INTERNATIONAL JOURNAL OF LEPROSY Volume 34, Number 2
Printed in U.S.A.

The Karimui Trial of BCG

2. Tuberculin Reactions in a Leprosy-endemic but Tuberculosis-free Population[1]

G. C. Scott, S. G. Wigley and D. A. Russell[2]

A preliminary report of the "blind" controlled trial of BCG in progress at Karimui in the Eastern Highlands of the Territory of Papua and New Guinea has been published ([19]). In March 1963, 85 per cent of the 5,000 persons comprising the Karimui population were tested with 0.1 ml. of 1:1,000 OT (10 TU). In March 1964, a sample of 1,331 persons was retested and the results of these tuberculin surveys will be used to examine the following hypotheses.

(1) No transmission of *M. tuberculosis* is occurring within the Karimui population at the present time.

(2) The tuberculin reactivity observed at Karimui is unlikely to be due to antigenic stimulation with anonymous mycobacteria.

(3) Overt infection with *M. leprae* does not induce tuberculin reactivity.

(4) Presumed latent infection or recovery from infection with *M. leprae* does not induce tuberculin reactivity.

Karimui was selected for the trial of BCG vaccination as a prophylactic against leprosy in the belief that the area is virtually tuberculosis-free. The requirements of the trial prohibit the use of lepromin; hence it is not possible to study the relationship between the tuberculin and lepromin tests. Many surveys have indicated that the tuberculin index is very low in the highlands of New Guinea; in a total of 85,500 tuberculin tests in the Eastern and Western Highlands, the natural conversion rate ranges from 2.2 per cent in areas with 15 years of European contact to 0.2 per cent where such contact has been minimal. Leiker ([10]) reports similar results in the western half of the island; however, for assessment of the results of this trial, it is necessary to prove that transmission of *M. tuberculosis* is not occurring among the population. Table 1 shows the age and sex-specific tuberculin indices of the Karimui population who were tested and whose tests were read during March 1963.

The population is defined as the number of persons enumerated at the census and leprosy survey conducted in October 1962. Eleven persons known to have had a previous BCG inoculation are excluded. The proportion of tuberculin-positive reactors is remarkably low. The male/female ratio is approximately 4 to 1. For comparison with the Karimui data and to indicate the incidence of tuberculosis that may be associated with a given tuberculin index, two studies are available in which intensive case-finding has been carried out in an area with low tuberculin indices ([4, 24]). In a tuberculin and case-finding survey among San Francisco school children, Curry ([4]) found that for a tuberculin index of 8 per cent in the 6-18 year age group, approximately two cases might be expected among the children and their families per thousand tests. In Canberra, the Australian Federal Capital, a tuberculin index of 4 per cent in the same age group was associated with a tuberculosis incidence of 0.5 per thousand per annum. The tuberculin

[1]Received for publication November 29, 1965.

[2]G. C. Scott, M.B., B.S., D.P.H., D.T.M.&H. (Sydney), School of Public Health and Tropical Medicine, University of Sydney, Sydney, Australia. S. C. Wigley, M.B., B.S. (Melbourne), M.R.C.P., and D. A. Russell, M.B., B.S. (Madras), D.P.H. (Sydney), Department of Public Health, Port Moresby, Territory of Papua and New Guinea.

TABLE 1. *Prevalence of positive tuberculin reactions at March 1963.*

	Males		Females		Population 1962	
Age group	Prop. of pop. tested and read (%)	% Tuberculin positive[a]	Prop. of pop. tested and read (%)	% Tuberculin positive[a]	M	F
0-9	84.4	0.3	85.2	0.0	787	702
10-19	83.8	2.1	84.7	0.5	790	471
20-29	84.3	10.6	83.5	1.5	426	550
30-39	86.3	13.0	86.4	2.7	417	464
40 & over	88.4	14.6	84.0	3.0	241	238
All ages	84.9	5.9	84.8	1.3	2,661	2,425

[a] "Positive" indicates a diameter of induration of 5 mm. and over.

index for the Karimui population of the same age was 0.8 per cent (18 positive reactors among 2,323 persons aged 0-19 tested and read). Bovine tuberculosis is absent in the Territory of Papua and New Guinea; the Department of Agriculture maintains a close watch on the tuberculin reactions in dairy and beef herds and no tuberculous infection has been detected as yet. In 1963 all positive tuberculin reactors among the Karimui population, except for 14 persons who were absent, were subjected to a large film radiologic examination of the chest. Not one showed any evidence of active tuberculosis, but in 14 films some calcification could be seen; three of these were consistent with a radiologic diagnosis of healed histoplasmosis and the remainder suggested the presence of a healed primary complex of tuberculosis.

It is possible, however, that groups of closely associated tuberculin-positive reactors may exist, and in order to substantiate the first hypothesis, viz., that no transmission of *M. tuberculosis* is occurring, it is necessary to demonstrate that no familial aggregates of tuberculin-positive reactors exist or that if such aggregates do occur there is no evidence that the younger positive reactors, the most sensitive indicators of transmission, are associated with adults who are also positive to tuberculin. The results of the 1963 tuberculin survey were recorded on the same cards as were used for the 1962 leprosy survey and these cards were arranged and numbered in serial order in such a way that the people attended for examination in self-selected family groups, which were designated "households." These groups were for the most part based on males of marriageable age and represented the nuclear family. The size of these "households" varies from one, an unmarried male or widow, to over twenty persons. These family groups usually reside in the one house, and for the greater part of the year live in family houses situated close to their gardens. Only occasionally, at times of celebration, mourning, or visits by census patrols, would the people gather in their villages for any length of time. As with other societies, the degree of personal contact would be greatest among family members. During the leprosy survey care was taken to record as accurately as possible the names of the natural parents of every person interviewed; from this material it was possible to construct genealogies which when tested at a subsequent visit to Karimui, have been shown to be reliable.

After the names and other personal details of the tuberculin reactors were entered in a register, it became apparent that some of these persons were associated, either by marriage or by sibship, and from our records it was possible to determine a "population at risk" consisting of the members of the households in which tuberculin-positive persons resided and who might reasonably be expected to have been exposed to the positive reactors. Table 2 demonstrates the results of this analysis.

In six cases, both husband and wife were tuberculin-positive, but of six adults and fifteen children under 20 years of age exposed to these tuberculin-positive married couples, not one positive reactor was found.

TABLE 2. *Married couples, siblings and others who were tuberculin-positive and number of positive reactions among persons exposed to these positive reactors.*

Relationships of positive reactors	No. of relationships	No. reactors with this relationship	No. household members exposed to these positive reactors		No. positive reactors among household members	
			Children (0-19)	Adults (20 & over)	Children (0-19)	Adults (20 & over)
Group A (Husband-wife)	6	12	15	6	0	0
Group B (Siblings)	21	47	120	65	1	2
Group C (All other positive reactors)	99	99	274	175	1	0
Total		158	409	246	2	2

Twenty-one sibships, comprising 47 persons, could be distinguished among the positive reactors; exposed to these were 65 adults and 120 children, among whom two adults, spouses of two of the positive reactors, and one child were found to be tuberculin-positive. All three of these persons resided in widely separated households. There remained 99 reactors for whom no marital or sibling relationship could be established; exposed to these were 175 adults and 274 children, and among them only one child, an adopted son, was found to be positive. The evidence in support of our first hypothesis, that no transmission of *M. tuberculosis* is occurring in Karimui at the present time, appears conclusive.

The frequency distribution of the size of positive reactions found in March 1963 is presented in Table 3.

The increased frequency of small diameter reactions of 5-10 mm. to doses of 5 TU, which has been found in tropical

TABLE 3. *Frequency distribution of diameter of positive tuberculin reactions by age, sex, leprosy status and membership in a leprous household.*

Diameter of reactions (mm.)	Sex		Age Both sexes			Affected pers ns	Members of leprous households
	M	F	0-19	20+	Total		
6-7	5	4	2	7	9	1	1
8-9	7	1	1	7	8	0	1
10-11	23	5	1	27	28	0	8
12-13	19	5	2	22	24	2	6
14-15	33	2	7	28	35	3	3
16-17	16	3	3	19	19	2	1
18-19	7	0	0	7	7	1	0
20-21	4	3	0	7	7	0	0
22-23	5	0	0	5	5	0	2
24-25	3	1	0	4	4	0	1
26-27	0	0	0	0	0	0	0
28-29	2	0	0	2	2	0	0
30-31	0	1	0	1	1	0	1
Not recorded	8	1	2	7	9	0	0
Total	132	26	18	140	158	9	24

populations, is considered to be due to stimulation with weak mycobacterial antigens, whereas reactions of 12-15 mm. or more are indicative of previous infection with pathogenic mycobacteria ([5]). The Karimui distribution most closely resembles that of Bechuanaland quoted by Nyboe ([18]), and compared to the other countries mentioned in his report there is a markedly decreased proportion of reactions in the range 5-10 mm. Although the number of positive reactors found at Karimui is small, there is no indication that sex, age, infection with *M. leprae* or membership of a leprous household are related to the size of the tuberculin reaction. Of 149 positive reactors for whom the diameter of induration was recorded, 80 had a reading of 14 mm. or more and thus might be regarded as having been infected at some time in the past with *M. tuberculosis*. The natural tuberculin conversion observed in the Karimui people results from a combination of two factors. First, the most important, is infection of some of the older members, particularly the males, with *M. tuberculosis* at some time previously and associated with trading journeys to coastal areas where tuberculosis is endemic; the detection of 47 sibling-related reactors would tend to support this conclusion. Secondly, some small degree of antigenic stimulation by anonymous mycobacteria may be involved, although it is difficult to entertain this possibility seriously, as the people live "close to the soil," the females being most concerned with horticultural activity. If anonymous mycobacteria were responsible, it is difficult to account for the predominance of males and the very small number of positive reactors under 15 years of age. The prevalence of mycobacterial infection in pigs and game in the Karimui region is unknown, but is probably an unimportant factor in inducing tuberculin reactivity among the human population.

The extent to which tuberculin reactivity may wax and wane in this population may be estimated by comparing the results of the 1963 tuberculin survey and the sample of the population retested in 1964. Recent experience in the study of long-term conversion rates following BCG vaccination in isolated populations indicates that these rates tend to decrease with the passage of time ([8, 21]), and support the view that some factor may be responsible for the failure of these peoples to maintain a long-term tuberculin-positive status although some workers maintain that low sensitivity following BCG vaccination is no indication of the degree of resistance to infection ([6]). The three-month conversion rate among the BCG-inoculated group at Karimui was 87.4 per cent, with a mean diameter of induration of 17.8 mm. However, the 12-month conversion rate among the sample retested in March 1964 was 60.4 per cent and in order to maintain tuberculin positivity, the entire group of BCG receptors participating in the trial were revaccinated.

Table 4 shows the variation in tuberculin reactivity among 664 persons who were tested initially in March 1963 but did not receive BCG inoculation and were retested in March 1964.

The dotted line drawn across the table between 8 and 9 min. might be considered to represent a range of observer error of 5 mm. ± 3 mm., despite precautions to keep this factor to a minimum. A variation in tuberculin reactivity of approximately 8 per 664 tests, or 1.2 per cent per annum, might therefore be expected among the Karimui population. The reason for this variation is not known, but the small numbers involved give added confidence to the observations made during this trial, and a variation of 1 per cent per annum in natural tuberculin reactivity would not be sufficient to warrant lack of acceptance of the results of the 1963 tuberculin survey as an indicator of mycobacterial infection.

ROLE OF *M. LEPRAE* IN INDUCING TUBERCULIN REACTIVITY

Although the general consensus of opinion expressed by most authors is that infection with *M. leprae* does not result in tuberculin reactivity ([11, 14, 23, 25]), some workers adopt a more guarded attitude and regard the evidence as inconclusive ([1, 7, 12, 13, 17]). However, some authors have provided evidence that *M. leprae* may be a factor in

TABLE 4. *Tuberculin reactions among 664 non-BCG-vaccinated persons tested in March 1963 and retested March 1964.*

Diameter of reaction (mm.)	Result of tuberculin test	
	Number of reactors	
	Tuberculin-negative 1963[a] Tuberculin-positive 1964	Tuberculin-positive 1963 Tuberculin-negative 1964[a]
5	3	—
7	—	2
8	2	—
9	1	—
11	1	—
12	—	2
15	—	1
17	—	1
Not recorded	1	1
Total	8	7

[a]Tuberculin-negative signifies a reaction less than 5 mm. diameter.

TABLE 5. *Tuberculin reactivity of leprous and healthy persons.*

Age	Leprous		Healthy	
	No. tested and read	% Tuberculin positive (5 mm. & over)	No. tested and read	% Tuberculin positive (5 mm & over)
Males				
0-9	15	0	649	0.31
10-19	68	1.47	594	2.19
20-29	42	11.90	317	10.41
30-39	16	6.25	344	13.37
40 & over	10	20.00	203	14.29
All ages	151	5.96	2,107	5.84
Females				
0-9	15	0	581	0
10-19	40	0	358	0.56
20-29	37	0	422	1.66
30-39	14	0	386	2.85
40 & over	10	0	192	3.13
All ages	116	0	1,939	1.34

inducing reactivity to tuberculin ([2, 3, 9, 15, 16, 20, 22]). If our first two hypotheses are accepted, Karimui presents an opportunity to study tuberculin reactivity and its relationship to infection with *M. leprae* in a situation in which *M. tuberculosis* is absent and in which anonymous mycobacteria are probably not ecologically important. Table 5 illustrates the tuberculin reactivity observed in affected and healthy males and females at Karimui. The differences observed are not significant and $P = 0.80$ for both males and females.

It is possible, however, that the tuberculin-positive reactors represent a proportion of persons who may have been exposed to and infected with *M. leprae*, but are suffering from a latent or inapparent infection. It seems reasonable to assume that those persons exposed to infection would

TABLE 6. *Tuberculin positivity among members of leprous and nonleprous households.*

Age	Leprous households		Nonleprous households	
	No. tested	% Positive	No. tested	% Positive
Males				
0-9	140	0	524	0.4
10-19	151	0.7	511	2.5
20-29	69	7.3	290	11.4
30-39	77	13.0	283	13.1
40 & over	41	9.8	172	15.7
All ages	478	4.2	1,780	6.3
Females				
0-9	151	0	447	0
10-19	96	0	303	0.7
20-29	121	0.8	338	1.8
30-39	76	2.6	325	2.8
40 & over	44	2.3	156	3.2
All ages	488	0.8	1,569	1.4

be members of leprous households (a leprous household is defined as a self-selected family group which contains one or more cases of leprosy). If a latent, inapparent or previous infection with *M. leprae* were responsible for tuberculin reactivity, a greater proportion of tuberculin-positive reactors might be expected among the members of leprous households. Table 6 demonstrates the prevalence of tuberculin-positive reactors in leprous and nonleprous households by age and sex. The differences observed are not statistically significant, and it is concluded that presumed latent or inapparent infection is not associated with tuberculin reactivity at Karimui. Finally when tuberculin reactivity was studied in persons affected by (a) tuberculoid leprosy and (b) all other types, no significant differences were detected. Among 121 males with tuberculoid leprosy, who were tuberculin-tested and read, 8 positive reactors were found; the number of positive reactors expected in the light of the tuberculin-positive rates prevailing in the total male population was found to be 7.9. Among 30 males affected by leprosy other than the tuberculoid type, one positive reactor was observed; the number expected was 1.47. Among 103 females with tuberculoid leprosy and 13 females affected by other types of leprosy, not one tuberculin-positive reactor was found.

SUMMARY

The people of the Karimui area in the Eastern Highlands of the Territory of Papua and New Guinea, the site of a "blind" controlled trial to test the efficacy of BCG as a prophylactic against leprosy, represent a population in which leprosy is endemic but tuberculosis disease is absent. Tuberculin surveys indicate that infection with *M. tuberculosis* at some time in the past may have resulted in a small number of positive tuberculin reactions. Anonymous mycobacteria are probably unimportant as a cause of these reactions. Clinical evidence of infection with *M. leprae* is not associated with tuberculin reactivity, nor is presumed latent or inapparent infection, nor the tuberculoid form of the disease when compared to all other types. The variation in natural tuberculin reactivity is of the order of 1 per cent per annum.

RESUMEN

La población del área de Karimui en los altos territorios del Este de los territorios de Papua y Nueva Guinea, el sitio de un control ciego para probar la efficacia del BCG como un profiláctico contra la lepra, representa una población en la cual la lepra es endémica pero la enfermedad tuberculosa está ausente. Las investigaciones con tuberculina indican que la infección con el *M. tuberculosis* en algun tiem-

po en el pasado, puede haber resultado en un pequeño número de reacciones tuberculinicas positivas. Micobacterias anónimas probablemente son sin importancia como una causa de estas reacciones. La infección con *M. leprae* no muestra evidencia clínica de estar asociada con la reactividad tuberculínica, ni se presume como una infección latente o inaparente, ni la forma tuberculoide de la enfermedad, cuando es comparada con todos los otros tipos. La variación en la reactividad natural tuberculínica es del orden del 1 porciento anual.

RÉSUMÉ

La population de la région de Karimui, dans les contrées montagneuses de la partie orientale du territoire de Papouasie et Nouvelle Guinée, a été choisie pour étudier l'efficacité du BCG en tant qu'agent prophylactique contre la lèpre, au moyen d'une étude menée par la méthode de l'incognito (blind study) et faisant appel à l'emploi de tèmoins (controlled trial). La lèpre est endémique dans cette population, alors que la tuberculose en est absente. Des enquêtes tuberculiniques indiquent que l'infection par *M. tuberculosis* dans le passé peut avoir résulté en un petit nombre de réactions positives à la tuberculine. Les mycobactéries anonymes sont probablement sans importance comme origine de ces réactions. L'infection par *M. leprae*, jugée d'après l'évidence clinique, n'est pas associée avec la réactivité à la tuberculine, pas plus que ne le sont l'infection présumée latente ou inapparente, ou la forme tuberculoide de la maladie comparée à tous les autres types. La variation dans la réactivité naturelle à la tuberculine est de l'ordre de 1 pour cent par an.

Acknowledgment. The authors' thanks are due to the Director, Public Health Department, Territory of Papua and New Guinea, and to the Director-General of Health, Commonwealth of Australia, for permission to publish this paper.

REFERENCES

1. Brown, J. A. K. and Stone, M. M. A trial of BCG vaccination in the prophylaxis of leprosy. Leprosy Rev. **34** (1963) 118-122.
2. Convit, J., Gonzales, C. L. and Rassi, E. Estudios sobre lepra en el grupo etnico aleman de la Colonia Tovar, Venezuela. Internat. J. Leprosy **20** (1952) 185-193.
3. Convit, J. and Rassi, E. Lepromin and tuberculin tests in Venezuelan leprosy foci, induction of lepromin reactivity by BCG vaccination. Internat. J. Leprosy **22** (1954) 303-310.
4. Curry, F. J. Tuberculin testing in San Francisco schools as an instrument in tuberculosis case finding. Dis. Chest **42** (1962) 489.
5. [Expert Committee on Tuberculosis]. WHO Tech. Rep. Series No. 195, 1960.
6. Gernez-Rieux, C. and Gervois, M. The peculiarity of weak sensitivity to tuberculin in subjects previously vaccinated with BCG. Ann. Inst. Pasteur (Lille) **13** (1962) 89-98.
7. Guinto, R. S., Doull, J. A. and Mabalay, E. B. Tuberculization and reactivity to lepromin. Association between lepromin and tuberculin reactions in school children in Cordova and Opon, Cebu, Philippines. Internat. J. Leprosy **23** (1955) 32-47.
8. Guinto, R. S., Mabalay, M. C. and Doull, J. A. Reactivity of children to lepromin and various tuberculins, as affected by recent and older BCG vaccination. Internat. J. Leprosy **30** (1962) 284-290.
9. Kooij, R. and Rutgers, A. W. F. Leprosy and tuberculosis. A comparative study with the aid of skin tests with tuberculin, killed BCG and the Dharmendra lepromin in South African Bantus. Internat. J. Leprosy **26** (1958) 24-40.
10. Leiker, D. L. Epidemiological and immunological surveys in Netherlands New Guinea. Leprosy Rev. **31** (1960) 241-259.
11. Lewis, N. G., Fite, G. L. and Bogen, E. Comparison of reactions to human and avian tuberculins in leprosy patients. Internat. J. Leprosy **29** (1961) 355-358.
12. Lowe, J. and Davey, T. F. Tuberculin and lepromin reactions in Nigeria. An analysis of the data of Lowe and McNulty. Internat. J. Leprosy **24** (1956) 419-423.
13. Lowe, J. and McFadzean, J. A. Tuberculosis and leprosy—further immunological studies. Leprosy Rev. **27** (1956) 140-147.
14. Lowe, J. and McNulty, F. Tuberculosis and leprosy: Immunological studies in healthy persons. Brit. Med. J. **2** (1953) 579-584.

15. MELSOM, R. S. Tuberculin hypersensitiveness in guinea-pigs inoculated intradermally with human leprous nodules. Internat. J. Leprosy **6** (1938) 462 (abstract).
16. MELSOM, R. Experiments inoculating guinea-pigs with leprous nodules. Acta Dermato-venereol. **20** (1939) 451-462.
17. MUIR, E. Relationship of leprosy to tuberculosis. Leprosy Rev. **28** (1957) 11-19.
18. NYBOE, J. The efficacy of the tuberculin test; an analysis based on results from 33 countries. Bull. WHO **22** (1960) 5-37.
19. RUSSELL, D. A., SCOTT, G. C. and WIGLEY, S. C. BCG vaccination in leprosy. A prelimniary report of a "blind" controlled trial. Internat. J. Leprosy **32** (1964) 235-247.
20. RUTGERS, A. W. F. Lepra en tuberkulose. (Doctorate thesis, University of Amsterdam. Zoandijk, Vitgeverij der Firma J. Heijnis Trz., 1956, 217 pp.) (*Abstract in* Internat. J. Leprosy **25** (1957) 78.)
21. SAKULA, A. Tuberculosis in the Tristan da Cunha Community. Tubercle **44** (1963) 225-229.
22. TAYLOR, C. E. Contributions from animal experiments to the understanding of sensitivity to *M. leprae*. Internat. J. Leprosy **31** (1963) 53-67.
23. TRAPPMANN, R. A study of lepromin and tuberculin reactions. Internat. J. Leprosy **26** (1958) 102-110.
24. TREMAYNE, J. Commonwealth Department of Health, Canberra. Personal communication.
25. WADE, H. W. Reactions to tuberculins in leprosy. A review. Internat. J. Leprosy **18** (1950) 373-388.