Papers and Originals

Incidence of Intrathoracic Sarcoidosis Among Young Adults Participating in a Trial of Tuberculosis Vaccines

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In the course of the Medical Research Council's clinical trial of tuberculosis vaccines (Medical Research Council, 1956, 1959, 1963) records have been kept of the cases of definite or possible sarcoidosis which developed among the participants. These findings have now been analysed from several points of view ; (1) The effect of tuberculin status on entry to the trial, and of B.C.G. and vole-bacillus vaccination, on the subsequent incidence of sarcoidosis. (2) The attack rate of intrathoracic sarcoidosis in the total participants, originally living in urban or suburban areas in England, and observed between the ages of about 15 and 25 years. (3) The relation between sarcoidosis and tuberculin sensitivity, as shown by the periodic tuberculin tests made during the trial.

On entry to the vaccines trial in 1950-2 the 54,239 participants were nearly all aged 14 to 15½ years, and lived in or near North London, Birmingham, and Manchester. Those with negative reactions to tuberculin at the first examination were vaccinated with B.C.G. or vole-bacillus vaccine or left unvaccinated, according to a method of random allocation. As a result of these tuberculin tests and vaccinations the participants were divided at the time of entry into the following five trial groups :

Negative to 100 tuberculin units (T.U.) of old tuberculin, left unvaccinated ...	12,867
Negative to 100 T.U., B.C.G.-vaccinated ...	13,598
Negative to 100 T.U., vole-bacillus-vaccinated ...	5,817
Positive to 3 T.U. ...	15,704
Negative to 3 T.U., positive to 100 T.U. ...	6,253

(Participants with no induration, or with greatest diameter of induration less than 5 mm. at 72 hours, were regarded as negative reactors ; those with induration 5 mm. or more in diameter were regarded as positive reactors.)

The participants (now adults aged about 27 years) were followed intensively by means of routine annual miniature chest radiographs (viewed independently by two readers), plus full-size films when any abnormality was detected), tuberculin tests, postal inquiries, and home visits by health visitors, until September 1960 ; and by routine annual postal inquiries thereafter. In addition, information has been made available throughout to the M.R.C. teams from chest clinic records and from the tuberculosis notification lists of local medical officers of health. Cases of tuberculosis and other chest diseases were thus discovered both by the periodic M.R.C. radiographic examinations and by the normal methods of the National Health Service.

All definite and suspected cases of tuberculosis, and all other pulmonary abnormalities persisting for more than 14 days, which came to the notice of the M.R.C. teams, were submitted for classification, with special reference to tuberculous disease,

to the independent trial assessor (nearly always Dr. V. H. Springett), who was kept unaware of the results of any tuberculin tests and whether vaccination had been performed. A proportion of these cases, increasing as the trial proceeded, was classified by the trial assessor as due to sarcoidosis.

Assessment of the Cases of Sarcoidosis

The material relevant to the present study was submitted for assessment, with special reference to sarcoidosis, to Professor J. G. Scadding. He reviewed the following categories of case : (1) all cases assessed as sarcoidosis by the trial assessor ; (2) all cases in which sarcoidosis had been explicitly considered by the trial assessor as a possible alternative to his final classification ; (3) all cases assessed as hilar lymph-node enlargement, without other evidence of tuberculosis ; (4) all cases in which erythema nodosum had been reported, with or without other evidence of tuberculosis. In addition, about 20 cases, classified by the trial assessor as pulmonary tuberculosis, with either miliary-type lesions or limited non-cavitated lesions (not exceeding two rib interspaces in extent), but not bacteriologically proved, and in which there appeared to be an element of doubt in the diagnosis, were also submitted to the special assessor, but none was classified by him as a case of sarcoidosis.

The assessments were made from the periodic radiographs and all the available clinical and laboratory information, but without knowledge of the results of any tuberculin tests and whether any vaccination had been performed.

The special assessor classified 52 of the trial participants as cases of sarcoidosis, and a further five as cases of possible sarcoidosis (not included in the ensuing analyses ; all had had at least one abnormal radiograph before the end of 1963. The date of the first abnormal radiograph has been taken as the starting-point of the disease. Some patients had earlier symptoms, but these were either too indefinite for dating purposes or, when definite—for example, erythema nodosum—closely preceded the first abnormal radiograph. It will be appreciated that for some cases the starting-point, thus defined, may be a considerable time after the true, but unknown, date of onset of the disease. Of the 52 cases, 29 had been discovered by the periodic M.R.C. radiographic examinations and 23 by the National Health Service (the latter including six as a result of a routine radiographic examination).

Having completed the assessments, the special assessor was told the results of the tuberculin tests and the vaccination status for each patient, to discover whether the withholding of this information had seriously hampered him in making the assessments. With this extra information he would have regarded one of the 52 cases of sarcoidosis as primary tuberculosis, and three of the cases of possible sarcoidosis as definite sarcoidosis,

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primary tuberculosis, and a non-specific acute infection, respectively. The total would thus have remained at 52, with only a gain of one case (positive to 3 T.U. on entry to the trial) and a loss of one case (negative to 100 T.U. on entry).

It is of value to record the separate judgments of the trial assessor and the patient's physician on the 52 cases assessed as sarcoidosis by the special assessor. In 42 cases both the trial assessor and the patient's physician also regarded sarcoidosis as the definite or a likely diagnosis, sometimes with reservations where there was no confirmation by biopsy. In a further eight cases one of these two physicians favoured a diagnosis of sarcoidosis and the other a diagnosis of primary tuberculosis; in the remaining two cases both the trial assessor and the patient's physician diagnosed primary tuberculosis. There is thus a close measure of agreement with the classifications made by the special assessor.

Forms of Sarcoidosis

Because of the emphasis on chest radiography in the vaccines trial, intrathoracic sarcoidosis is more likely to have come to the notice of the M.R.C. teams than exclusively extrathoracic forms of the disease, though the periodic postal inquiries and home visits were a means of discovering cases in the latter category. This report should nevertheless be considered as primarily concerned with intrathoracic sarcoidosis, and, in fact, as already stated, all the 52 cases had at least one abnormal chest radiograph.

As with tuberculosis detected in trial participants, the further investigations and any treatment of sarcoidosis were carried out by physicians at local chest clinics or hospitals and were not the responsibility of the M.R.C. team physicians (but the cases were retained by the M.R.C. for their tuberculosis follow-up and some have therefore had further tuberculin tests). There has consequently been no uniform pattern of investigation or management of the cases, and no opportunity for the M.R.C. teams to initiate special examinations, such as biopsies; this must be borne in mind when considering the clinical features of these cases.

None of the 52 patients gave any past history of relevant symptoms, and 23 had no symptoms at the time of the first abnormal radiograph. Of the others, 11 had had recent erythema nodosum (with or without other symptoms), 11 reported respiratory symptoms (cough, dyspnoea, etc.), and 7 had other miscellaneous symptoms. Table I summarizes the

TABLE I.—Principal Features of Cases of Sarcoidosis

Radiographic and Clinical Features*	No. of Patients	Biopsies†		Kveim Tests	
		No.	Pos.	No.	Pos.
Bilateral hilar lymph-node enlargement:					
Alone	25	2	1	1	1
With pulmonary abnormality ..	12	5	5	0	—
With erythema nodosum ..	7	0	—	1	1
With pulmonary abnormality and erythema nodosum ..	4	2	2	1	1
Pulmonary abnormality alone ..	4	4	1	0	—
All patients	52	13	9	3	3

* Three patients complained of joint pains and 7 had palpable peripheral lymph nodes.

† Three liver and 10 lymph-node (6 scalene, 4 other) biopsies.

principal features during the course of the disease. Of the 52 patients, 48 showed bilateral hilar lymph-node enlargement, 20 showed pulmonary abnormalities, and 11 had erythema nodosum. No eye, bone, or skin abnormalities (apart from erythema nodosum) were reported in any patient, but detailed eye examinations were not made, nor were bone radiographs taken as a routine.

The course of the disease in this series has been benign and relatively short. No patient has died of sarcoidosis. Of the

52 patients, 47 were re-examined by chest radiography within 12 months of their first abnormal radiograph; in 13 the lesions had resolved completely, in 23 they had diminished, in seven they showed no change, and in four they had extended. The other five patients, and (to date) 13 of the 34 not resolving within a year, were re-examined by chest radiography at intervals ranging from one to five years after their first abnormal radiograph; in 11 of these 18 the lesions had resolved completely at the last examination, in six they had diminished, and in one they had extended (at 13 months, too recently for subsequent examination).

In 16 of the 52 cases (see Table I) the patient's physician sought confirmation of the diagnosis by biopsy (three liver and 10 lymph-node biopsies, and three Kveim tests); 12 of these 16 biopsies were classified as positive for sarcoidosis. Histological evidence was thus not often available, and in most cases the diagnosis of sarcoidosis was made on clinical and radiographic grounds only. Although this is a disadvantage, there is evidence which indicates that the risk of misdiagnosis, in the absence of biopsy data, has not been important. Thus the trial assessor and the patient's physician both agreed with the classification of sarcoidosis made by the special assessor, not merely in the 12 biopsy-confirmed cases but also in the four cases in which the biopsy was negative. Further, the clinical features of the 40 unconfirmed cases were similar to those of the 12 biopsy-confirmed cases; 37 of the 40 and 11 of the 12 had hilar lymph-node enlargement which was bilateral, 7 of the 40 and 4 of the 12 had erythema nodosum, and among those re-examined by chest radiography within 12 months of their first abnormal radiograph, 27 out of 38 and 9 out of 9, respectively, showed resolution or diminution of the lesions. (It may be mentioned also that the epidemiological findings below are essentially similar for the histologically confirmed and for the unconfirmed cases.)

Incidence of Sarcoidosis in the Five Trial Groups

Because many of the 52 cases were detected only by routine chest radiography, and the disease often followed a benign and relatively short course, it is likely that a number of other cases of sarcoidosis will have occurred in this population but remained undetected, particularly in the later years of the follow-up, when the frequency of routine chest radiography became less (as stated above, the special M.R.C. scheme for routine chest radiography of the participants ended in September 1960). The figures calculated below for the incidence of intrathoracic sarcoidosis must therefore be regarded as underestimates of the true incidence of the disease, especially at the higher ages. However, the frequency of routine chest radiography, and the distribution of intervals between successive radiographs, were closely similar in the five trial groups. The degree of underestimation may therefore be regarded as similar in each group, and a comparison of the observed incidences of sarcoidosis will give a valid indication of the relative magnitude of the true incidences in the five groups. (In the course of the first 8.8 years of intensive follow-up the average number of radiographs taken was 4.5 per participant. The distribution of the intervals between these radiographs was skew, and only 15% of the intervals exceeded two years.)

The numbers of cases and the incidence of sarcoidosis found in the five trial groups are shown in Table II, subdivided according to the interval since entry to the trial in 1950–2. Up to the end of 1963 there were 15 cases among the 12,867 initially tuberculin-negative unvaccinated participants (by which time about 40% of these participants had become tuberculin-positive), 13 among the 13,598 B.C.G.-vaccinated, and four among the 5,817 vole-bacillus-vaccinated participants. The mean annual incidence over the whole period was rather smaller in the two vaccinated groups (0.79 and 0.57 per 10,000 respectively) than in the unvaccinated group (0.98

per 10,000), but the differences are not statistically significant. If there were a slight protective effect from the vaccines, this might be expected to be more noticeable in the first five years after vaccination than subsequently. The annual incidence of sarcoidosis in this period was 0.44 among the B.C.G.-vaccinated and 0.31 among the negative unvaccinated participants; in the two vaccinated groups combined the incidence was also 0.31. The numbers of cases in the first five years are very small, but these rates do not suggest any protection from vaccination. It is worth observing that if vaccination had been as effective against sarcoidosis in this trial as it was against tuberculosis, only four or five cases of sarcoidosis would have been expected in the vaccinated groups combined, up to the end of 1963, which is significantly less* (at the 0.1% level) than the 17 actually observed.

In the group of participants who were initially positive to 3 T.U., and in those negative to 3 T.U. but positive to 100 T.U., the mean annual incidences of sarcoidosis over the whole period were 0.74 and 0.80 per 10,000 respectively; these rates are similar to those in the vaccinated groups, and do not differ significantly from that in the negative unvaccinated group.

Of the 12 cases of sarcoidosis which were confirmed by biopsy or Kveim test, three were in the negative unvaccinated group, four in the B.C.G.-vaccinated group, none in the vole-bacillus-vaccinated group, three in the group initially positive to 3 T.U., and two in the group negative to 3 T.U. but positive to 100 T.U. The distribution of these 12 cases is similar to what would be expected if the subsequent development of sarcoidosis was independent of tuberculosis vaccination and the initial tuberculin status—namely, 2.8 cases in the negative unvaccinated group, 4.3 in the vaccinated groups combined, and 4.9 in the initially tuberculin-positive groups combined.

Thus tuberculosis vaccination at the age of 14 years did not appear either to protect against sarcoidosis or to promote this disease. Moreover, there is no evidence that the initial tuberculin status of the unvaccinated participants influenced the subsequent incidence of sarcoidosis in this population group over a period of more than 10 years.

Attack Rate of Sarcoidosis in the Total Participants

According to the foregoing conclusions the initial skin-test and vaccination group was irrelevant to the subsequent development of sarcoidosis. The information from all the trial groups combined may therefore be used directly to give an indication of the attack rate of intrathoracic sarcoidosis in young adults living in urban or suburban areas in England. Since many more cases arose in the second five years after entry to the trial (34) than in the first five years (7), it is clear that the incidence is closely dependent upon age. The data have therefore been rearranged (Table III) to show the incidence of intrathoracic sarcoidosis in the entire vaccines trial population, according to age and sex.

The final column of Table III shows a rapid increase in incidence after the age of 15 years for both sexes together. There were no cases in the short period of observation below the age of 15; the annual incidence was 0.15 per 10,000 at ages 15–17½ years, 0.52 at 17½–20, and 1.49 at 20–22½ years. Thereafter there was a decrease, the annual incidence being 1.12 at ages 22½–25 years, and (provisionally) 0.87 at 25–27½ years. Because of the diminished intensity of radiographic examination in the later years, however, it is uncertain whether this represents a genuine reduction in the incidence of the disease or simply a decrease in the proportion of cases of the disease which were detected.

In each age-group the incidence was substantially greater among females than among males; the average annual incidence at 15–25 years was 1.28 per 10,000 in females, about three times as great as the rate among males—namely, 0.39.

It is of interest to compare the pattern of the sarcoidosis attack rates with that of tuberculosis in this same population. The tuberculosis figures given in Table IV are estimates of the attack rates which would have occurred in the absence of vaccination—that is, assuming that the incidence in the two vaccinated groups had been the same as that observed in the tuberculin-negative unvaccinated group.

The attack rate of tuberculosis in both sexes together in the trial population (discounting the effect of vaccination) increased

TABLE II.—Cases of Sarcoidosis, According to Trial Group and Interval Between Entry to Trial and First Abnormal Radiograph (the Starting-point of the Disease)

Tuberculin Test and Vaccination Group on Entry to Vaccines Trial (in 1950–2)	No. of Participants	Cases of Sarcoidosis				Annual Incidence per 10,000 Participants*			
		Total (Up to 31 Dec. 1963)	Starting within 5 Years of Entry	Starting 5–10 Years after Entry	Starting 10–15 Years after Entry (about 40% Complete)	Up to 31 Dec. 1963†	0–5 Years	5–10 Years	10–15 Years†
Negative to 100 T.U., unvaccinated ..	12,867	15	2	12	1	0.98	0.31	1.90	0.38
Negative, B.C.G.-vaccinated ..	13,598	13	3	9	1	0.79	0.44	1.33	0.35
Negative, vole-bacillus-vaccinated ..	5,817	4	0	2	2	0.57	0.00	0.69	1.63
Positive to 3 T.U. ..	15,704	14	2	8	4	0.74	0.26	1.03	1.22
Negative to 3 T.U., positive to 100 T.U. ..	6,253	6	0	3	3	0.80	0.00	0.97	2.29
All groups ..	54,239	52	7	34	11	0.80	0.26	1.27	0.97

* After allowing for removals from the population at risk—that is, by death or by contracting tuberculosis or sarcoidosis.

† Incidence per 10,000 person-years of observation up to 31 December 1963.

TABLE III.—Attack Rate of Sarcoidosis in the Entire Vaccines Trial Population, According to Age and Sex (Cases Starting Before 31 December 1963)

Age (Years)	Males			Females			Both Sexes		
	Person-years of Observation of 28,230 Males when in Stated Age-range*	Cases of Sarcoidosis		Person-years of Observation of 26,009 Females when in Stated Age-range*	Cases of Sarcoidosis		Person-years of Observation of 54,239 Subjects when in Stated Age-range*	Cases of Sarcoidosis	
		No.	Annual Rate per 10,000 Participants		No.	Annual Rate per 10,000 Participants		No.	Annual Rate per 10,000 Participants
Under 15 ..	9,124	0	(0.00)†	8,379	0	(0.00)†	17,503	0	(0.00)†
15– ..	70,133	0	0.00	64,560	2	0.31	134,693	2	0.15
17½– ..	70,095	3	0.43	64,540	4	0.62	134,635	7	0.52
20– ..	69,767	3	0.43	64,278	17	2.64	134,045	20	1.49
22½– ..	69,518	5	0.72	64,102	10	1.56	133,620	15	1.12
25–27½ ..	47,606‡	4	0.84	43,922‡	4	0.91	91,528‡	8	0.87
15–25 ..	279,513	11	0.39	257,480	33	1.28	536,993	44	0.82

* After allowing for removals from the population at risk—that is, by death or by contracting tuberculosis or sarcoidosis.

† Rates in parentheses are based on a short period of observation.

‡ Up to 31 December 1963.

from an annual rate of 10.0 per 10,000 at ages under 15 years to about 20 between 15 and 20 years. The rate fell to 10.6 at 20–22½ and to 5.6 at 22½–25 years. The rates in most age-groups were rather larger in females than in males; the annual rate at 15–25 years was 15.6 per 10,000 in females, about 15% greater than the rate of 13.5 in males.

TABLE IV.—*Estimated Incidence of Tuberculosis in the Entire Vaccines Trial Population in the Absence of Vaccination,* According to Age and Sex (Based on Cases of Tuberculosis Starting Before 31 December 1963)*

Age (Years)	Estimated Annual Incidence of Tuberculosis per 10,000 Participants†		
	Among 28,230 Males	Among 26,009 Females	Among 54,239 Subjects
Under 15 ..	(9.8)‡	(10.2)‡	(10.0)‡
15– ..	18.9	23.4	21.1
17½– ..	18.6	22.5	20.5
20– ..	11.6	9.6	10.6
22½– ..	4.6	6.7	5.6
25–27½ ..	2.8	3.0	2.9
15–25 ..	13.5	15.6	14.5

* That is, taking the incidence in the vaccinated groups to be the same as that in the negative unvaccinated group.
† After allowing for removals from the population at risk—that is, by death or by contracting tuberculosis or sarcoidosis.
‡ Rates in parentheses are based on a short period of observation.

Thus the tuberculosis attack rate rose to its peak in this population group between the ages of 15 and 20 years, whereas the sarcoidosis attack rate increased more gradually and had not reached a peak by the age of 20 years. Moreover, the attack rate of tuberculosis was only slightly greater in females than in males, whereas sarcoidosis occurred three times as often.

In addition to these close associations with age and sex, the attack rate of sarcoidosis varied substantially with area of residence. Among those entering the trial from suburban areas in or near North London there were 22 cases, corresponding to an annual incidence of 1.25 per 10,000; among the entrants from Birmingham, Coventry, and near-by towns there were 14 cases, the annual incidence being 0.54; and among the entrants from Manchester, Leeds, Bradford, and near-by towns there were 16 cases, the annual incidence being 0.74. Moreover, there were differences in the clinical features of the disease; of the London cases, 13 (59%) showed pulmonary abnormalities, compared with six (43%) of the Birmingham and two (12%) of the Manchester cases. There were differences in the frequency of routine chest radiography of participants from the three areas, the mean numbers of radiographs taken being 5.1, 4.1, and 4.4 respectively, but these differences would appear to be insufficient to account for the differences in attack rate and clinical features.

It is also of interest that these regional attack rates for sarcoidosis were out of line with the corresponding attack rates for tuberculosis. The annual attack rates for tuberculosis between the ages of 15 and 25 years were 11.5, 16.1, and 15.0 per 1,000 among those entering the trial in the London, Birmingham, and Manchester areas, respectively (these rates, like those above, are estimates of what would have occurred in the absence of vaccination). The differences between the sarcoidosis rates are in the opposite sense to, and are proportionately larger than, those between the tuberculosis rates.

Because the frequency of attempted confirmation of the diagnosis by biopsy or Kveim test varied with the age, sex, and area of residence of the participant, no additional information of value is obtained from a separate analysis of the 12 biopsy-confirmed cases of sarcoidosis according to these three factors.

Results of Serial Tuberculin Tests

As already stated, routine tuberculin-testing formed part of the follow-up of all participants in the vaccines trial. There is thus an unusual opportunity, not merely to examine the results of these routine tests in the sarcoidosis patients, made at various intervals before and after the starting-point of their

disease, but also to compare, in some detail, the results with the tuberculin sensitivity shown after similar periods of follow-up in the trial by all the other participants, who did not develop the disease.

In all, 222 tuberculin tests were made on the 52 sarcoidosis patients in the course of the trial. Because most of the cases of sarcoidosis started more than five years after entry to the trial, and tuberculin tests continued only for eight to ten years, 187 out of the 222 tests were made before the start of the sarcoidosis. In the negative unvaccinated and originally positive groups the total number of tests ranged from two to eight per patient (average 4.6), while in the two vaccinated groups (in which the pre-vaccination tests were inadmissible and were not included) the number ranged from one to six per patient (average 3.6). These numbers are not large enough for a detailed examination of the course of tuberculin sensitivity in each individual patient, but they do permit the sensitivity of the sarcoidosis patients, as a group, to be compared with that of the participants who did not develop the disease.

This comparison with the experience of the other trial participants was made as follows. A comprehensive table was prepared from the records for each of the five trial groups, showing the results of all the tuberculin tests on participants in that trial group, in six-month periods from the time of entry to the trial. These provided a series of standard, or “expected,” distributions of tuberculin sensitivity for successive periods after entry, with which the observed results of the tests in the sarcoidosis patients could be compared. Each test in a sarcoidosis patient was then classified according to the interval between entry to the trial and the test, and also according to the interval between the test and the starting-point of the disease, and the result was compared with the appropriate expected result, derived from the results of tests on the other participants in the same trial group, tested in the same period after entry to the trial. The results of these comparisons are summarized in Table V for the five trial groups separately, and in Table VI according to the intervals between the test and the starting-point of the sarcoidosis.

Occurrence of Sarcoidosis in Relation to Previous Tuberculin Sensitivity

It will be recalled that the figures in Table II gave no evidence of any association between the *initial* tuberculin status of the participant and the subsequent incidence of sarcoidosis. A study of all the tuberculin tests made before the start of the disease (Table V) enables an extension of this point to be examined—namely, whether there is any association between the *general level* of tuberculin sensitivity of an individual, as shown by a series of tuberculin tests, and the propensity to develop sarcoidosis. No such association appears in Table V from the figures for all trial groups combined; there was a close similarity between the results of the tuberculin tests in the sarcoidosis patients before they developed the disease and the distribution of results expected from the experience of all the other trial participants. When the trial groups are considered separately the only unexpected finding is among the six patients initially positive only to 100 T.U.; none of the 19 tests in these patients was negative to 100 T.U.—that is, showed 0–4 mm. induration—whereas five such results would have been expected. It would seem, however, that this must be a chance occurrence.

It should be recorded also that all 17 B.C.G. and vole bacillus participants who developed sarcoidosis had shown normal conversion to tuberculin sensitivity after their vaccination, and in addition (as is clear from Table V) none gave any later indication of reversion to negativity to 100 T.U. Thus there is no suggestion that sarcoidosis was particularly likely to develop in those who had failed to be converted to tuberculin sensitivity by vaccination, or in those who subsequently reverted to tuberculin negativity.

Changes in Tuberculin Sensitivity Associated with Development of Sarcoidosis

In Table VI the data are rearranged to discover whether there is any *alteration* of tuberculin sensitivity associated with the development of sarcoidosis. Here the 187 tuberculin tests made before the start of the sarcoidosis have been divided according to the interval by which they preceded the start of the disease, and supplemented with the small number of tests—namely 35—made later, divided according to the interval by which they followed the disease.

Among the 187 tests made before the starting-point of the sarcoidosis there are no important differences between the observed and expected distributions of sensitivity in any period preceding the start of the disease. The similarity of observed and expected results extends even to the very small number of test results within a year before the starting-point. The 35 tests at or after the starting-point of the sarcoidosis were made on 24 of the 52 patients (none of these tests was made on a participant who was currently receiving or had received steroid treatment). In this period there was an excess of tests with negative results to 100 T.U. (0–4 mm. induration)—namely, 17 compared with an expected number of 10.0; there was a corresponding deficit of tests with 5 mm. induration or more to 3 T.U.—namely 11, compared with an expected number of 20.3. The statistical significance of these differences cannot be tested directly because the results of multiple tests on the same patient are likely to be correlated. It is possible, however, to assess the significance of the differences if they are expressed

in terms of *patients* rather than *tests*, by considering the first (or only) tuberculin test made at or after the starting-point for each of the 24 patients. It is then found that 12 patients (50%) were negative to 100 T.U., four were positive to 100 T.U. but not to 3 T.U., and eight (33%) were positive to 3 T.U., at or shortly after the start of their sarcoidosis, compared with expected numbers of 7.7 (32%), 3.4, and 12.9 (54%), respectively. Thus, in terms of patients, a similar shift towards reduced tuberculin sensitivity occurs as was noted from the total test results, but the number of patients is small, and the differences between the observed and expected numbers do not attain statistical significance.

In addition to these 24, however, a further seven of the patients had less informative tuberculin tests at or shortly after the starting-point of their disease. Four were found to be negative to 3 T.U. but were not tested with 100 T.U., two were negative to 10 T.U. (and hence could be classed as negative to 3 T.U.), and one was positive to 1 T.U. (and hence also to 3 T.U.). Incorporating these seven results with those for the 24 patients, 22 (71%) of the 31 patients were negative to 3 T.U., and nine (29%) were positive to 3 T.U., at or shortly after the start of their disease, compared with expected numbers of 12.5 (40%) and 18.5 (60%) respectively. The difference between the observed and expected numbers is significant at the 0.1% level.

It may therefore be concluded that there was a tendency for tuberculin sensitivity to be depressed in the sarcoidosis patients at and after the starting-point of their sarcoidosis, but not before.

TABLE V.—Summary of Results of Tuberculin Tests in Sarcoidosis Patients Before Start of Their Disease, Compared With Those Expected from the Experience of Other Participants, According to Trial Group

Tuberculin Test and Vaccination Group on Entry to Vaccines Trial	Total Patients	Total Tests	Results of all Tuberculin Tests made before Start of Sarcoidosis (in Order of Increasing Sensitivity to Tuberculin)											
			Distribution of Test Results	Negative to 100 T.U. (0-4 mm. Induration)	Negative to 3 T.U., Positive to 100 T.U.			Positive to 3 T.U.						
					Total Positive	Diameter of Induration (mm.)			Total Positive	Diameter of Induration (mm.)				
						5-9	10-14	15 +		5-9	10-14	15-19	20-24	25 +
Negative to 100 T.U., unvaccinated	15	60	{ Observed Expected	50 48.4	3 6.2	1 3.8	2 1.7	0 0.7	7 5.5	5 2.2	1 1.6	1 1.1	0 0.4	0 0.2
Negative, B.C.G.-vaccinated	13	40*	{ Observed Expected	0 0.5	5 6.3	0 0.8	3 2.0	2 3.5	35 33.2	12 13.0	14 13.6	6 5.1	2 1.2	1 0.3
Negative, vole-bacillus-vaccinated	4	11*	{ Observed Expected	0 1.3	5 2.8	3 0.7	0 1.1	2 1.0	6 7.0	3 3.4	3 2.2	0 0.9	0 0.3	0 0.2
Positive to 3 T.U.	14	57	{ Observed Expected	0 0.3	2 2.1	0 0.3	0 0.3	2 1.5	55 54.5	16 8.2	14 18.2	18 16.8	6 7.9	1 3.4
Negative to 3 T.U., positive to 100 T.U.	6	19	{ Observed Expected	0 5.2	12 7.5	2 3.5	7 2.7	3 1.3	7 6.3	1 2.8	3 2.1	3 1.0	0 0.3	0 0.1
All groups	52	187	{ Observed Expected	50 55.7	27 24.9	6 9.1	12 7.8	9 8.0	110 106.5	37 29.6	35 37.7	28 24.9	8 10.1	2 4.2

* Excluding the pre-vaccination tests.

TABLE VI.—Summary of Results of Tuberculin Tests in Sarcoidosis Patients, compared with those Expected from the Experience of Other Trial Participants, According to Interval Between Tuberculin Test and Starting-point of Sarcoidosis

Interval between Test and Starting-point of Sarcoidosis		No. of Patients Tested in Stated Period	Total Tests	Results of Tuberculin Tests (in Order of Increasing Sensitivity to Tuberculin)											
				Distribution of Test Results	Negative to 100 T.U. (0-4 mm. Induration)	Negative to 3 T.U., Positive to 100 T.U.			Positive to 3 T.U.						
						Total Positive	Diameter of Induration (mm.)			Total Positive	Diameter of Induration (mm.)				
							5-9	10-14	15 +		5-9	10-14	15-19	20-24	25 +
Tests before starting-point	5 years or more before	42	96	{ Observed Expected	29 31.7	11 13.3	4 5.0	5 4.1	2 4.2	56 51.0	16 13.9	23 17.4	12 11.9	4 5.4	1 2.4
	3 to 5 years before	35	41	{ Observed Expected	11 12.0	6 5.2	0 2.1	3 1.6	3 1.5	24 23.9	11 6.5	3 8.5	6 5.7	4 2.3	0 0.9
	1 to 3 years before	34	45	{ Observed Expected	9 11.0	8 5.8	2 1.8	4 1.9	2 2.1	28 28.3	10 8.4	8 10.7	9 6.3	0 2.2	1 0.7
	Less than 1 year before	5	5	{ Observed Expected	1 1.0	2 0.6	0 0.2	0 0.2	2 0.2	2 3.5	0 0.8	1 1.2	1 1.0	0 0.4	0 0.1
Tests at or after starting-point	At, or up to 1 year after	21	22	{ Observed Expected	12 8.4	4 3.5	0 1.1	4 1.3	0 1.1	6 10.2	1 3.2	3 3.8	1 2.3	1 0.7	0 0.2
	1 to 3 years after	7	13*	{ Observed Expected	5 1.6	3 1.3	0 0.3	2 0.4	1 0.6	5 10.1	0 2.2	1 3.8	2 2.7	2 1.1	0 0.3
All intervals		52	222	{ Observed Expected	67 65.7	34 29.7	6 10.5	18 9.5	10 9.7	121 127.0	38 35.0	39 45.4	31 29.9	11 12.1	2 4.6

* Including one test 5 years and 7 months after the starting-point.

It is of interest that the depression of tuberculin sensitivity at and after the start of the disease was similar for the biopsy-confirmed and for the unconfirmed cases. Of the 12 biopsy-confirmed cases, seven had complete (or less informative) tuberculin tests at or shortly after the start of their sarcoidosis; six (86%) were then negative to 3 T.U. and one was positive to 3 T.U., compared with expected numbers of 3.3 (47%) and 3.7 respectively. Of the 24 biopsy-unconfirmed cases with tuberculin tests in the appropriate period, 16 (67%) were negative to 3 T.U. and eight were positive to 3 T.U., compared with expected numbers of 9.2 (38%) and 14.8 respectively.

Having shown a tendency for sensitivity to be depressed in this group of sarcoidosis patients, it is of interest to see how often the effect can be detected in individual patients. (For simplicity this section is confined to the 24 with completed tuberculin tests. It will be recalled that 12 patients were tuberculin-positive at or shortly after the starting-point of their sarcoidosis, and so show no clear depression of sensitivity.) Of the 12 patients who were found to be negative to 100 T.U. at this time eight were in the tuberculin-negative unvaccinated group, three were in the B.C.G.-vaccinated group, and one was positive to 3 T.U. on entry to the trial. Those initially tuberculin-negative did not show any tuberculin sensitivity at any subsequent test, and so also provide no individual examples of depression of sensitivity. (In these eight cases the intervals between the last previous negative tuberculin test and the starting-point of the disease were 11, 12, 13, 15, 25, 27, 73, and 75 months respectively; in the last two cases it is therefore quite possible for an undetected conversion to tuberculin positivity to have occurred, followed by a reversion to negativity at the starting-point of the disease, but this is less likely in the other cases.)

The three patients who had been B.C.G.-vaccinated all showed normal conversion to tuberculin sensitivity to 3 T.U. after vaccination, and were still tuberculin-positive 33, 24, and 14 months, respectively, before the starting-point of their sarcoidosis. One was found to be tuberculin-negative, with no induration at all to 100 T.U., at the starting-point, one three months later, and one both at the starting-point and 12 months later; this last patient had positive results (12 mm. and 25 mm. induration to 100 T.U.) 25 and 29 months, respectively, after the starting-point. The one patient initially positive to 3 T.U. was still positive five months before the starting-point of the sarcoidosis, but was negative to 3 T.U. (not tested further) 10 months after and negative to 100 T.U. 26 months after the starting-point. Thus only these last four patients show clear evidence of individual depression of tuberculin sensitivity associated with the development of their sarcoidosis. There was nothing unusual about the clinical features of these four cases; all had bilateral hilar lymph-node enlargement, accompanied in one by a pulmonary abnormality.

Thus, although this study of a group of sarcoidosis patients has revealed a general tendency for tuberculin sensitivity to be depressed at and shortly after the starting-point of their disease, it has been possible to observe this happening in only four of the 24 patients, taken individually.

Discussion

In comparison with earlier reports on the incidence of sarcoidosis, the present investigation has a number of unique features. In the first place, so far as we are aware, it is the only investigation in which so large a population group has been followed by means of periodic chest radiography for a decade, and it consequently provides an unusual opportunity to study the epidemiology of intrathoracic sarcoidosis between the ages of 15 and 25 years. Secondly, it permits a reliable evaluation whether tuberculosis vaccination prevents (or promotes) sarcoidosis. Thirdly, it enables the relationship between sarcoidosis and skin sensitivity to tuberculin to be examined

rather more closely than hitherto, by comparing the tuberculin sensitivity in the sarcoidosis patients, both before and after the start of their disease, with parallel results for large numbers of similar individuals observed similarly over the same period in the same areas, but who remained free of the disease.

Despite these advantages, there are shortcomings in the available data, mainly because the investigation was designed as a study of tuberculosis rather than sarcoidosis. Thus the detection of the cases has been largely based on routine chest radiography, and in fact all the 52 cases had at least one abnormal chest radiograph. The emphasis on chest radiography may have contributed to the absence from our series of cases presenting with eye, bone, or skin lesions (apart from erythema nodosum). However, the periodic postal inquiries and home visits might have been expected to discover at least some such cases, had they occurred; moreover, our findings are in keeping with recent reports (James, 1959; Douglas, 1961; James *et al.*, 1964) which indicate that in Britain skin and eye lesions are uncommon among subjects with sarcoidosis under the age of 30. Whatever the explanation, the conclusions of this report should be regarded as relating to intrathoracic sarcoidosis rather than to the disease in general.

Another shortcoming is that three-quarters of the diagnoses were made without confirmation by biopsy or Kveim test. Nevertheless, there was close agreement between these diagnoses by the special assessor for the present study and those made by the National Health Service physicians managing the patients, as well as those made by the routine assessor for the vaccines trial. Moreover, the radiographic and clinical manifestations, and the course of the disease, in the cases without confirmation by biopsy were similar to those in the cases with a positive biopsy. It therefore does not seem that the risk of misdiagnosis, in the absence of biopsy data, could have been important.

The benign and often short-lived nature of the hilar and pulmonary manifestations of the disease, and the frequent absence of other symptoms, make it clear that even with periodic routine chest radiography (which discovered 35 of the 52 patients in the present study) some cases of intrathoracic sarcoidosis are likely to have been missed, particularly in the later years when the special M.R.C. scheme for routine chest radiography was discontinued. However, although the total number of cases discovered here is thus probably an underestimate of the true total, especially at the higher ages, the frequency of chest radiography (and consequently the degree of underestimation) was closely similar in the five trial groups (differing in tuberculin and vaccination status from the start of the trial), and it is therefore valid to compare the incidence of sarcoidosis in these groups.

The present findings are of particular relevance to the current debate on the role of the tubercle bacillus, and other mycobacteria, in the aetiology of this disease. In fact, it is remarkable how little positive support the data provide for a link between this disease and any mycobacterium. First, there is no evidence that vaccination of 14-year-old children with either B.C.G. or the vole bacillus has reduced the attack rate of sarcoidosis during the next 10 years, effective though both vaccines have been in preventing tuberculosis in the same population. Secondly, there is no evidence that those already positive to tuberculin at the age of 14 years, whether this was positivity to 3 T.U. (presumably indicating infection with human or bovine tubercle bacilli) or positivity only to 100 T.U. (indicating infection either with mammalian tubercle bacilli or some other mycobacterium—Hart *et al.*, 1962; Sutherland *et al.*, 1964), had different subsequent attack rates of sarcoidosis from those without any detectable mycobacterial infection at the same age. Thirdly, the age-and-sex and the geographical distributions of the attack rate of sarcoidosis in this population, between the ages of 15 and 25 years, were different from those of tuberculosis in the same population. None of these findings, of course, disproves the existence of some association between

intrathoracic sarcoidosis and mycobacterial infection, but the underlying relationship would have to be complex rather than simple if it was to account for all these negative findings.

It has been suggested by a number of workers (see Hart *et al.*, 1964) that the appearance of sarcoidosis may be related to previous B.C.G. vaccination, although others—for example, Oudet and Roegel (1962)—have argued that the reported instances of the disease following vaccination are coincidental. The present findings support this latter contention, since they indicate that B.C.G. (and also vole-bacillus) vaccination, at least at the age of 14 years, does not increase the attack rate of sarcoidosis during the next 10 years.

Patients with sarcoidosis often show weak or absent tuberculin sensitivity, but there has been some uncertainty whether this is a depression of sensitivity associated with the development of the disease, or whether sarcoidosis is particularly likely to develop in individuals who have a persistently weak level or absence of tuberculin sensitivity. This uncertainty is resolved by the present inquiry, since the results of the tests in the patients who developed sarcoidosis, both before and after the start of their disease, may be compared directly with the results of the corresponding tests on all the other vaccines trial participants who did not develop the disease. The findings indicate that before the development of the sarcoidosis the tuberculin sensitivity in these two groups ran a closely similar course. In other words, there is no evidence of anything special about the tuberculin status of those who later developed sarcoidosis, either at the age of about 14 (when they first came under observation) or at any later age up to the time the disease became manifest.

There is, however, evidence (on a regrettably small number of observations) of a depression of sensitivity at and shortly after the start of the sarcoidosis. At the same time the comparison with the corresponding results among the healthy participants in the vaccines trial shows that this depression is by no means universal, and is of less extent than might have been expected from some previous reports. Our finding that the depression of sensitivity is only of moderate extent is in agreement with the observations in what is apparently the only other study to include comparative data from individuals in the general population without sarcoidosis (Comstock *et al.*, 1961). These authors found that of their 148 matched control individuals 61% were non-reactors to 5 T.U. of PPD-S, whereas for the 74 sarcoidosis patients the proportions were 74% (when they were tested at the same time as the controls) and 85% (when tested at the time of initial diagnosis, at least one year previously).

It is of particular interest to compare the findings of the present report on intrathoracic sarcoidosis with our observations (Hart *et al.*, 1964) on the Kveim test in apparently healthy subjects (also from the vaccines trial). In the earlier paper a number of such subjects, with no evidence of past or present clinical sarcoidosis, were found to give positive Kveim reactions. This Kveim positivity appeared to be related to persistent tuberculin anergy (despite B.C.G. vaccination), and also to previous B.C.G. vaccination itself. In the present study there was no evidence of any association between clinical sarcoidosis and the general level of previous tuberculin sensitivity of the individual, nor was there any suggestion that B.C.G. vaccination promoted clinical sarcoidosis. This complete contrast in findings makes it important to discover whether the subjects in the earlier inquiry had some form of occult sarcoidosis or whether their Kveim positivity had some immunological basis not directly related to sarcoidosis. This problem is the subject of a current collaborative inquiry with Dr. L. E. Siltzbach.

Summary

The 54,239 participants in the Medical Research Council trial of tuberculosis vaccines have now been followed from the

age of about 14 years (in 1950–2) to an age of about 27, with routine chest radiography, tuberculin tests, postal inquiries, and home visits. Up to the end of 1963, 52 cases of sarcoidosis had been discovered among them. Thirty-five of the cases were detected as a result of routine chest radiography, and all 52 had at least one abnormal chest radiograph.

These cases were classified as sarcoidosis by a special assessor, who was kept unaware of the results of tuberculin tests and whether any vaccination had been performed. Biopsy information was not often available, but the diagnoses made by the patient's own physician and the routine trial assessor agreed closely with the classifications of the special assessor.

Of the 52 patients, 48 showed bilateral hilar lymph-node enlargement, 20 showed pulmonary abnormalities, and 11 had erythema nodosum; no eye, bone, or other skin abnormalities were reported. The course of the disease has been benign and relatively short.

The incidence of intrathoracic sarcoidosis was similar in those who were vaccinated on entry to the trial (whether with B.C.G. or vole-bacillus vaccine); in those, also initially tuberculin-negative, who were left unvaccinated (by random selection); and in those who were initially tuberculin-positive (whether the degree of sensitivity was strong or weak). It is concluded that tuberculosis vaccination at the age of 14 years did not protect against sarcoidosis, or promote this disease, and that the incidence of sarcoidosis in this population group over a period of more than 10 years was not influenced by the initial tuberculin status of the participant.

The attack rate of sarcoidosis in the whole population group was closely dependent on age, rising steeply to an annual rate of 1.49 per 10,000 at ages 20–22½ years, though this may underestimate the true incidence. The average annual incidence at 15–25 years was three times as great in females as in males. The sex and age pattern of sarcoidosis differed noticeably from that of tuberculosis in this same population. There were also geographical differences in sarcoidosis incidence (the trial was undertaken in the London, Birmingham, and Manchester areas), which were not in line with the differences in tuberculosis incidence.

A detailed comparison was made of the results of routine tuberculin tests in the sarcoidosis patients, both before and after they developed the disease, with corresponding results in those who did not contract sarcoidosis. No differences in sensitivity were apparent before the start of the disease, suggesting that the incidence of sarcoidosis was not related to the level of previous tuberculin sensitivity; but there was a tendency for tuberculin sensitivity to be depressed in the sarcoidosis patients at and shortly after the start of their disease.

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