we compare the prevalence of hyperuricaemia in relatives and controls, using rather strict criteria for hyperuricaemia and considering only data obtained by the enzymatic spectrophotometric method (Table V, overleaf), we get a much lower *K* value of approximately 5. The position is therefore very complex and—depending upon which set of data is used and the genetic hypothesis selected—the estimated predisposition frequency ranges from 1 to 10 per cent.

One difficulty of accepting a low predisposition frequency for gout is the fact that hyperuricaemia which has been widely accepted as evidence of the gouty trait has a rather high prevalence in most population samples. Now it is known that many environmental factors can influence the concentration of uric acid in the serum. Not only have we uricosuric drugs which reduce it, but there are other drugs and dietary peculiarities that can increase it. A purine-free diet decreases the serum uric acid by only about 1 mg. per cent. (Seegmiller, Grayzel, Laster, and Liddle, 1961), but factors decreasing urate clearance have a much greater effect. Thus a

TABLE IV
GOUT IN RELATIVES AND CONTROLS

Author	Date	Relatives			Controls		
		Total No.	With Gout		Total No.	With Gout	
			No.	per cent.		No.	per cent.
Talbott	1940	136	0	0	—		
Smyth, Cotterman, and Freyberg	1948	87	3	3.4	Estimate		0.09
Hauge and Harvald	1955	261	16	6.1	266	?1	20.4
Brown and Lingg	1961	—			c.5,000	20	0.4
Anderson and Duthie	1963	—			1,422	2	0.14
Rakic, Davidson, Valkenburg, Engels, Neel, and Duff	1962, 1964	240	19	7.9	c.6,000	c.27	0.45
Popert and Hewitt Hewitt, Lawrence, and Bremner	1962 1964	73	2 ⁽¹⁾ 6 ⁽²⁾	2.7 8.2	3,259	5	0.15

(1) by new criteria (Kellgren and others, 1963) (2) by our old criteria

Note: The relatives in this Table are of both sexes and consist of all available relatives in the samples of Talbott, and Smyth and others, otherwise of mainly 1st degree adult relatives. The controls are of both sexes except in the samples of Brown and Lingg and Anderson and Duthie where they comprise only males

TABLE V
HYPERURICAEMIA IN RELATIVES AND CONTROLS

Hyperuricaemia is defined as serum uric acid above 7 mg. per cent. in males and above 6 mg. per cent. in females

Author	Survey	Date	Sex	Relatives			Controls			K
				Total No.	With Hyper-uricaemia		Total No.	With Hyper-uricaemia		
					No.	per cent.		No.	per cent.	
Hauge and Harvald	Manchester	1955	M	48	11	22.9	130	7	5.4	5.4
			F	57	15	26.3	150	6	4.0	
M and F		105	26	24.8	280	13	4.6			
Hewitt, Lawrence, and Bremner	Manchester	1964	M	34	7	20.6	144	5	3.5	4.9
			F	32	2	6.1	144	3	2.1	
			M and F	66	9	13.6	288	8	2.8	
Popert and Hewitt	Wensleydale	1962	M	10	2	20.0	436	4	0.9	11.4
			F	6	0	0	475	6	1.3	
		1963	M and F	16	2	12.5	911	10	1.1	

Note: In the first two surveys above the relatives belong to gouty probands, in the third they belong to hyperuricaemic probands. If, in the Wensleydale survey, the female controls are corrected for age distribution, K works out as 15.6

high consumption of alcohol (Lieber, Jones, Losowsky, and Davidson, 1962), or a high fat diet, or starvation (Ogryzlo, 1960; Scott, McCallum, and Holloway, 1964) can in extreme circumstances increase the serum uric acid by more than 5 mg. per cent. Many drugs have a similar effect. Pyrazinamide (Kershbaum, Feinberg, de Leon, and Bellet, 1960; Schneeweiss and Poole, 1960) is remarkably potent and also produces rises of over 5 mg. per cent.; the latter authors quote reports of joint pains in from 10 to 48 per cent. of patients taking this drug. A similar but

lesser effect is produced by the chlorthiazides and by a wide range of drugs prescribed for hypertension (Dollery, Duncan, and Schumer, 1960; Bryant, Yü, Berger, Schwartz, Torosdag, Fletcher, Fertig, Schwartz, and Quan, 1962), and by aspirin in low dosage (Brøchner-Mortensen, 1958). Many other drugs may also have a similar effect. The possibility of drug-induced gout (Lane, 1960) and diet-induced gout cannot therefore be excluded. In Western society gout is also more prevalent amongst the executive and professional classes.

The distribution of serum uric acid levels in various populations of males as reported by Hauge and Harvald (1955), Decker, Lane, and Reynolds (1962, 1963), Cobb (1963a, b), Popert and Hewitt (1962), Hewitt, Lawrence, and Bremner (1964) is shown in Figs 3 to 5. The same enzymatic spectrophotometric method was used by these authors, so that differences are unlikely to be due to variations in technique.

The curves in Fig. 3 show a more or less normal distribution about a mean of 4.8 mg. per cent., with a small secondary peak at about 8.5 mg. per cent. which is in the gouty range. The proportion of hyperuricaemics—with serum uric acid above 7 mg. per cent.—varies from 0.9 per cent. in Wensleydale to 5.4 per cent. in the Danish samples. Some of these populations are rather unrepresentative. This is especially true of the men from Wensleydale which is a marginal hill-farming area offering limited economic opportunities. The inhabitants eat a mainly carbohydrate diet, and consume little alcohol and few drugs. There are virtually no professionals and executives amongst them, and any young man with enough ability and drive to enter these classes would

necessarily have to leave the valley. As might be expected, the serum uric acid values from Wensleydale are exceptionally low. The spouses of patients attending the Manchester rheumatism department and the Danish controls are probably more representative of the general population. The American craftsmen and penitentiary inmates are selected in other ways.

The distribution of serum uric acid levels amongst male relatives of gouty probands and amongst Filipinos living on the West Coast of America is shown in Fig. 4 (overleaf). These curves are similar and could have been even more alike if the probands had been included with their relatives. Only Stecher, Hersh, and Solomon (1949) give this detailed information for both probands and relatives, and their results obtained by Benedict's colormetric method are shown in Fig. 6 (overleaf). As expected, the second "gouty" peak is large and represents in the two figures about a quarter and a third of the total, but the main peak is at about 6 mg. per cent. instead of at 4 to 5 mg. per cent. as in the various control series (Figs 6 and 3). Very similar curves are reported for Maori men (Rose and Isdale, 1963; Prior

Fig. 3.—Distribution of serum uric acid values in various male population samples:

- 436 Men from Wensleydale } (Hewitt, Lawrence, and Bremner, 1964)
- - - 144 Manchester Spouses
- 130 Danish Controls (Hauge and Harvald, 1955)
- · - 532 Craftsmen (Cobb, 1963a, b)
- - - 90 Penitentiary Inmates (Decker and others, 1962, 1963)
- | Unweighted mean average of the above five samples

In this and the three subsequent figures showing the distribution of serum uric acid in population samples, class intervals of 0.5 mg. per cent. have been chosen throughout, and random variations—which would have been rather disturbing in the curves representing the smaller samples—have been evened out considerably by using moving averages of the data from each consecutive pair of class intervals; e.g. the proportion of individuals entered at 5 mg. per cent. consists of half the sum of the proportions falling into class intervals 4.6-5.0 mg. per cent. plus 5.1-5.5 mg. per cent., the entry at 5.5 mg. per cent. consists of half the sum of the proportions falling into class intervals 5.1-5.5 mg. per cent. plus 5.6-6.0 mg. per cent., and so on.

Fig. 4.—Distribution of serum uric acid values in males from gouty families and Filipinos:

- 118 Filipinos (Decker, 1962, 1963)
 - - - 81 Relatives of Gouty Probands (Hauge and Harvald, 1955; Hewitt, Lawrence, and Bremner, 1964)
 | Unweighted mean average of the five samples shown in Fig. 3.

and Rose, 1963)—data on the latter investigation obtained by Beale's modification of Folin's method are also included in Fig. 6—and it would seem that the indigenous inhabitants of the Pacific area are one large gouty family. Lennane, Rose, and Isdale (1960) produce evidence to suggest that gout has only recently become prevalent amongst the Maori, so that their previous environment, possibly their diet of roots, fruit, and fish, must in some way have protected them from gout in spite of their apparent predisposition. There is also an impression that gout was rather rare in Europe during and just after the recent world war, which would imply an environmental effect. If we now examine the distribution of uric acid values amongst American executives and medical students reported by Cobb (1963), shown in Fig. 5 (opposite), we see a large secondary peak at 6 mg. per cent., only the executives showing a definite but small peak in the gouty range. From an analysis of these results, Dunn, Brooks, Mausner, Rodnan, and Cobb (1963) conclude that hyperuricaemia is related to the personal characteristics favouring entry into the executive and professional classes and that this rather than high living accounts for the excess of gout found in these classes.

The explanation for the peak at 6 mg. per cent. in these various curves is not clear, but it may possibly represent a population of heterozygotes with the "gouty" peak representing homozygotes. Since there may be two genes involved, one determining overproduction and the other underexcretion of uric acid, the "gouty" populations might also include individuals heterozygous for both. If this were so,

genetically-determined predisposition for some degree of hyperuricaemia would have a much greater frequency than previously supposed and in Europe this could be in the 5 to 10 per cent. range suggested by the *K* values derived from studies of hyperuricaemia. Environmental factors that could alter the serum uric acid level by 2 to 3 mg. per cent. could then produce big differences in the prevalence of gout, which would be consistent with the historical data.

In osteo-arthritis and disk degeneration, we still lack adequate definition of many aetiologically distinct types which might be genetically determined, except in isolated examples such as osteochondrodystrophies (Allison and Blumberg, 1958) and congenital dislocation of the hip (Calandriello, 1963). Heberden's nodes, however, have been studied extensively by Stecher (1940, 1941), Stecher and Hersh (1944), and Stecher, Hersh, and Hauser (1953), and Stecher himself devoted a previous Oration to this subject (1956). Our own more limited survey (Kellgren, Lawrence, and Bier, 1963) gives results of the same order. Heberden's nodes are some 2½ times more frequent in female relatives than in controls, which means that—assuming the dominant hypothesis—somewhat less than 25 per cent. of the female population are predisposed (Table VI, opposite). Since according to the findings of Stecher (1940) and our own records, more than 30 per cent. of women over 80 years of age have nodes, the manifestation becomes complete if the individual lives long enough, and a considerable proportion of nodes should result from purely environmental factors.

Fig. 5.—Distribution of serum uric acid values in male executives and medical students:

--- 96 Students from Medical School } (Cobb, 1963a, b)
— 339 Executives
| Unweighted mean average of the five samples shown in Fig. 3.

Fig. 6.—Distribution of serum uric acid values in males from gouty families, male Maoris, and normal hospital population of both sexes:

— 135 Maoris (Prior and Rose, 1963)
--- 85 Gouty Probands and Relatives
..... 56 Relatives Only in Above Sample
- . - . 927 Tests on 878 Males and Females of Normal Hospital Population } (Stecher and others, 1949)

TABLE VI
HEBERDEN'S NODES IN FEMALE RELATIVES

Authors	Date	Sisters and Mothers					K
		Age (years)	Total No.	Affected			
				No.	per cent. of Total		
					Observed	Expected*	
Stecher	1941, 1956	50 +	148	50	34	15	2.3
Kellgren and others	1963	45 +	31	14	45	10	4.5

* From control samples of more than 600 and more than 400

The importance of mechanical stress in the production of degenerative joint disease is well established, as exemplified by traumatic Heberden's nodes and the fact that Heberden's nodes do not form in paralysed hands (Stecher and Karnosh, 1947). Certain occupations are associated with degenerative changes in appropriate joints, such as increased degeneration of lumbar disks in miners and other groups of workers engaged in heavy lifting (Kellgren and Lawrence, 1952; Lawrence, 1955) or osteoarthrosis of the fingers of cotton workers (Lawrence, 1961a).

The climatic environment has not been shown to influence the prevalence and severity of joint disease, but it does appear to influence the complaint threshold. Thus, for a given degree of radiological change, pain and disability is greater than expected in men working in a cold wet environment (Lawrence, 1955) and less than expected in those working in hot dry environment (Lawrence and Molyneux, 1964). This is in accord with popular belief and could indeed have been predicted from observations of the effect of cooling on deep pain sensibility (Kellgren, McGowan, and Hughes, 1948).

Racial differences have also been reported. Thus Stecher (1940) observed a very low prevalence of idiopathic Heberden's nodes in Negro women living in the United States, although the prevalence of traumatic nodes was similar in both the white and coloured women he studied. Eskimos in Alaska also have a rather low prevalence of osteo-arthritis (Blumberg, Bloch, Black, and Dotter, 1961) and the disease is reported to be uncommon in Japan (Shichikawa, 1963). Genetically-determined susceptibility to degenerative joint disease has also been studied extensively in laboratory animals (Sokoloff, Crittenden, Yamamoto, and Jay, 1962; Sokoloff, 1963). There is thus an urgent need for new data on the familial aggregation of various forms of degenerative joint disease in man before studies of other environmental factors such as diet can be undertaken with confidence.

Rheumatic fever shows only a slight degree of familial aggregation as compared with the incidence in the general population (Stevenson and Cheeseman, 1953; Glynn and others, 1959) giving low *K* values of approximately 1.5, which means that nearly half the population is genetically predisposed. Since the incidence of rheumatic fever is very much less, environment is most important, and indeed rheumatic fever shows all the characteristics of a disease due predominantly to environment. Its incidence varies greatly in different countries and in different social classes. Important variations of incidence with time are also well recognized, epidemics of rheumatic

fever being clearly related to epidemics of streptococcal pharyngitis, and over the last hundred years there has been a marked decline of its severity and incidence in the more affluent communities. For instance, in Copenhagen the annual notifications of rheumatic fever fell from over 40 per 1,000 inhabitants in 1878 to 4.6 per 1,000 inhabitants in 1945 (Clemmesen, 1949). Certified deaths from scarlet fever in England and Wales over the same period showed an even greater decline, the death rate from this cause per million inhabitants falling from 1,500 in the middle of the 19th century to practically nothing today. A similar but less dramatic decline in mortality from rheumatic fever and disease of the mitral valve has also been observed in England and Wales during the last 40 years (Fig. 7). These changes could have resulted from improved socio-economic conditions and medical treatment or from biological decline in the virulence of the streptococcus, but the fact that rheumatic fever is still very prevalent today in some of the less affluent popula-

Fig. 7.—Mortality from diseases of the mitral valve, rheumatic fever, and rheumatoid arthritis and related diseases in England and Wales, based on the Registrar General's Statistical Reviews for England and Wales. The sudden drop in certified deaths from rheumatoid arthritis in 1950 corresponded with the introduction of new instructions for certification.

tions suggests that the former is certainly important.

By contrast, there is no evidence for any marked decline in the prevalence or severity of rheumatoid

arthritis, although we have much less information about this disease. Certainly it was important in the time of William Heberden, who stated that:

"The distemper of which I am speaking seems confined to no sex, and hardly to any age. The rich and the poor are equally liable to it. It has happened to me to see rather more women than men afflicted with it. In some it has begun at the age of twelve years; in others not till they were past sixty. Is it not in some degree hereditary?" (p. 499).

What can we add to this statement made over 160 years ago?

The question of heredity has been more clearly defined in that several authors have reported significant familial aggregation (Table VII). The K value derived from these results ranges from 4.0 to 5.9, with the exception of the anomalous results of Neri Serneri and Bartoli (1956) which give a K value of 16.1. If we take an approximate mean K value of 5, this gives a predisposition frequency on the various genetic hypotheses of between 6 and 11 per cent. If we include all grades of rheumatoid arthritis, the prevalence of disease in the oldest age groups approaches this figure (Lawrence, 1961b). This suggests that the effect of environment is mainly to determine the age at onset and the severity of manifest disease. It might therefore be informative to study young adults with severe disease, but with such a high predisposition frequency the number of homozygotes would be sufficient to account for a significant proportion of such cases and we have at present no reliable method of determining homozygosity for the rheumatoid trait. None of the characteristics associated with environmental causes of disease have so far been observed in rheumatoid arthritis. Thus the social classes appear to be equally affected and no association with occupation has been noted. If environment is important, it seems likely that the factor(s) concerned operate

fairly uniformly throughout the populations that have so far been studied.

The geographic incidence of the disease seems to be rather uniform in North-Western Europe (De Graaff, Laine, and Lawrence, 1963). In North America (Cobb, Warren, Merchant, and Thompson, 1957; Mikkelsen, Dodge, Duff, Epstein, and Napier, 1963), the prevalence may be a little less, and amongst the Eskimos (Blumberg and others, 1961) and the Japanese (Shichikawa, 1963) it appears to be even lower. Neri Serneri and Bartoli (1956) also noted a lower prevalence in Italy, but the increased familial aggregation observed by them suggests that this finding might be accounted for by a lower predisposition frequency in the population they were studying. No country or race has so far been shown to be free from rheumatoid arthritis, except the 259 inhabitants of Tristan da Cunha (Black, Lewis, Thacker, and Thould, 1963).

One of our difficulties is the complexity of the rheumatoid process. On the one hand there is the arthritis which is some three times more prevalent in women than men—a sex difference which may be related to the more delicate structure and earlier decline of the supporting tissues in females. On the other hand, we have a variety of immunological phenomena of which rheumatoid factor, which occurs equally in both sexes, is the most characteristic. In population studies rheumatoid factor is frequently found in the absence of arthritis. Furthermore, it occurs rather frequently in other diseases, such as systemic lupus erythematosus, scleroderma, pulmonary fibrosis, etc. Conversely, L.E. cells and various antinuclear factors occur at some stage in many patients with severe rheumatoid arthritis. Thus we may be dealing with a pleomorphic disease with both articular and non-articular manifestations (Ziff, 1961). If this is so, the absence of arthritis may not be synonymous with the absence of manifest disease.

TABLE VII
RHEUMATOID ARTHRITIS IN RELATIVES AND CONTROLS

Author	Date	Relatives			Controls			K
		Total No.	With Rheumatoid Arthritis		Total No.	With Rheumatoid Arthritis		
			No.	per cent.		No.	per cent.	
Stecher, Solomon, and Wolpaw	1953	1,443	49	3.4	2,759	16	0.6	5.9
Miall	1955	354	11	3.1	502	3	0.6	5.2
Neri Serneri and Bartoli	1956	1,163	71	6.1	2,857	11	0.4	16.1
Lawrence and Ball	1958	183	16	8.7	183	4	2.2	4.0
De Blécourt and others	1961	741	25	3.4	2,441	20	0.8	4.1

Note: The relatives in this Table consist of parents, sibs, and mostly adult offspring of both sexes, with the exception of Miall's sample in which they consist of fathers and brothers only. The controls are distributed accordingly

An extensive survey recently completed by Ansell and Lawrence (1963) has not revealed any excess of rheumatoid arthritis amongst the relatives of probands with lupus erythematosus, which is against any interaction between the genetic predisposition to these two diseases. The presence of manifest rheumatoid arthritis may however predispose to the development of some of the characteristics of lupus erythematosus.

A dual aetiology has been proposed by Lawrence (1963b) and my own working hypothesis is that a proportion of our population is genetically predisposed to develop certain immunological abnormalities, of which we at present possess only indirect indices. Whether the immunological abnormalities develop or not may be determined by environmental factors such as repeated infections and other forms of antigenic stimulation (Christian, 1963). The development of clinically manifest disease and its localization in joints could be determined by quite other factors such as mechanical stress and indeed anything which can influence the maintenance of connective tissues. A whole series of factors could therefore lead to the development of rheumatoid arthritis and these could differ both qualitatively and quantitatively in individual cases.

The aetiology of rheumatoid arthritis has recently been discussed by many authors (Burnet, 1959; Ziff, 1961; Burch, 1963; Lawrence, 1963b; Ford, 1963), but we need more information about the nature of the disease process and more data on populations in which the prevalence and form of rheumatoid disease on the one hand and of serological abnormalities on the other differ from those studied so far before the relative merits of rival hypotheses can be assessed. The results from the surveys in Jamaica (Lawrence, 1963c) and the various Indian Reserves in America (Burch, O'Brien, Lawrence, Bennett, and Bunim, 1963) are likely to be of the greatest value, and studies of communities in Asia and Africa are urgently required.

This review of the aetiology of rheumatic disease has of necessity been very superficial, but the broad view may sometimes reveal useful perspectives. What seems to me to emerge is that genetically-determined predisposition and environmental factors are of roughly equal importance in the causation of most rheumatic diseases, and that we should think in terms of multiple causes when planning epidemiological studies or clinical investigations and even when undertaking the care of individual patients.

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