The need for a study which includes the recording of respiratory function is emphasized.

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AWARENESS OF FAMILY AND CONTACT HISTORY OF TUBERCULOSIS IN GENERALIZED SARCOIDOSIS

BY

VICTOR PARSONS, M.A., B.M., M.R.C.P.

Registrar, Department of Medicine, King's College Hospital, London

Sarcoidosis can only be defined at the histological level as the picture of a granuloma containing non-caseating tubercle follicles. Although this is now well known to occur as a local response to a variety of toxic agents and diseases, there is a striking absence of satisfactory evidence that any of these is responsible for the generalized disorder, which is recognized as an entity by its distinctive clinical pattern and course. In spite of this, Jonathan Hutchinson's (1898) original suggestion, that lupus pernio might be tuberculous in origin, has persisted in a belief that generalized sarcoidosis may be a curiously modified form of infection with *Mycobacterium tuberculosis*. The arguments for and against this hypothesis have been reviewed repeatedly in the literature (Pinner, 1938; Hoyle, 1947; Siltzbach, 1958) without result because of the lack of any consistent bacteriological proof. Scadding (1960), in reviewing 230 patients with generalized sarcoidosis, has recorded an interchange between tuberculosis and sarcoidosis in a few individual patients with regard to the disease process, the recovery of bacilli, the immune response, and the effects of appropriate therapy.

It may well be that this type of sarcoidosis is one of an increasing number of disease processes that are being recognized, the basis of which is possibly part infectious and part immune, and which do not fulfil Koch's postulates.

One aspect that may throw some further light on the problem is the incidence of family tuberculosis and of contact with this disease among patients with

sarcoidosis. Baas and Vader (1957) have reported contacts with human or bovine tuberculosis surrounding one in three of 128 patients with sarcoidosis—a finding, so far, not implemented in this country. It is the purpose of this investigation to compare and contrast the family and contact history of tuberculosis in a group of patients with sarcoidosis and those of patients with pulmonary tuberculosis on the one hand and with bronchial asthma or bronchitis on the other.

Methods of the Survey

Three series of patients were assembled. The first consisted of 315 patients with pulmonary tuberculosis between the ages of 15 and 55 seen consecutively at the Brompton Hospital between 1950 and 1958 by two physicians. For all these patients a standard form was used and details of family history and contact were taken as part of their history on first admission. These were abstracted from the notes, together with a record of the sputum state during investigation, and the time from contact to the onset of clinical symptoms was noted. Of the 315 reviewed, 80% had *M. tuberculosis* in their sputum.

The second series consisted of 210 patients with sarcoidosis, seen mainly by one physician at King's College Hospital and the Brompton Hospital from 1940 to 1959. The details were taken from the clinical notes, which included the family and contact history of tuberculosis as a routine part of the history. Six patients were questioned where such a record was not noted initially. A note was also made of histological proof, positive in 60% of the 210 patients and of the type of disease. Many without biopsy proof have been followed for several years and have run the same course as the others.

The third series consisted of 214 consecutive patients with asthma and/or bronchitis selected only with regard to age and attending during 1957–9. One group was attending a special clinic at King's College Hospital, where their family and contact histories were taken by those in charge. A second and smaller group was included from the Brompton Hospital to supplement these, using the histories recorded in the admission notes on standard forms. This latter group was used to see if there was a higher incidence of history of contact in asthmatic patients attending a chest hospital with special interest in pulmonary tuberculosis. No evidence of this was found.

It is hoped that the data collected in this way avoid some of the difficulties where interrogation is done by one person who is aware of the issues in question. Fairbairn *et al.* (1959) reported the results of a survey from a questionnaire by trained doctors and health visitors and showed how the data can vary according to the interpretation and persistence of the questioner. It is hoped that, among the twenty or so doctors covering the period and clinics involved in this survey, the enthusiastic over-reporters will have been matched by those with opposite qualities.

Definitions

The age of each patient was recorded as that when the history was first taken, in order to avoid errors in estimating the duration of the disease. Occupation was noted for all males and single females and classified according to the Index of Occupations collected by the Registrar-General in the census of 1951.

The history of contact with tuberculosis was recorded as good or poor. The former implied that the index case had lived with or worked in proximity to a person known to be suffering from tuberculosis. Where the contact was at work or with a lodger it had to be for at least three months. Nurses and doctors were included in this group only if they had attended patients with tuberculosis. All index cases with less definite or less-sustained contact were allocated to the poor-contact group. Similarly, unless details of the histories of parents, siblings, or children were available the family history was regarded as poor.

An attempt was made to time the contact in relation to the onset of illness in the index cases, particularly those with sarcoidosis. A rough estimate was often possible from the appearance of skin or eye sarcoidosis or from an early radiograph; and in others the natural history of the disease (Smellie and Hoyle, 1960) allowed an estimate to be made. In order to make any relationship clearer an arbitrary period of two years was chosen as recent contact. This, rather than a longer time, was chosen because Aspin (1951) found that over half the index cases from families with previous or subsequent tuberculosis occurred within two years and that by five years the rate approached a normally expected value. Springett (1956), in his study of minimal pulmonary tuberculosis, also used a two-year dividing line, so that by choosing this here a comparison is possible. Where the onset of the disease could not be reasonably placed within the two years of contact the patient was allocated to the poor-contact-history group. The timing of the onset of bronchitis and asthma was more difficult, but a large proportion of patients were questioned within two years of their being referred for symptoms of wheezing, breathlessness, and persistent expectoration.

On these considerations the family and contact histories were classified into five groups: Good contact history within two years of the estimated onset of the disease (1) with near relatives, or (2) with those outside the family. Other contact history (3) with near relatives, (4) with distant relatives, or (5) with anyone outside the family.

Occasionally when there was both a family history and an outside contact history the patient was included in the more relevant group.

Results

The age distribution of the patients in five-year groupings is shown in Fig. 1. Those for tuberculosis and sarcoidosis follow each other closely except in the age-groups 15-19 years and above 49 years. The higher proportion of tuberculous patients in the younger age-group contrasts with the sarcoid group where there were no patients below the age of 17. On the contrary, more patients with sarcoidosis than tuberculosis were included beyond the fifth decade, a finding which may well be due to the tendency for older patients with tuberculosis to be treated without reference to a special centre. The contrasting incidence of asthma and bronchitis with increasing age is in keeping with their progressive natural history.

Table I shows the incidence of family and contact history for each of the three series using the classification outlined above. Applying a χ^2 test to the three groups A, B, and C shows a highly significant difference between the three series ($\chi^2=27.5$, d.f.=4, $P>0.001$). The main

difference lies in fact in the proportion of patients with good two-year contact histories, which were 12% for sarcoidosis compared with 2% for the asthmatic group.

If, on the other hand, separate groups are taken, such as other contact history outside the family (pulmonary tuberculosis 34/315, 10.8%; sarcoidosis

FIG. 1.—Age-group distribution of patients among the three series.

39/210, 18.5%; bronchitis 17/214, 7.8%), a further difference, in the same direction though significant at a lower level, appears ($\chi^2=11.3$, d.f.=2, $P>0.01$). This suggests that the sarcoid series has a higher incidence of contact outside the family, for if all the family contact—good and other—is compounded (pulmonary tuberculosis 90/315, 28.5%; sarcoidosis 35/210, 16.6%;

TABLE I.—Contact History Among the Three Series

	Pulmonary Tuberculosis		Sarcoidosis		Asthma and Bronchitis	
	No.	%	No.	%	No.	%
A. Good contact history within 2 years:						
Near relatives ..	31	10	12	6	2	1
Outside the family ..	20	6	14	6	2	1
Total ..	51	16	26	12	4	2
B. Other contact history:						
Near relatives ..	43	14	15	7	23	11
Distant ..	16	5	8	4	21	10
Outside the family ..	34	11	39	19	17	8
Total ..	93	30	62	30	61	29
C. No contact history ..	171	54	122	58	149	69
Totals ..	315		210		214	

bronchitis 46/215, 21.4%) and these are compared, another but less significant difference in the opposite direction appears ($\chi^2=9.2$, d.f.=2, $P=0.01$). This might represent a relative immunity to tuberculosis among the sarcoid patients' families; however, the tendency to put the less definite type of contact into the "other contact" group may have increased the numbers disproportionately.

An attempt was made to correlate the main clinical manifestation of sarcoidosis with the incidence of recent contact both within and outside the family (Table II). There seems to be a higher incidence of recent sustained contact when hilar node enlargement, erythema nodosum, pulmonary infiltration, and ocular sarcoidosis are present. Also, although the numbers are small, 11 of the 61 patients out of the whole group with a positive liver biopsy came from the 26 patients with a good contact history, an incidence of 42%.

TABLE II.—Type of Sarcoidosis in Relation to Contact History

	Total	No. with a Good Contact History	No. with a Poor Contact History	No. with No History of Contact
Hilar nodes ± erythema nodosum	34	9 (26%)	10	15
Hilar nodes ± erythema nodosum with pulmonary infiltration	64	10 (15%)	16	38
Pulmonary infiltration	43	1 (2%)	14	28
Pulmonary and eye involvement	34	5 (15%)	14	15
Pulmonary and skin involvement	19	0	4	15
Eye skin glandular involvement, together or separately	16	1	4	11
Total	210	26	62	122

Fig. 2 gives an analysis of the occupations of the males in the two groups, together with the division in the normal population in the Greater London conurbation and the south-eastern counties. The groups with sarcoidosis and tuberculosis deviate similarly from the normal and the contrast groups; the

FIG. 2.—Distribution of occupations among the men in the three series. 1-15, agricultural, manual, engineering and allied occupations; 16-18, administrators, commercial and finance occupations; 19, professional and technical occupations; 23, clerks and typists. The remainder include unskilled occupations and those still under full-time education. (The groupings for asthma and bronchitis are similar to those of the population of Greater London and S.E. conurbation.)

latter are alike, and are represented as one pie diagram. Although not apparent in these large groupings, there were few agricultural or rural workers (tuberculosis group 2, sarcoidosis group 4, asthmatic group 2, and census group 2), who might be more exposed to pine pollen, suggested as a possible aetiological factor by Cummings *et al.* (1959). There is by contrast an obvious excess of the professional classes (group 19), which includes nurses and doctors. The similar occupational distribution of the group with sarcoidosis deserves comment in the light of the joint difference in contact history which these two groups show from the asthmatic group. Any preponderance of professional patients due to the fact that they might be expected to be referred more often to special clinics for review would be likely to apply to all three groups equally and not to the first two.

Before the results of this investigation can be regarded as valid there are possible sources of bias which need to be examined. One is that the groups may not be comparable and that the incidence of a good contact history has therefore little relationship to the sarcoid process. Table III shows that there are differences between the three series in respect of age, sex, and occupation (Group 19), but further analysis shows that these do not affect the differences in good contact history between the groups.

This inquiry may have been prejudiced by under-reporting in the tuberculosis and asthmatic groups. An external check of this tendency is available if this series

is compared with the results collected before the war in groups under supervision by Daniels *et al.* (1948) (see Table IV). The comparison may be invalidated by the wider age range covered in this series, but at least there does not seem to be under-reporting in any of the groupings. If over-reporting is a tendency in this series it probably would affect all three groups similarly.

TABLE III.—Sex, Age, and Occupation of Group 19 (Professional Classes)

	Tuberculosis		Sarcoidosis		Asthma and Bronchitis	
	No.	%	No.	%	No.	%
Male	166	52	86	41	85	39
Female	147	48	124	59	129	61
Under 35	204	65	123	59	89	41
Over 35	109	35	87	41	125	59
Occupation group 19	31	10	14	7	7	3

TABLE IV.—Contact History in the Prophit Survey and This Series

	Pulmonary Tuberculosis		Controls	
	Prophit	This Series	Prophit	Asthmatics
Good contact history within the family	5.3%	10.2%	5.9%	1%
Poor contact history within the family	19.1%	19.4%		21%
Good contact history outside the family	3.4%	6.6%	2.3%	1%
Other contact history	9.8%	11.2%		8%
No contact	62.4%	52.6%	91.8%	69%

One further source of bias was examined. In so far as the sarcoidosis group might contain a number of deviants which were introduced into the series because they were x-rayed as part of the follow-up of index cases suffering from pulmonary tuberculosis, it is possible that they would unduly weight the contact history of their group. Every patient in the sarcoidosis group with a good and recent contact history was therefore reviewed in regard to this point and the mode of presentation analysed (Table V). Only 3 of the 26

TABLE V.—Route or Symptoms which Brought Patients with a Good History of Contact Under Investigation

Routine M.M.R. or incidental chest x-ray examination before employment or during pregnancy, etc.	8
Skin symptoms—mainly erythema nodosum	7
Pulmonary symptoms	4
Eye symptoms	4
M.M.R. because of follow-up of the index contact patient	3

were found because they were x-rayed as part of the survey around an index case. For those with contact remote from the onset of symptoms the chance of inclusion in a contact survey is very rare.

Discussion

If, as these critical analyses suggest, the three groups in the investigation are comparable, then the results indicate that there is an increased awareness of contact with tuberculosis among the patients with sarcoidosis at every level compared with the asthmatic group. A majority of the population are unaware of the contact with tuberculosis responsible for their positive tuberculin reaction. For those who develop active tuberculosis in this age range, awareness of contact probably goes with a heavier dosage of tubercle bacilli over a longer period as a post-primary infection which leads to disease within two years. The results of this survey show that patients with sarcoidosis are exposed by their environment within the family and their occupation to a much higher level

of possible tuberculous infection than a contrast series: and that it approaches that of a group of patients suffering from pulmonary tuberculosis. Bass and Vader (1957), in Eindhoven, collected a series of 128 patients with sarcoidosis, the diagnosis being made on clinical grounds mainly, biopsy evidence being positive in 16. Contact with active tuberculosis, often with longer intervals than two years, within and without the family totalled 23 (18%), to which they added contact with inactive tuberculosis in 17 (13%) and with cattle in 6 (5%), giving them a total of 36% with tuberculous contacts; both latter groups were inaccessible in our patient questionnaire retrospective survey. It seems that their higher incidence may be partly due to different means of selection of the patients, different definition of contact history, and the advantages of a full radiological survey of the possible contacts.

These significant findings clearly bear upon the problem of the part which tuberculous infection may play in the genesis of sarcoidosis. They suggest that contact with tuberculosis may well be a substantial rather than a minor cause; for, if the contact history is a mere coincidence, it is difficult to explain why it should differ from that of the contrast group. This evidence of a relationship between tuberculous infection and the onset of sarcoidosis raises many further problems. It may, for instance, well be that the role of infection with *M. tuberculosis* is catalytic for an immune process of a highly specific type. Evidence for altered immune reactions in patients with active sarcoidosis has been recorded by Greenwood *et al.* (1958).

The familial aspects of tuberculosis in this series of patients with sarcoidosis lends support to this in that there seems to be some evidence of inherited resistance to tuberculosis. There are five families in this series with sarcoidosis. The relationship is close in all of them, and yet in only one of these families is another relative known to have tuberculosis, and there the contact was not recent. Although this is a small experience it does suggest that there may well be an immune process which is determined genetically. There seems to be a place for a longer survey of the contacts of patients with tuberculosis, particularly where the population is compact and stable.

Summary

Three series of patients, with tuberculosis, sarcoidosis, and asthma or bronchitis, have been investigated for contact with tuberculosis, and this has been correlated with the onset of the disease in the first two series. Similar incidence of recent contact was found in the series with sarcoidosis (12% of 210) and with tuberculosis (16% of 315), contrasting with the control group (2% of 214). The relationship of this to the aetiology of sarcoidosis is discussed.

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KWASHIORKOR IN AFRICAN CHILDREN IN DURBAN

BY

JOAN SCRAGG, M.B., Ch.B., D.C.H.

*Lecturer, Paediatric Department, University of Natal and
King Edward VIII Hospital, Durban*

AND

CAROL RUBIDGE, M.B., Ch.B., D.C.H.

*Registrar, Paediatric Department, King Edward VIII
Hospital, Durban*

Since Williams's (1933) classic description of kwashiorkor in West Africa and Trowell's (1937) comprehensive study in Uganda, a considerable amount has been contributed to the literature on this subject. It is now apparent that there are many minor variations on the major theme of this malnutritional syndrome, and this becomes apparent from the 1,565 cases of kwashiorkor studied at this hospital during 1955 and 1956. This is a record of in-patients only, and selection has been applied here in the sense that as only the worst cases were admitted these are the ones described. The less severe cases (and these were very numerous) had to be treated as out-patients because of the heavy demand for beds. Since the condition is, unfortunately, so common in Durban, we are unusually well placed to record the incidence of various clinical signs, their relation to biochemical data, the influence of infections on prognosis, and the response to treatment.

Criteria for Diagnosis

Our criteria for diagnosis were: (1) a dietary history suggesting protein malnutrition; (2) oedema associated with hypoalbuminaemia—the latter unexplained on the basis of renal, cardiac, or other disease; (3) retardation of growth, irritability, apathy, and anorexia; (4) a variable dermatosis.

Cases diagnosed as suffering from "malnutrition" and "marasmus" are not included in this study, for we have not been able to determine with confidence whether such cases (Fig. 1, a, b) were of the atrophic type (Altman, 1948) and were simply *undernourished* (starved), as opposed to being *malnourished* as in kwashiorkor. Adequate pathological and biochemical studies have not yet been done in these cases.

As stated by Brock (1955), "... the greatest difficulty lies in the fact that there is a spectrum of clinical