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The epidemiology of sarcoidosis

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Summary

The nationality, social factors, exposures, morbidity, mortality, and hospital discharge notes have been analysed in a series of patients with histologically proven sarcoidosis, and correlated with clinical and radiological features.

Compared with the expected prevalence according to the Central London population obtained from the 1961 Census, Irish and West Indians attended the Sarcoidosis Clinic twice as frequently as British, whereas African Negroes are under-represented.

Sarcoidosis is slightly commoner in women, particularly those in the childbearing years of life.

Mass miniature radiography rates per 100,000 population reveal prevalence rates of twenty overall, forty-three in those aged 25–34 years, and ten in those aged over 45 years.

Erythema nodosum, other skin lesions, and ocular involvement occurred twice as often in women.

The death-rate of about $1{\cdot}7/10^6$ population is slightly higher in women and in those living in rural districts.

Hospital discharge rates are about three per 100,000 people at risk each year.

Introduction

Sarcoidosis is confined to human beings. Nothing quite like it has so far been found in the veterinary world, and this may be one reason why nobody has yet succeeded in transmitting it to an experimental animal. Non-specific local sarcoid-tissue reactions are, of course, easily produced in animals but these are quite different from the generalized multi-system disease, sarcoidosis. Is man uniquely susceptible because of his peculiar social habits or are certain humans particularly vulnerable as a consequence of their internal or external environment? We have collected data in an endeavour to detect any possible human factors which may predispose to sarcoidosis.

Materials and methods

Nationality

All patients were personally examined in the Royal Northern Hospital Sarcoidosis Clinic; they comprised 454 with both histological confirmation of the diagnosis and known nationality. They were grouped into British (English, Scots and Welsh), Irish (including Northern Ireland), West Indian, Cypriot, African Negro and 'Others'. The prevalence of each of these national groups was compared with its expected prevalence according to the Central London population obtained from the 1961 Census. Thereafter, for further analyses the Cypriots and African Negroes were included under Others to make four compact groups—British, Irish, West Indian and Others. 'Others' comprised nineteen various Europeans, five Cypriots, two African Negroes, two American Negroes, two Indians and two Pakistanis. Chest X-ray appearances consisted of bilateral hilar node enlargement (Stage 1); bilateral hilar lymphadenopathy with pulmonary infiltration (Stage 2); pulmonary infiltration with or without fibrosis (Stage 3); and a normal chest radiograph (Stage 0). The prevalence of erythema nodosum, lymph-node enlargement, skin and eye lesions were compared in the four national groups in relation to these X-ray categories, and the results expressed as the rate per 100 patients in each X-ray category.

Social factors

An unselected group of 895 patients were asked to complete a questionnaire (Table 1) couched in terms comprehensible to the layman. When each patient returned the form he was interviewed so that we could obtain information on more complicated medical points which are included in the results of this survey. Four hundred and fifty-four patients completed the survey. The patients who returned the survey form did not, surprisingly, differ significantly

TABLE 1. The questionnaire answered by 327 patients with sarcoidosis and 127 control subjects.

Name Date of birth No.
Mr. Mrs. Miss Place of birth Year of onset
Diagnosis (controls)
Single, Married, Widowed

1. *Occupation*: Type of work
Industry
Do you come into contact with:
(a) Hay
(b) Farm animals (specify types)
(c) Trees or sawdust (specify type of tree)
(d) Dusts or coal, silica, asbestos, beryllium; other dusts (specify types)

2. Hobbies
Material used

3. Places of residence in this country and abroad (residence of over 6 months only need be included from the age of 16 to the present)

Town	*Country*	*Dates*

4. Were any of the places you lived in close to woods or forests?
If yes, which?

Place	*How close*	*Kind of trees*

5. Pets: Have you ever kept pets in the family or been in contact with them?

Type of pets	*Approximate dates*

6. List fuels used for home heating or cooking and indicate approximate dates of use.

7. At what age did you start smoking stop smoking
Do you smoke manufactured cigarettes (Tipped/untipped) yes/no
Cigars yes/no
Hand rolled cigarettes yes/no
Pipe yes/no
How many cigarettes do you smoke a day?
How many ounces of tobacco do you smoke a week?

8. *Obstetric history*
Year
Number of pregnancies
Pica (during pregnancy or at any other time) *Outcome* (full term, abortion, etc.)
Menstrual history *Details of feeding*

Further family history

	Age if alive	Date of death	Age at death	Cause of death
Mother				
Father				
Brothers and sisters				
Children				
Details of any family history suggestive of:				
Sarcoidosis (skin, chest, eye disease)				
Tuberculosis				
Allergies				

from those who failed to do so. The figure of 454 comprises 257 with histologically confirmed sarcoidosis; seventy in whom the diagnosis was made on clinical and radiological grounds, but without histological proof; and 127 cases in which sarcoidosis was excluded by our investigations and by their subsequent clinical course. The sarcoidosis patients with histological proof did not show any significant differences from those without histological proof when analysed separately, so the two sub-groups of 257 and seventy patients were combined and compared with the non-sarcoid group. This 'non-sarcoid' group comprised conditions which most frequently present in a sarcoidosis clinic in the differential diagnosis of sarcoidosis; namely, uveitis, pulmonary infiltration including tuberculosis, neoplasms and reticuloses, and hepatic granulomas. The series of 127 patients in which sarcoidosis was subsequently disproved provided a conveniently built-in control group since they had been given the

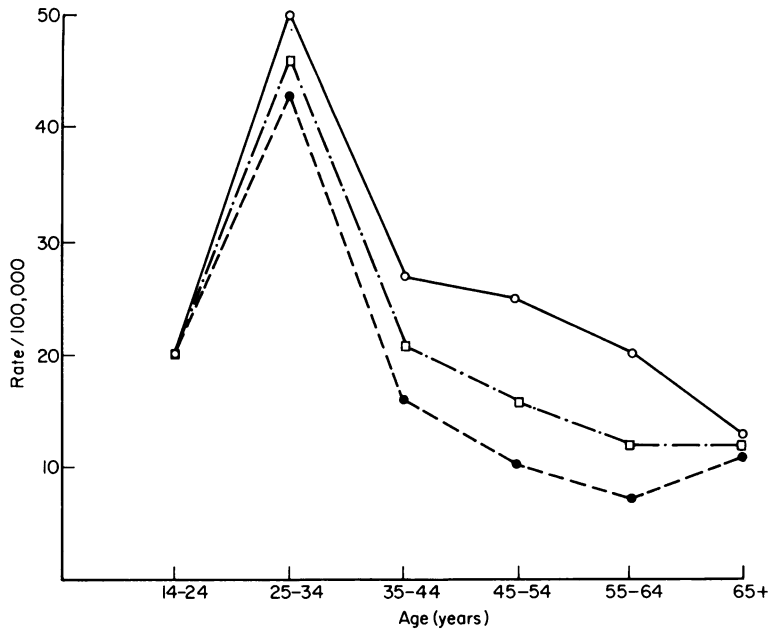

FIG. 1. Prevalence rate of suspected sarcoidosis/100,000 discovered by mass miniature chest radiography in England and Wales, 1961–64. O, Female; □, total; ●, male.

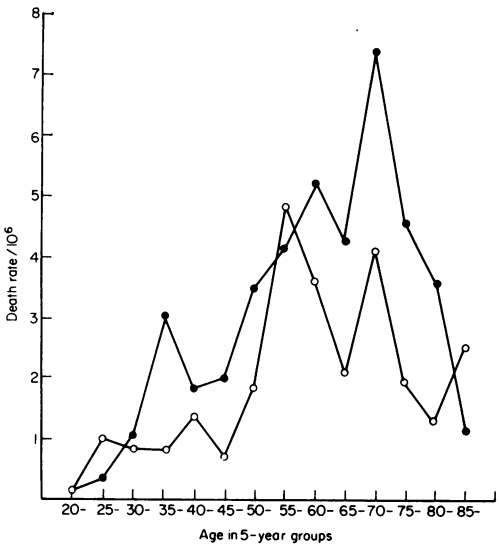

FIG. 2. Mean death rates for sarcoidosis/10^6, 1962–65. O, Male; ●, female.

questionnaire and interviewed in exactly the same way as had the 327 patients with sarcoidosis.

Mortality and morbidity

Data from mass miniature radiography are presented as in previous reports (James & Brett, 1964) as the number of suspected cases of sarcoidosis discovered by mass miniature radiography in England and Wales for the years 1961–64 with the rate per 100,000 X-rayed, expressed according to age and sex (Table 2 and Fig. 1).

Death-rates for sarcoidosis per 10^6 population in England and Wales for the years 1962–65 are expressed according to age, sex and geographical distribution (Table 3 and Fig. 2). They were compiled by the Registrar General's Office from the analysis of all death certificates in England and Wales using the International Classification of Disease Code No. 138·0, and the underlying cause of death in Part 1 of the death certificate. Geographical comparisons are made only with 1962–64 figures since the boundaries were changed in 1965 and are not strictly comparable (Table 4). Death-rates for 1963–65 are presented according to the size of community the patient had lived in (Table 5). These figures were not available for 1962.

Hospital discharge rates

Estimated hospital discharge rates for sarcoidosis derived from the Hospital In-Patient Enquiry are given for hospital regions (Table 6). This enquiry is organized by the Ministry of Health and the Registrar General's Office. Medical and demographic data are collected for one patient in every ten who are discharged from, or die in, non-psychiatric hospitals in England and Wales.

TABLE 2. Prevalence rates per 100,000 X-rayed of suspected sarcoidosis discovered by mass miniature radiography in England and Wales in the years 1961–64 (figures are from the Registrar General)

Age	Male			Female			Total		
	No. discovered	No. surveyed	Rate	No. discovered	No. surveyed	Rate	No. discovered	No. surveyed	Rate
All ages	1504	7,534,620	20	1462	5,350,670	27	2966	12,885,290	23
14–24	320	1,622,980	20	347	1,730,930	20	667	3,353,910	20
25–34	671	1,561,020	43	484	974,140	50	1155	2,535,160	46
35–44	263	1,619,910	16	284	1,045,170	27	547	2,665,080	21
45–54	145	1,455,570	10	213	856,860	25	358	2,312,430	16
55–64	74	995,030	7·4	104	516,050	20	178	1,511,080	12
65 and over	31	280,110	11	30	227,520	13	61	507,630	12

TABLE 3. Deaths at all ages from sarcoidosis in England and Wales 1962–65

Year	Male		Female		Total	
	No. of deaths	Death rate/10^6 population	No. of deaths	Death rate/10^6 population	No. of deaths	Death rate/10^6 population
1962	37	1·63	44	1·83	81	1·73
1963	24	1·05	58	2·40	82	1·74
1964	21	0·91	56	2·30	77	1·62
1965	26	1·12	40	1·63	66	1·38

TABLE 4. Mean death rate for sarcoidosis/10^6 population 1962–64 according to region

Region	Death rate/10^6			1951–61
	Males	Females	Persons	Persons
Northern	0·83	0·60	0·71	1·16
East and West Ridings	0·81	1·53	1·18	0·61
North Western	0·31	1·74	1·06	0·63
North Midland	2·23	1·77	2·06	1·28
Midland	0·97	1·76	1·37	1·25
Eastern	0·87	3·70	2·30	1·58
London and South Eastern	1·06	1·81	1·45	1·48
Southern	0·90	2·87	1·90	1·71
South Western	3·51	4·81	4·18	2·09
Wales I (Breconshire, Carmarthenshire, Glamorgan and Monmouthshire)	0·71	2·74	1·74	1·39
Wales II (remainder)	3·69	2·57	3·11	1·62

TABLE 5. Death rates for sarcoidosis/10^6 population according to size of community

	1963–65			1952–61
	Males	Females	Persons	Persons
Conurbations	0·61	1·40	1·02	
Urban areas, 100,000 +	1·20	1·65	1·43	0·82
Urban areas, 50,000–100,000	0·79	1·91	1·37	1·51
Urban areas, 50,000	1·98	3·36	2·69	1·46
Rural districts	1·58	2·84	2·21	1·74

TABLE 6. Hospital discharge rate for sarcoidosis according to hospital region 1961–64

Hospital region	Discharge rate 100,000		
	Male	Female	Persons
All regions	2·8	3·0	2·9
Newcastle	2·1	2·2	2·1
Leeds	1·0	1·9	1·5
Sheffield	2·7	2·7	2·7
East Anglia	2·7	4·0	3·4
Wessex	3·2	2·8	3·0
Oxford	4·5	5·9	5·2
South Western	2·8	3·2	3·0
Wales	5·5	4·3	4·9
Birmingham	1·9	1·7	1·8
Manchester	2·2	1·7	1·9
Liverpool	2·2	1·6	1·9
Metropolitan Regions			
North West	4·4	4·2	4·3
North East	2·9	4·4	3·7
South East	1·9	3·2	2·6
South West	4·0	3·1	3·5

The discharge rate is estimated from a 10% sample and expressed per 100,000 people at risk (data from Hospital in-patient Enquiry).

Results

Nationality

The prevalence of British and Cypriot patients attending the Sarcoidosis Clinic is similar to their prevalence in the London population (Table 8 and Fig. 3). The Africans are under-represented at the Clinic, attending half as frequently as the English, while the Irish and West Indians appear 2·5 and 2·3 times more frequently than their numbers in the population would suggest.

Females are slightly commoner in the different national groups, in the ratio 248 females to 206 males (Table 7).

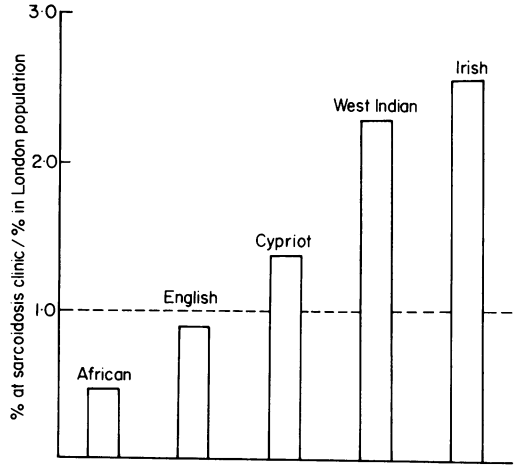

FIG. 3. The ratio of various nationalities presenting at the Sarcoidosis Clinic compared with their prevalence in the London Population Census of 1961.

TABLE 7. Sex ratio and nationality

	Male	Female	Total	M/F ratio
British	151	188	339	0·80
Irish	28	32	60	0·88
West Indian	11	12	23	0·92
Other	16	16	32	1·0
Total	206	248	454	0·83

Chest radiographic appearances are similar in all groups, except that the Irish had fewer normal X-rays (Table 9 and Fig. 5). Only 3% of the Irish had a normal chest radiograph compared with 13% of the total, whereas 80% had Stage 1 and 2 chest X-ray abnormalities, slightly more than the average.

Erythema nodosum was commoner in the Irish than in any other group; and, interestingly, it was not noted in this group of West Indians (Table 10). It was twice as common in women (Table 11) and also more frequently associated with intrathoracic hilar lymphadenopathy (Fig. 4).

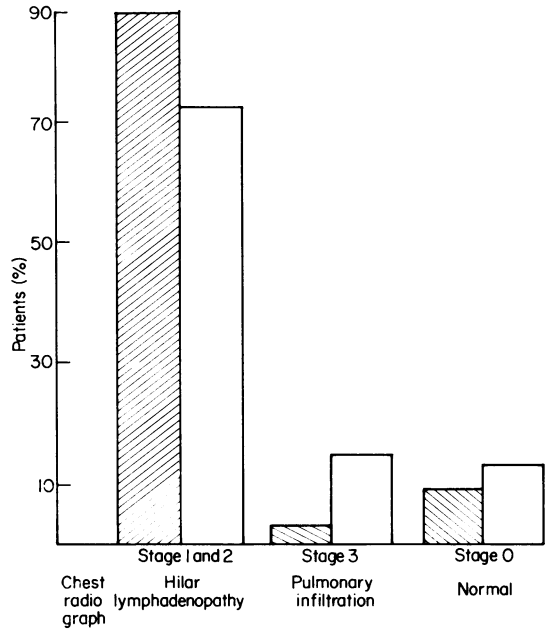

FIG. 4. Chest radiograph appearances associated with erythema nodosum (hatched columns) compared with the whole series (open columns).

Peripheral lymphadenopathy was noted in nearly half the West Indians compared with one-third of the other nationalities (Table 10).

TABLE 8. Different nationalities attending the Royal Northern Hospital sarcoidosis clinic compared with the Central London Population Census (1961)

	Sarcoidosis patient		Central London Population Census	
	No.	%	No.	%
British	339	75	2,553,609	80
Irish	60	13	152,905	4·8
West Indian	23	5	70,139	2·2
African	2	0·4	27,757	0·9
Cypriot	5	1·1	26,308	0·8
Other	25	5·5	369,766	11·3
Total	454	100	3,200,484	100

TABLE 9. Chest X-ray appearances compared with nationality

Chest X-ray stage	British		Irish		West Indian		Others		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
0	48	14	2	3	4	17	6	19	60	13
1	156	46	31	52	10	43	16	50	213	47
2	85	25	17	28	5	22	7	22	114	25
3	50	15	10	17	4	18	3	9	67	15
Total	339	100	60	100	23	100	32	100	454	100

TABLE 10. Frequency of various clinical manifestations in relation to nationality

	Total	Erythema nodosum		Peripheral lymphadenopathy		Skin lesions		Eye lesions	
		No.	%	No.	%	No.	%	No.	%
British	339	117	34·5	98	28·6	88	26	93	27·4
Irish	60	32	55	19	31·7	13	21·7	13	21·7
West Indian	23	0	0	11	48	9	39	7	30·5
Other	32	9	28	12	37·5	4	12·5	7	21·8
Total	454	158	34·8	140	30·8	114	25·1	120	26·4

TABLE 11. Frequency of various clinical manifestations in relation to sex and nationality

	Erythema nodosum			Peripheral lymphadenopathy			Skin lesions			Eye lesions		
	M	F	M/F	M	F	M/F	M	F	M/F	M	F	M/F
British	38	79	0·48	50	48	1·04	29	59	0·49	30	63	0·48
Irish	13	20	0·65	9	10	0·9	4	9	0·44	6	7	0·86
West Indian	—	—	—	5	6	0·83	3	6	0·5	2	5	0·4
Other	2	7	0·29	7	5	1·4	3	1	3·0	5	2	2·5
Total	53	106	0·50	71	69	1·0	39	75	0·52	43	77	0·56

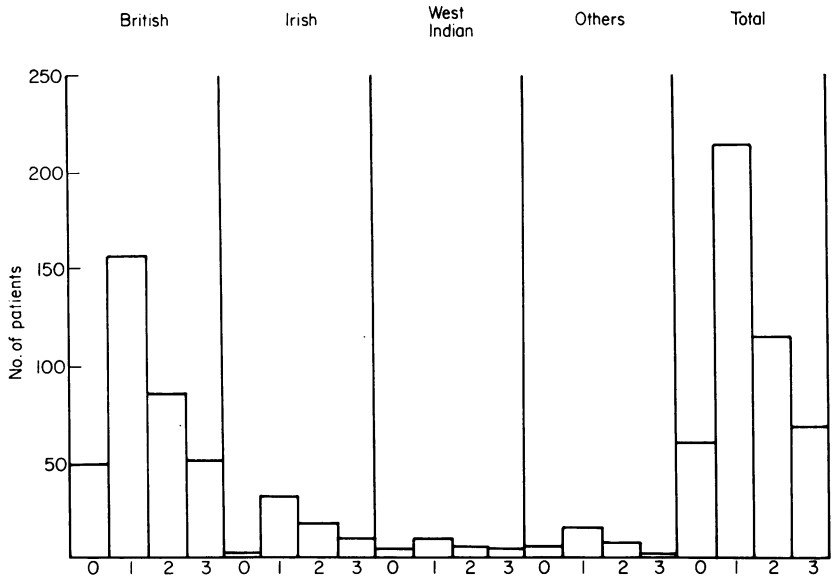

FIG. 5. Chest X-ray appearances compared with nationality.

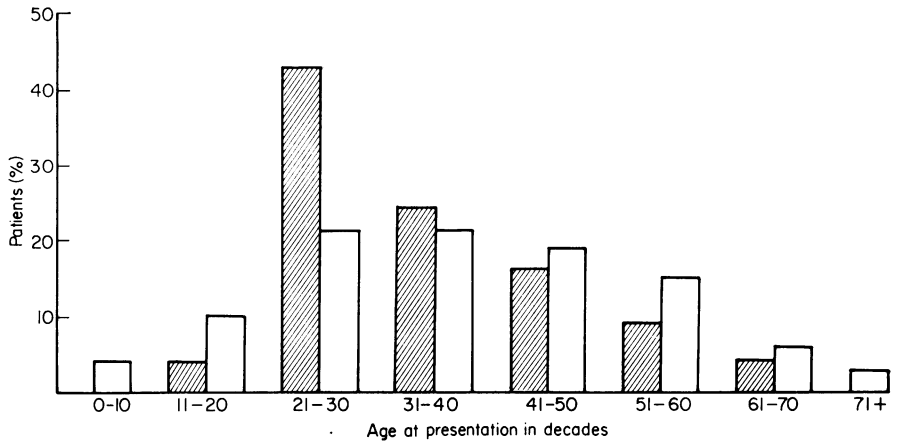

FIG. 6. Decade at presentation of 327 patients with sarcoidosis (hatched columns) and 127 control subjects (open columns).

Skin lesions, other than erythema nodosum were noted in one-quarter of the whole series, being somewhat more frequent in West Indians in whom they were seen in 39% (Table 10). They were always common in women (Table 11).

Eye lesions occurred in 120 of the 454 (26·4%), again more commonly in women, but equally distributed amongst nationalities.

Social factors

Age and sex. The majority of patients in both groups were in the third or fourth decades of life at the onset of their illnesses (Fig. 5). This tendency was more pronounced in the group with sarcoidosis in whom 218 of the 327 (67%) were between 20 and 40 years of age, compared with forty-three of 127 (33%) of the controls.

The sex incidence was similar in both groups; 152 of 327 (47%) sarcoidosis patients and forty-eight of 127 (38%) controls were male.

Associations (*Table* 12). *Contact with tuberculosis:* Ninety-seven of the 327 (27%) patients with sarcoidosis and thirty-three of the 127 (27%) control group admitted direct contact with tuberculosis at some time during their lives.

TABLE 12. History of contact in 327 patients with sarcoidosis compared with 127 controls

	Sarcoidosis		Other diseases	
	No.	%	No.	%
Known contact with tuberculosis	87	27	33	27
History of chest disease in relatives	48	15	39	31
Possible respiratory irritants				
Pine	8	3	2	2
Other trees	55	19	19	16
Cotton	7	2	0	0
Clay	1	1	0	0
Minerals	59	20	17	24
Domestic fuel				
Coal	241	79	99	77
Gas	192	63	90	70
Oil	70	23	30	23
Electricity	125	41	55	43
Pets				
Dogs	181	55	64	52
Cats	143	43	59	47
Birds	73	22	29	23
Smoking				
Cigarettes	121	37	43	34
Pipes	27	9	1	1
Cigars	17	5	2	2
Pregnancies (as no. of children per woman)	1·4		1·6	
Breast-fed children	141/260	54	68/125	54
Urban birthplace	210	63	87	65
Rural birthplace	117	37	40	34
Urban domicile for more than 10 years	282	86	114	90
Rural domicile for more than 10 years	104	32	31	24

Chest disease in their relatives: Forty-eight of the 327 (15%) sarcoidosis patients and thirty-nine of the 127 (31%) controls registered a family history of other chest disease, including bronchial carcinoma, bronchitis and asthma.

Exposure to inhalants: Both sarcoidosis and control groups claimed the same exposure to pine and other trees, cotton, clay, coal and other minerals.

Domestic fuel: The majority of both groups used coal or gas; somewhat fewer used electricity and one-quarter were exposed to oil. About 5% lived in smokeless zones.

Smoking: There was no significant difference between the smoking habits of sarcoidosis patients and control subjects. About one-third smoked cigarettes, fewer smoked a pipe and still fewer smoked cigars.

Pets: In this predominantly white English community about one-half kept dogs, nearly as many kept cats, and nearly one-quarter had pet birds. Pet-keeping was equally common in sarcoidosis and control groups.

Pregnancy and breast-feeding: As estimated by the number of children per woman, sarcoidosis patients had 1·4 children and the control group 1·6 (54% of women in both groups breast-fed their children).

Morbidity and mortality.

The mass radiography figures show the usual peak incidence around the age of 30 years. It is slightly higher in women, and the discovery rate remains fairly high in women well on into the sixth decade, whereas it falls off more sharply in men (Fig. 1 and Table 2).

Death-rates are slightly higher in women, and have shown no tendency to increase in recent years (Table 3). The mean death-rate is $1{\cdot}6/10^6$ for the years 1962–65. The peak in death-rate occurs between 55 and 70 years, and is earlier and somewhat lower in men (Fig. 2).

Regional analysis of death-rate shows a higher rate in the South West and part of Wales, with a fairly high rate for women in East Anglia and the Southern region also (Table 4).

The death-rate is higher in towns of less than 50,000 inhabitants and in rural areas than in larger towns and big cities (Table 5).

When discharge rates are analysed by hospital regions (Table 6), the results for the South West are not especially high and so do not support the higher death-rate found there. Conversely the North West, which has a low death-rate, has a fairly high discharge rate, whereas Wales has both a fairly high discharge and death-rate. The overall discharge rate is three patients discharged per 100,000 population at risk per year.

Discussion

These results confirm the well-known increased frequency of sarcoidosis in West Indians and Irish (James & Brett, 1964; Brett, 1965), but the increase of between two and three times the frequency of the local population is modest compared with that between Negro and White Americans which is tenfold (Siltzbach, 1964). Figures for Cypriots, a group in which sarcoidosis is usually considered to be uncommon, may be biased by the Royal Northern Hospital's proximity to the largest Cypriot community in London, but sarcoidosis may be more common than is realized. This could be tested by mass radiography of the now large Cypriot community.

Sarcoidosis is relatively uncommon in Africa, and these figures though very small support this concept. Siltzbach would attribute this to the scarcity of physicians, and also to the frequency of tuberculosis, with which it may be confused. Once tuberculosis is eradicated from a community, sarcoidosis always becomes more evident.

Sarcoidosis is only slightly commoner in women, occurring in 302 of 537 (56%) patients with histological confirmation in the Royal Northern Hospital Series, but erythema nodosum, skin and eye lesions are much more frequent in women. Erythema nodosum was particularly frequent in Irish women. It would be interesting to learn whether this nonspecific hypersensitivity reaction when due to other causes is also more frequent in Irish women because of their distinctively fair complexion or some other genetic factor. It is certainly rare in those with the opposite colouring; it was not seen in twenty-three West Indians in this series, and it is regarded as very rare in the American Negro with sarcoidosis.

The relationship between sarcoidosis and tuberculosis has been hotly debated. The evidence for and against tuberculosis as an aetiological factor in sarcoidosis has been admirably summarized by Siltzbach (1968) who concludes that the one disease is not a cause of the other. In this series exposure to the tubercle bacillus was precisely similar (27%) in both sarcoidosis and control subjects; tuberculosis did not seem to give rise to or to protect against sarcoidosis. Comstock and his co-workers (Comstock, 1949; Comstock, Keltz & Sencer, 1961) have shown similar results in a study of seventy-four patients, predominantly coloured, in Georgia. They found a negative association of family tuberculosis or household association with the disease, which was however not statistically significant: they emphasize that it is unlikely that chance would have obscured a strongly positive association. In a study of the distribution of the two diseases in Denmark, Horwitz (1961) compared the geographic distribution of sarcoidosis with the tuberculin pattern in the general population (as represented by participants in a mass immunization campaign), the geographic tuberculin pattern in cattle, and the geographic pattern for the incidence of pulmonary tuberculosis. He found no correlation between sarcoidosis and these factors. Shook and his colleagues (Shook *et al.*, 1962) likewise concluded that there was no association between sarcoidosis and tuberculosis in Oklahoma.

A family history of other chest disease including carcinoma of the bronchus, chronic bronchitis and congestive cardiac failure was sought from our patients. There was no significant difference in the incidence of these illnesses in patients and control subjects. The apparently higher incidence of chest disease in the families of controls possibly occurs because the greater number of women in this group were more prone to report illnesses amongst their relatives (Table 12).

Cummings and his colleagues (Cummings *et al.*, 1956; Cummings, Dunner & Williams, 1959) showed that the distribution of sarcoidosis was similar to that of pine trees, both predominating in the South-Eastern United States. In this country 2% of record patients and only 3% of sarcoidosis subjects express exposure to conifers. Our findings serve to minimize the association between sarcoidosis and pine trees and are in line with similar epidemiological data in Denmark (Horwitz, 1961), Japan (Nobechi, 1961), Switzerland (Uehlinger, 1961), Belgium (leBacq, Verhaegen & Gyselen, 1961) and Uruguay (Purriel & Navarrette, 1961).

Exposure to dusts of mineral, vegetables or animal sources was also considered. The possible significance of clay-eating as an aetiological factor in sarcoidosis in Georgia was investigated by Comstock and his colleagues (Comstock *et al.*, 1961) who found that it occurred twice as often in their group of sarcoidosis patients as amongst the controls. Although the clay contains a small amount of beryllium which is known to provoke sarcoid granulomata, they did not regard clay-eating as a primary aetiological factor, but rather as a secondary or trigger mechanism. In the present series, there was no difference in the degree of exposure to clay or to dusts from coal, other minerals, or cotton in

sarcoidosis and control patients. Nor was there any difference in the type of household fuel used, or in contact with domestic pets, or allergens produced by them.

Since Comstock and his co-workers (Comstock *et al.*, 1961) had found a negative association between sarcoidosis and cigarette smoking, evidence was sought in the present series. In fact tobacco and alcohol consumption were similar in both our sarcoidosis and control subjects. They had also felt that pregnancy might be a predisposing factor since the number of children borne by sarcoidosis patients (3·1 children/woman) was greater than amongst controls (2·4 children/woman) although male sarcoidosis patients had the same-sized families as controls.

From the accumulated data of this series, it is possible to visualize a composite social picture of the sarcoidosis sufferer in London. It is that of an adult of the child-bearing years of life and if not English she will be Irish or West Indian. Erythema nodosum is common in Irish but rare in West Indians. If erythema nodosum or another skin lesion or even ocular involvement is present, then the odds are 2 : 1 that it is a woman but the history of pregnancies and breast feeding is the same as the rest of the community. Whereas a normal chest radiograph was observed in 13% of all patients, it was only found in 3% of Irish patients. The prevalence rate per 100,000 population varies from twenty at all ages to forty-three in the 25–34 year-old group and to about ten in those over 45 years of age. The death rate is about $1{\cdot}7/10^6$ population, being slightly higher in women and in rural areas. The hospital discharge rate is about three per 100,000 people at risk per year.

Sarcoidosis in London is similar in many respects to sarcoidosis in New York, where Siltzbach (1967) has observed that 71% of his patients were under 40 years, and women outnumbered men by 2 to 1. The great difference is the ethnic background, for Negroes constitute almost one-half of the New York series. He has drawn attention to the frequency of erythema nodosum among Puerto Rican migrants to New York much as we have noted its frequency in Irish women in London.

Acknowledgment

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