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FURTHER STUDIES OF GEOGRAPHIC VARIATION IN NATURALLY ACQUIRED TUBERCULIN SENSITIVITY

WHO TUBERCULOSIS RESEARCH OFFICE *

SYNOPSIS

This paper presents the results of the tuberculin-testing of over 3,600 patients in tuberculosis hospitals and of nearly 34,000 schoolchildren in widely separated areas where arrangements could be made for specially trained personnel to work with uniform materials and techniques. Both patients and children were tested with an intradermal dose of 5 TU, and the children were retested with 100 TU if the reactions were less than 5 mm.

The results confirm those of earlier papers, that at least two different kinds of naturally acquired tuberculin sensitivity are found in many human populations : a high-grade sensitivity, designated as *specific* for virulent tuberculous infection, and a low-grade kind designated as *non-specific*, or not specific for tuberculous infection. Specific sensitivity is the kind found in tuberculous patients and in some schoolchildren everywhere. It follows a remarkably uniform pattern wherever it is found, apparently varying only in prevalence, not in degree, from place to place. In contrast, non-specific sensitivity varies both in prevalence and in degree. It ranges from nearly universal prevalence in some localities to almost complete absence in others, from a low degree to a relatively high degree approaching that of specific sensitivity. Non-specific sensitivity is not correlated with specific sensitivity and may have different causes in different places.

Serious practical problems are encountered as the prevalence and intensity of non-specific sensitivity increase, because the larger non-specific reactions cannot be distinguished from the smaller specific reactions with the tuberculin products in use today. A better, though not entirely satisfactory, separation of infected and uninfected persons might be obtained by using different criteria in different geographic areas for what is called a positive reaction to the 5 TU test. Changing the current criterion would probably provide a better estimate of the prevalence of infection in some communities : a lower proportion of the uninfected would be called positive at the expense of calling a few infected persons negative.

The analogous problem of separating specific from non-specific sensitivity in cattle has been provisionally solved by the veterinarians by comparative testing with tuberculins made from different types of mycobacteria. Similar methods are now being investigated for possible application to tuberculosis control work in human populations.

* The material in this report was collected by field staff of the WHO Tuberculosis Research Office, the WHO/UNICEF BCG programmes, the Tuberculosis Division of the United States Public Health Service, and the Madanapalle Field Research Station, India. The report was prepared for publication by Lydia B. Edwards, Carroll E. Palmer, and Phyllis Q. Edwards.

Extension of public health from a national to the international arena often involves the application of procedures in situations that may be quite different from those where the procedures have been developed or used before. Whenever and wherever this is done, the question arises : How well will a particular procedure or technique work ? Will it accomplish in a new setting what is expected of it from earlier experience in a different setting ? No better examples can be found of what answering this question may mean than the extension of BCG vaccination from a few national programmes to the recent international mass campaigns. Nor can better examples illustrate the fact that answering the pertinent questions should not simply be left to " experience " gathered during the course of carrying out large-scale service programmes. Rather, systematic public health research must either precede or at least go hand in hand with first attempts to extend public health work from the local to the international field.

In 1948, when three Scandinavian voluntary organizations joined with UNICEF to create what was popularly called the International Tuberculosis Campaign to organize an international BCG vaccination programme, it was decided to continue the common practice of tuberculin-testing before vaccination in order to exclude persons who had already had a tuberculous infection, and particularly to exclude those with active disease. Exclusion of persons previously infected was based mainly on the belief that they did not need vaccination, partly on the desire to avoid the unpleasant lesions that often appear at the site of intradermal vaccination, and partly to prevent BCG from being blamed for disease due to an earlier virulent infection. As a " positive " tuberculin reaction has generally been regarded as evidence of tuberculous infection, past or present, the decision was made to exclude all " positives " and to vaccinate only those with " negative " reactions.

This decision necessarily involved the adoption of specific criteria for what should be regarded as positive reactions ; and, largely on the basis of experience in the Scandinavian countries, provisional criteria were adopted. As mass BCG programmes proceeded under the auspices of the International Tuberculosis Campaign, and as they have continued under WHO/UNICEF, it has become apparent that these criteria were perhaps more provisional than was thought at the time they were adopted. They have been changed several times since 1948, and systematic field research set up to go along with the vaccination programmes now clearly demonstrates that our knowledge of tuberculin sensitivity in man is far from complete, that a good deal of research is still needed, and that the rules for practical work should probably be changed again, this time to provide different criteria for different situations.

During the past few years it has been possible, first through the national auspices of the United States Public Health Service, and later the international auspices of the World Health Organization, to study the problem of naturally acquired tuberculin sensitivity in various parts of the world.

Through the use of uniform materials, techniques, and procedures differences have been demonstrated in the pattern of tuberculin sensitivity in different areas, and, to a more limited extent, some understanding has been gained of what these differences imply.

It has thus become increasingly evident that at least two different kinds of naturally acquired tuberculin sensitivity are found in many human populations.[1, 3, 8] First, there is the high-grade kind of sensitivity brought out as fairly large reactions with a weak dose of tuberculin, a dose close to 5 TU for the intradermal test. In earlier papers, this kind of sensitivity has been designated as *specific*. It is the kind found in almost all persons with active tuberculosis as well as in those with X-ray signs (pulmonary calcifications or lesions) of having had the disease. It varies with the prevalence of tuberculosis; it is very often found in apparently healthy persons who give a history of contact with tuberculosis, much less often in those with no known contact.

Secondly, there is the low-grade kind of sensitivity brought out as small reactions with the 5 TU test and as fairly large reactions by retesting with a stronger dose of tuberculin (100 TU or 250 TU). We have designated this kind of sensitivity as *non-specific*, that is, as not specific for tuberculous infection, and have indicated that its prevalence is not correlated with specific sensitivity. Nor is it associated with X-ray evidence of tuberculous infection or the prevalence of tuberculosis or known contact with the disease. It is clearly related to place of residence, being highly prevalent in some areas and apparently absent in others; we have postulated that it may be caused by infection with an organism closely related antigenically to the tubercle bacillus.

The present paper is a further study of geographic variations in the pattern of naturally acquired tuberculin sensitivity in human populations. It is based on results of tuberculin-testing surveys among tuberculous patients and schoolchildren in different parts of the world and represents an attempt to synthesize and interpret the material with special reference to the needs of international tuberculosis control programmes.

Material and Methods [a]

Through the co-operation of national and local authorities, tuberculin-testing was done on patients in tuberculosis hospitals in Denmark, England, India, Pakistan, the Philippines, the Sudan, the United States of America, and Viet Nam. Groups of schoolchildren were also tested in these countries as well as in Ethiopia, Iran, Mexico, and Turkey. Pertinent information about the patients is given in table I and about the schoolchildren in table II.

[a] A more detailed description of methods is given in Chapter I of *BCG Vaccination*, Geneva, 1953 (*World Health Organization : Monograph Series* No. 12).

TABLE I. INFORMATION ON TUBERCULIN-TESTING OF PATIENTS IN TUBERCULOSIS HOSPITALS

Country	Location	Hospital	Date of study	Number in group	Number with 5 TU reactions read	PPD product
Denmark	Copenhagen	Øresund Hospital	May 1954	258	101 [a]	RT XIX-XX-XXI
England	Middlesex	Harefield Hospital	Nov. 1953	330	156 [a]	RT XIX-XX-XXI
North India	Kasauli and Dharampore villages	Lady Linlithgow Sanatorium King Edward Sanatorium Lady Hardinge Sanatorium	April 1953	299	290	RT XIX-XX-XXI
South India	Madanapalle, Chittoor district	UMT Sanatorium and Rajkumari Amrit Kaur TB Hospital [b]	Dec. 1951-June 1952	686	646	RT XIX-XX-XXI
Pakistan	Lahore, and Samli village	Gulabdevi TB Hospital TB Institute, Mayo Hospital Infectious Diseases Hospital, tuberculosis wards	Nov. 1952-Jan. 1953	355	288 [c]	RT XIX-XX-XXI
Philippines	Manila	San Lazaro Hospital	April 1954	289	246	RT XIX-XX-XXI
Sudan	Khartoum	River Hospital Omdurman Hospital	Sept. 1954	159	156	RT XIX-XX-XXI
South USA	Georgia	Battey State Hospital	March 1952	1,700	1,592	PPD-S
Viet Nam	Cholon	President Tinh Hospital	July 1954	159	150	RT XIX-XX-XXI

[a] Some of the patients (selected at random) were tested with 1 TU.

[b] Tuberculin-testing results for these patients were reported by P. Benjamin and J. Frimodt-Møller at the XIth Tuberculosis Workers' Conference, Nagpur, 2-5 February, 1954.

[c] In one hospital some of the patients (selected at random) were tested with 1 TU.

TABLE II. INFORMATION ON TUBERCULIN-TESTING OF SCHOOLCHILDREN

Country	Location	Number and character of schools	Date of study	Number in group	Number with 5 TU reactions read	Age range (years)	Estimated average age (years)	PPD product
Denmark	Viborg county, Jutland	81 rural schools	Feb.-May 1950	4,541	4,122	6-16	11.1	RT XIX-XX-XXI
England	Fulham district, London	4 urban schools	Nov. 1953	2,461	1,350 [a]	3-16	8.3	RT XIX-XX-XXI
Ethiopia	Shoa, Wollo, Harar, and Kaffa provinces	8 urban schools	Nov. 1953-June 1954	2,663	1,837	7-16	12.2	RT XXII
North India	Ajmer, Rajasthan, and Uttar Pradesh States	9 urban schools 6 rural schools	Jan.-March 1954	2,911	2,069	5-19	11.4	RT XIX-XX-XXI
South India	About 100 villages near Madanapalle	Children examined during survey of village populations	1950-51	5,228	2,561	5-19	10.5	RT XIX-XX-XXI
Iran	Shiraz	2 urban schools	Feb. 1953	817	798	6-18	10.1	RT XIX-XX-XXI
Mexico	Tulancingo, Pachuca province	3 urban schools	Aug. 1950	1,201	459 [b]	6-17	10.7	RT XIX-XX-XXI
Pakistan	Nawabshah and Hyderabad districts (Sind province), Kohat district (N.W. Frontier province), Gujrat district (Punjab province)	7 urban schools 5 rural schools	Oct.-Dec. 1952	3,555	2,675	4-22	9.6	RT XIX-XX-XXI
Philippines	Bulacan, Ilocos Sur, and Cebu provinces	3 urban schools 4 rural schools	Feb.-March 1954	2,786	1,972	6-15	10.1	RT XIX-XX-XXI
Sudan	Upper Nile province	2 urban schools 3 rural schools	April 1954	624	560	6-20	11.1	RT XIX-XX-XXI
Turkey	Tire district, Izmir province	3 urban schools 4 rural schools	Nov.-Dec. 1953	1,286	1,152	6-16	9.7	RT XIX-XX-XXI
North USA	Lapeer, Michigan	1 home for mentally deficient children	July 1947	1,500	1,022	5-19	13.3	RT XVIII
South USA	Columbus, Georgia	All schools in Muscogee County	April-May 1947	14,000	11,135	5-19	11.0	RT XVIII
Viet Nam	Saigon and Bien Hoa provinces	2 urban schools 1 rural school	April-June 1954	1,594	1,314	4-18	11.0	RT XIX-XX-XXI

[a] Some of the children (selected at random) were tested with 1 TU only.
[b] Alternate children were tested with 10 TU.

An effort was made to test all patients in residence in each of the tuberculosis hospitals; although some were missed or refused to be tested, there is no reason to believe that those not tested were a selected group with regard to tuberculin sensitivity. No effort was made to check the diagnosis, although it would seem likely that an occasional patient did not have active tuberculosis or, indeed, had never been infected. Nevertheless, all tuberculin test results are included in the present analysis except those for a few children in the Philippines hospital explicitly reported to have had non-tuberculous meningitis. In some hospitals the patients got two intradermal tests, 1 TU in one forearm and 5 TU in the other, according to a pre-arranged randomization scheme for selecting the dose to be used in each arm; in other hospitals the patients got only one intradermal test, either 1 TU or 5 TU, again according to a randomization scheme for selecting the dose to be given to each patient. Two doses were used to study the dose-response relation in tuberculous patients, and the randomization schemes were necessary to prevent bias in the reading of the reactions. Only the results of the 5 TU tests, however, are reported in this paper.

The children with few exceptions were pupils in municipal schools. As shown in table II, they ranged in age from about 5 to 19 years, with considerable variation in the age distribution within each group. (In some places age had to be estimated.) The youngest group were the children tested in England, where the average age was 8.3 years; the oldest were those tested in North USA, where the average was 13.3 years. For purposes of the present study, the children generally can be regarded as representative of the population of schoolchildren in their communities.

All children were given intradermal tests, first with a dose of 5 TU, followed by a dose of 100 TU for those with reactions measuring less than 5 mm of induration to the 5 TU test. (Though the criterion for giving the 100 TU test was 6 mm or 8 mm in some countries, the present analysis of 100 TU test results is based on the 5 mm criterion.)

Tuberculin-testing of both patients and children was done by selected field research personnel, either full-time staff members of the WHO Tuberculosis Research Office or of the US Public Health Service, or persons trained by them.[b] The work has been done during the past seven years, beginning with the testing of the groups in the USA in 1947 and ending with the patients in the Sudan in the fall of 1954. In general, the work was done

[b] *WHO* personnel, including TRO field staff, South East Asia and Western Pacific Regional BCG Assessment Teams and BCG Project personnel :

Agnes Bentsen, Johanne Weis Bentzon, Helena Burzynska, Ole Worm Christensen, Ingrid Schøning Clausen, Ragna Egemose, Eva Friis, Anton Geser, Catherine van Grunsven, Johannes Guld, Grete Hagen, Lis Halkjær-Lassen, Ellen Hansen, Birthe Johansen, Erik Kjølbye, Erna Kjølholt, Minna Madsen, Johannes Meijer, Per Stensrud, Inger Maria Thellesen

US Public Health Service tuberculosis field research personnel :

LeRoy Bates, Martin Brodsky, Mary Casey, Helen Gertz, George Graham, Muriel Graham, Lillian Lang, Marion La Venture, Olga Michaelsen, Erma Parr

Madanapalle Field Research Station field staff :

Philip Benjamin, P. Mathew, K. Seetherama Rao

in connexion with BCG vaccination programmes, the places selected being those where arrangements could be made with co-operative local and national authorities for carrying out the kind of precision work needed for research purposes. As such factors necessarily influence the geographic representativeness of the material now available for study, the results can serve only to high-light the kind of problems that must eventually be solved before international public health work can proceed effectively.

PPD tuberculin identified as RT XIX-XX-XXI from the Statens Serum-institut, Copenhagen, was used for the tests in all countries except Ethiopia, where RT XXII was used, and the USA, where RT XVIII was used for the shoolchildren and PPD-S for the patients. All the tuberculins are standardized products, and the 5 TU dilutions were prepared to contain 0.0001 mg of the dried powder (0.000066 mg for RT XXII). Tests were given on the volar surface of the forearm in the Philippines, the USA, and Viet Nam, and elsewhere on the dorsal surface. The reactions were read in the USA at 2 days, in other countries at 3 or 4 days ; they were carefully examined, and the widest transverse diameter of induration was measured and recorded. The field teams had been instructed not to try to classify the reactions as " positive " or " negative ".

Findings and Interpretations

Patients in tuberculosis hospitals: specific sensitivity

Altogether over 3,600 patients in tuberculosis hospitals were given the 5 TU tuberculin test, and the results are shown in fig. 1, separately for the hospitals in each locality. For the large hospital in South USA, the results are presented separately for white and negro patients; elsewhere the patients are not separated by race. In order to demonstrate the quantitative nature of tuberculin sensitivity and to provide material for direct visual analysis, results are presented as frequency distributions, the horizontal scale showing the measured diameter of induration of the reactions, the height of the columns showing the percentage of persons with reactions of specified sizes.

The distributions for all ten groups of patients are remarkably alike. Each is fairly symmetrical, with the modal value in most cases falling within the range of 14-18 mm. All show a gradual tapering off in the frequencies of reactions on either side of the central peak; few reactions exceed 25 mm in size, very few are smaller than 6 mm. Although the observed distributions may appear to deviate somewhat from the shape of a normal curve, their means and standard deviations provide a useful working description of their essential characteristics.

In order better to illustrate the similarity in the pattern of tuberculin sensitivity among tuberculous patients, fig. 2 has been prepared by drawing

FIG. 1. DISTRIBUTIONS BY SIZE OF REACTIONS TO THE INTRADERMAL 5 TU TEST AMONG TUBERCULOUS PATIENTS IN VARIOUS COUNTRIES

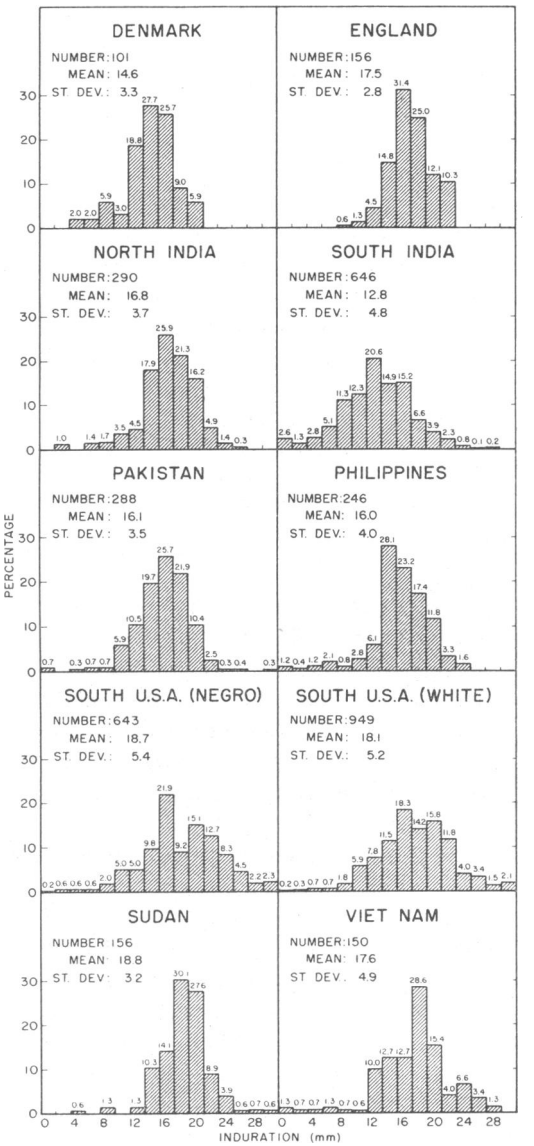
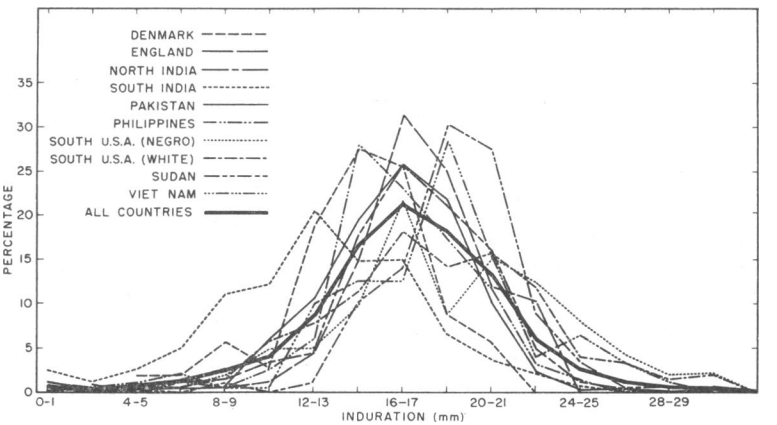


FIG. 2. FREQUENCY CURVES BY SIZE OF REACTIONS TO THE INTRADERMAL 5 TU TEST AMONG TUBERCULOUS PATIENTS IN VARIOUS COUNTRIES



the outlines of all 10 distributions on a single diagram. The heavy solid line represents the result of combining the distributions, and from this curve it may be estimated that the average reaction is about 16 mm in diameter and that less than 2% of all patients have reactions smaller than 6 mm, less than 3% smaller than 8 mm, and less than 4% smaller than 10 mm. In connexion with the finding that some of the patients have rather small reactions, it should be recognized that a few of them were critically ill and a few may not have had tuberculosis. Such patients might not be expected to react to tuberculin, the former because tuberculin sensitivity is often weak during critical illness,[5] the latter because they may never have had a tuberculous infection.

Broadly viewed, the results presented here agree with those in an earlier paper[9] that the pattern of tuberculin sensitivity is nearly uniform for groups of persons diagnosed in different parts of the world as having a virulent tuberculous infection. This seems to be true despite variations that must have occurred in testing technique, even though every effort was made to do the work uniformly. A basic pattern of sensitivity apparently supersedes all other factors that may tend to differentiate tuberculous patients : race, diet and nutritional status, concurrent and previous infections, etc. Moreover, as the 5 TU intradermal tuberculin test would seem appropriate for clearly bringing out that pattern, it would also seem appropriate as a single-dose test for the practical task of excluding from a general population those who may have active tuberculous disease. Only rarely does a patient have a reaction that is not definitely observable when tested intradermally with 5 TU of a standardized product, carefully given and read; and the number of large and disagreeable reactions is not so great as to create difficulties

in routine work. Tests with lower doses shift the entire distribution toward lower values and thereby increase the frequency of small, indefinite reactions, while higher doses are usually not acceptable for a single-dose test because, as the distribution is shifted toward higher values, there is an increased frequency of strong reactions.

Schoolchildren

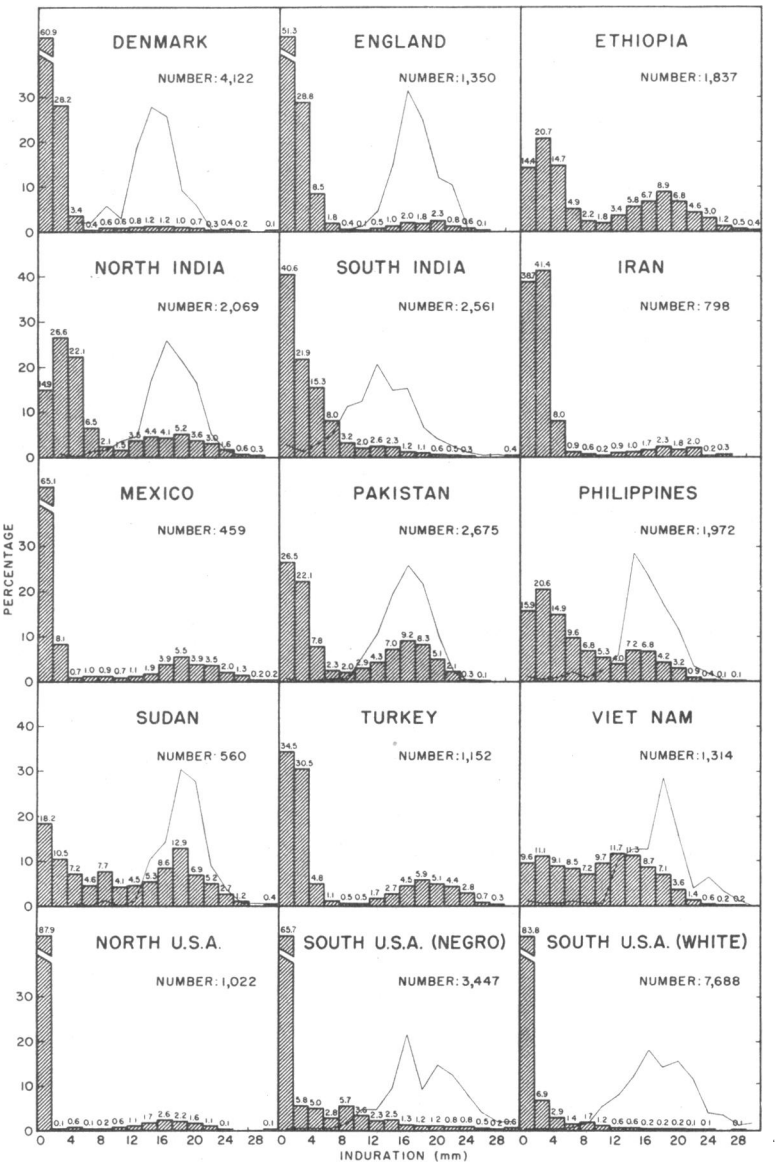
Tuberculin test results for almost 34,000 schoolchildren from the localities where tuberculous patients were tested and from four other localities are included in the present material. The results of the 5 TU test in the children are shown as frequency distributions in fig. 3. Just as for the patients, separate distributions are given for the white and negro children in South USA, but no separation has been made by race in the other places.

At first glance the distributions do not appear to be very much alike, but careful inspection reveals that most of them follow a consistent pattern. The reactions tend to be concentrated into two fairly distinct groups, one at the left-hand end of the scale, where the reactions are smaller than about 6 or 7 mm, the other toward the right, where the reactions are larger than about 11 or 12 mm. Between these two groups, in an intermediate zone ranging from around 6 mm to 12 mm, many of the distributions show a low frequency, where the larger reactions from the left-hand group may be seen as merging with the smaller reactions from the right-hand group.

The general form of each distribution varies considerably with the proportion of reactions that fall into the right-hand and left-hand groups, and with the proportion in the intermediate zone where the two groups merge. The separation of the distribution into two distinct groups is perhaps most clearly seen in the results from Mexico and Turkey, where very few reactions fall in the intermediate zone. In Denmark and among the white children in South USA, the frequencies of reactions in the right-hand groups are so low as to be barely discernible on the graph, while the frequencies in the left-hand groups are proportionately very high. In Ethiopia and Pakistan the frequencies in the right-hand groups are relatively higher and, as a consequence, proportionately lower in the left-hand groups. In Viet Nam there is apparently about the same proportion of reactions in each group, but the large number of smaller reactions from the right-hand group and larger reactions from the left-hand group fill in the intermediate zone and all but obscure the distinction between the two groups. In South India and South USA, the reactions of the left-hand groups appear to spill over toward the right and completely obliterate the intermediate zone.

Specific sensitivity. Superimposed on the distributions for the schoolchildren in fig. 3 are thin-line curves representing the distributions for tuberculous patients from the same geographic areas. In countries where a

FIG. 3. DISTRIBUTIONS BY SIZE OF REACTIONS TO THE INTRADERMAL 5 TU TEST AMONG SCHOOLCHILDREN IN VARIOUS COUNTRIES



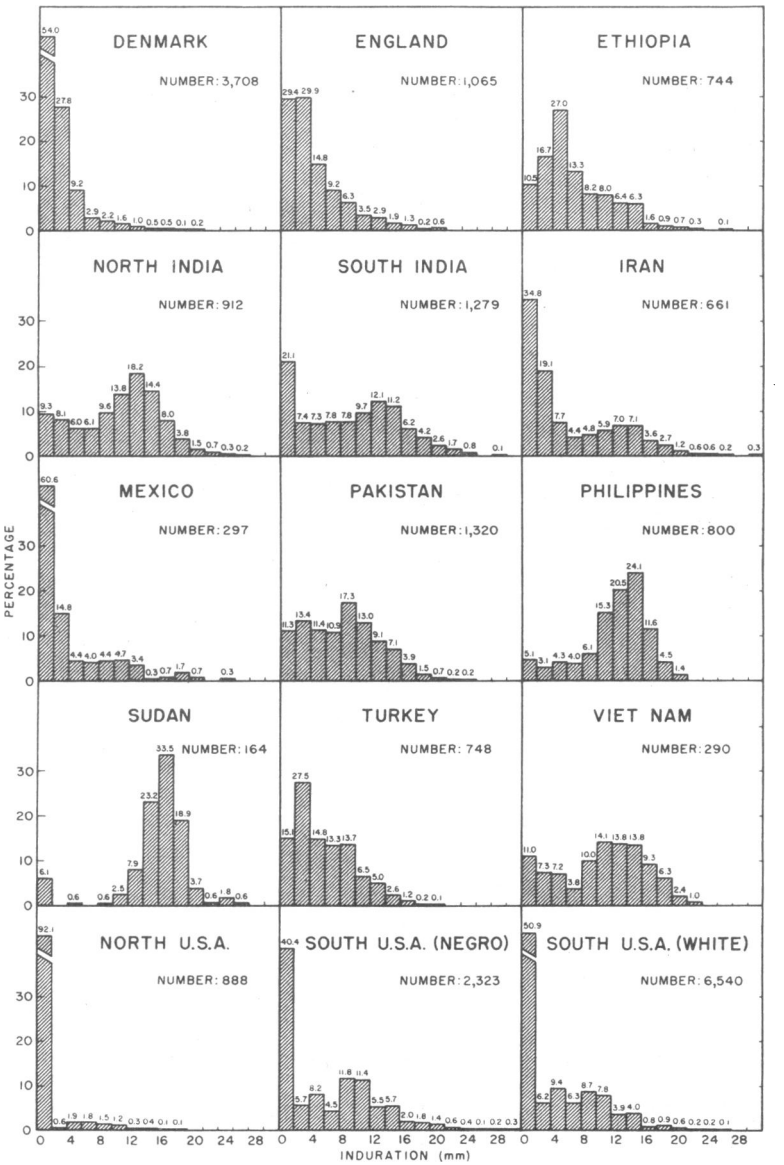
distinct and separate right-hand distribution of reactions is discernible for the children, its position and shape corresponds closely with the distribution of reactions for the patients. In other countries there are reactions throughout the range covered by the patients although a separate group cannot be clearly distinguished. If small though probably important variations are disregarded,[c] the distributions of reactions for both the patients and the groups of highly sensitive children cover about the same range and centre near the same place on the size scale; moreover, both tend to resemble the form of the normal probability curve. There can be little doubt, we believe, that each child population contains a group whose tuberculin sensitivity closely resembles that of tuberculous patients. The broad implication of this finding is that the pattern of tuberculin sensitivity is very much the same in groups of persons who have or have had a tuberculous infection, wherever such groups are found. It follows that few children who have tuberculosis or have had a tuberculous infection should have a reaction of less than 6 mm to the 5 TU intradermal test.

Non-specific sensitivity. The groups of reactions concentrated at the left-hand side of the distributions in fig. 3 differ strikingly from country to country and from place to place within the same country. In Denmark, England, Iran, Mexico, Turkey, and the USA, the combined frequencies of reactions are high in the first two columns (representing reactions of less than 4 mm); and relatively few reactions measure from 4 mm to about 10 or 12 mm. In general, this segment of the 5 TU distributions shows an abrupt drop from high to very low frequencies in the first few columns. In most of the other countries there are relatively fewer reactions in the 0-4 mm range, relatively more from 4 mm to 12 mm. The distributions bulge more toward the right; and, in some cases, become almost flat, as in Viet Nam.

These variations in form of the left-hand segment of the 5 TU distributions may be better understood by study of the results obtained when children with reactions of less than 5 mm were retested with 100 TU. As shown by the distributions in fig. 4, reaction patterns brought out by 100 TU differ in different parts of the world. In Denmark and Mexico, and particularly in North USA, most of the children either do not react at all or have very small reactions to 100 TU. In Pakistan more children have reactions, and larger ones, and the distribution somewhat resembles a plateau extending out to the 10 mm range and then tapering off. In the Philippines and the Sudan many children have large reactions and the distributions tend to resemble normal curves. The 100 TU test thus clearly brings out a kind of

[c] The most important of these is probably the tendency for non-specific sensitivity to influence the size of specific reactions. In most of the countries where non-specific sensitivity is highly prevalent, the distribution of specific reactions seems to be displaced slightly toward the left. In earlier papers we have suggested that this could be a sign of partial desensitization when specific infection is followed by the non-specific, and that persons first sensitized by the non-specific infection may partially resist further development of sensitivity when later infected by tubercle bacilli.

FIG. 4. DISTRIBUTIONS BY SIZE OF REACTIONS TO THE INTRADERMAL 100 TU TEST AMONG SCHOOLCHILDREN WITH REACTIONS OF LESS THAN 5 mm TO 5 TU IN VARIOUS COUNTRIES



tuberculin sensitivity that varies widely in prevalence in different parts of the world, ranging from almost universal prevalence in the Sudan to almost complete absence in North USA.

The need to interpret this kind of sensitivity led, several years ago, to the hypothesis that it must be *non-specific* for tuberculous infection. At that time, adequate material for study was rather limited and it was possible only to indicate the existence and geographic variation of non-specific sensitivity. The more extensive material presented here furnishes evidence that non-specific sensitivity varies not only in prevalence but also in degree or intensity.[d] The evidence is derived partly from variations in the form of the 100 TU distributions, partly from variations in what was referred to as the intermediate zone in the 5 TU distributions where reactions measure from 6 mm to 12 mm.

The most striking example of a relatively high degree of non-specific sensitivity is found in the results for the Sudan. With the 100 TU test, almost all the children have quite large reactions, on the average measuring 16-17 mm; and, with the 5 TU test, so many reactions measure 6-12 mm that the intermediate zone is rather well filled in. A fair proportion of the reactions in this zone probably represents children with strong non-specific sensitivity. The degree of non-specific sensitivity found in most of the other countries is lower than that found in the Sudan. In the Philippines, for example, there is a definite group centring at about 14 mm to the 100 TU test; in India, Iran, and Viet Nam a group centres at about 12 mm; in Pakistan and South USA at about 8 mm; and there may also be a group in both Mexico and Turkey centring at about 8 mm. In England it is difficult to find any indication of a definite group, yet a fair proportion of the children react to 100 TU, and in Denmark and North USA non-specific sensitivity is apparently very low in both frequency and intensity.

Although not entirely consistent, the evidence certainly suggests that the lower the *degree* of non-specific sensitivity, the less the tendency for the left-hand group of reactions to the 5 TU test to spill over into the intermediate zone, and consequently the more clear its separation from the right-hand group. This may be seen by comparing the 5 TU distributions for Turkey and Pakistan, on the one hand, with those for India, the Philippines, and Viet Nam, on the other. What might appear to be a clear-cut exception is seen in South USA, where, even though the non-specific sensitivity is of low intensity as measured by the 100 TU reactions, the intermediate zone is completely obliterated. The frequency of specific sensitivity, however, is so low in this area that the identification of a separate concentration of strong reactions to the 5 TU test becomes practically impossible.

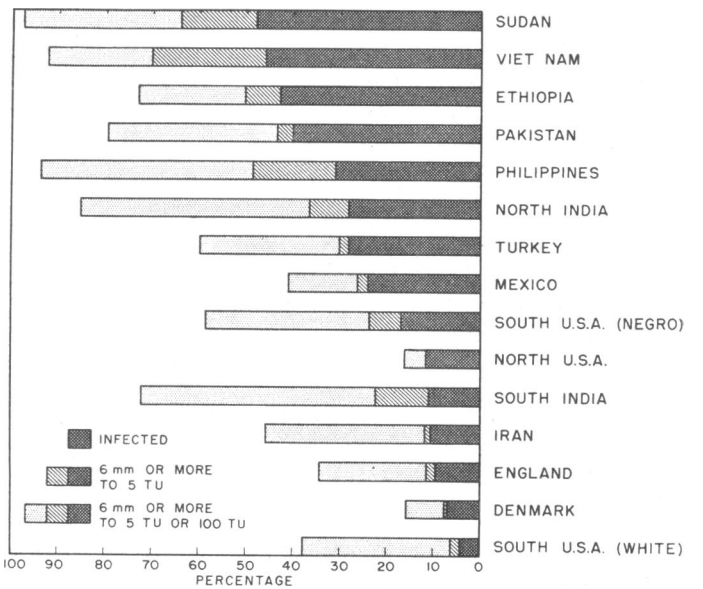
From the standpoint of using the 5 TU test to pick out the infected members of a population, the practical importance of non-specific sensitivity

[d] This finding would imply that non-specific sensitivity is caused by different agents in different places, as will be discussed in later papers.

relates directly to the frequency of 6-12 mm reactions that it produces to the 5 TU test. As the prevalence and intensity of non-specific sensitivity increase, the greater becomes the tendency for the reactions to spill over into the intermediate zone and merge with the smaller specific ones, so that reactions of 6-12 mm represent an inseparable mixture of both kinds of sensitivity. The proportions of specific and non-specific reactions in this mixture thus depend on the prevalence of specific sensitivity and the prevalence and intensity of non-specific sensitivity in the community.

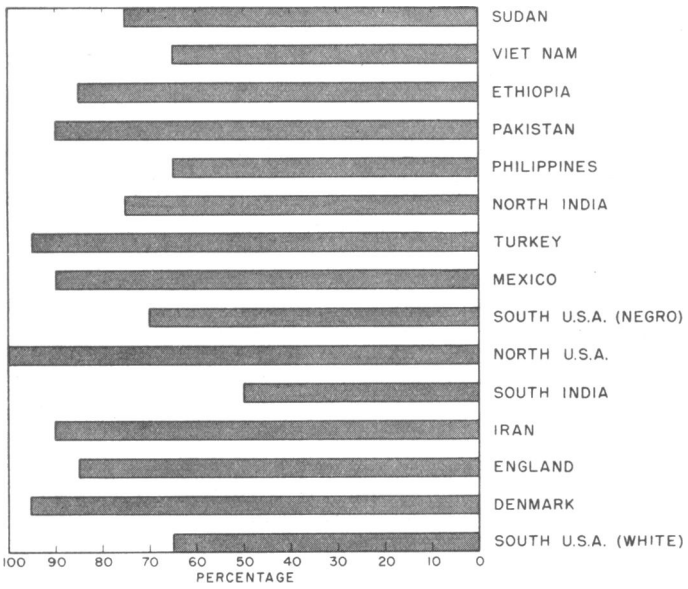
Prevalence of specific and non-specific sensitivity. If it is assumed that 5 TU reactions of persons infected with tuberculosis resemble a normal distribution, then an estimate of the prevalence of specific sensitivity in each locality may be made from the observed 5 TU distributions for the schoolchildren tested.[e] Results of such estimates are shown in fig. 5, where the black portion of each bar gives the percentage of children assumed to be infected with tuberculosis, and the cross-hatched portion gives the percentage believed to be uninfected though they have reactions of 6 mm or more to

FIG. 5. OBSERVED FREQUENCIES OF REACTIONS 6 mm OR MORE TO THE INTRADERMAL 5 TU TEST, AND TO THE 5 TU OR 100 TU TEST, AND ESTIMATED FREQUENCIES OF INFECTED AMONG SCHOOLCHILDREN IN VARIOUS COUNTRIES



[e] The estimates should be regarded as only crude approximations; they were made by sketching symmetrical, roughly normal curves on the right-hand segment of each 5 TU distribution, taking the area under the curve as representing a fair estimate of the distribution of specific reactions.

FIG. 6. ESTIMATED FREQUENCIES OF INFECTED AMONG SCHOOLCHILDREN WITH REACTIONS OF 6 mm OR MORE TO THE INTRADERMAL 5 TU TEST IN VARIOUS COUNTRIES



5 TU. The figure also shows, by the lightly-shaded portion of each bar, the observed percentage of children with reactions of 6 mm or more to 100 TU. Thus, the black portion of each bar gives an estimate of the prevalence of specific sensitivity, the combined cross-hatched and lightly-shaded portions the prevalence of non-specific sensitivity. As seen in the figure, the percentage of children believed to be infected with tuberculosis ranges from almost 50% in the Sudan to about 4% among white children in South USA, while the percentage of children who would be regarded as " positive ", by using the 6 mm criterion to 5 TU, ranges from nearly 75% in Viet Nam to about 7% both in Denmark and among white children in South USA. If a reaction of 6 mm or more to either the 5 TU or 100 TU test is regarded as " positive ", as has been advocated by some workers,[7,11,12] the percentages range from about 95 in the Philippines, the Sudan, and Viet Nam to about 15 in Denmark and North USA.

Fig. 6 (derived from fig. 5) emphasizes the discrepancies between the estimated frequencies of infected children and the frequencies of those called " positive " to 5 TU when the same criterion for a positive reaction (6 mm or more) is used in different geographic areas. For this graph, the total number of children called " positive " to 5 TU is shown as 100%, and the length of each bar gives the percentage of " positives " estimated to have

specific sensitivity. The percentages range from 100 in North USA, where essentially all children with reactions of 6 mm or more to 5 TU are believed to have had a tuberculous infection, to 50 in South India where only half of those called " positive " have probably been infected. In between these two extremes, the figure shows, for example, that 85% of the children called " positive " in England and Ethiopia have probably been infected, 65% in the Philippines, South USA, and Viet Nam. These results would indicate that the efficiency of the 5 TU test for separating the infected from the uninfected members of a population varies considerably in different parts of the world.

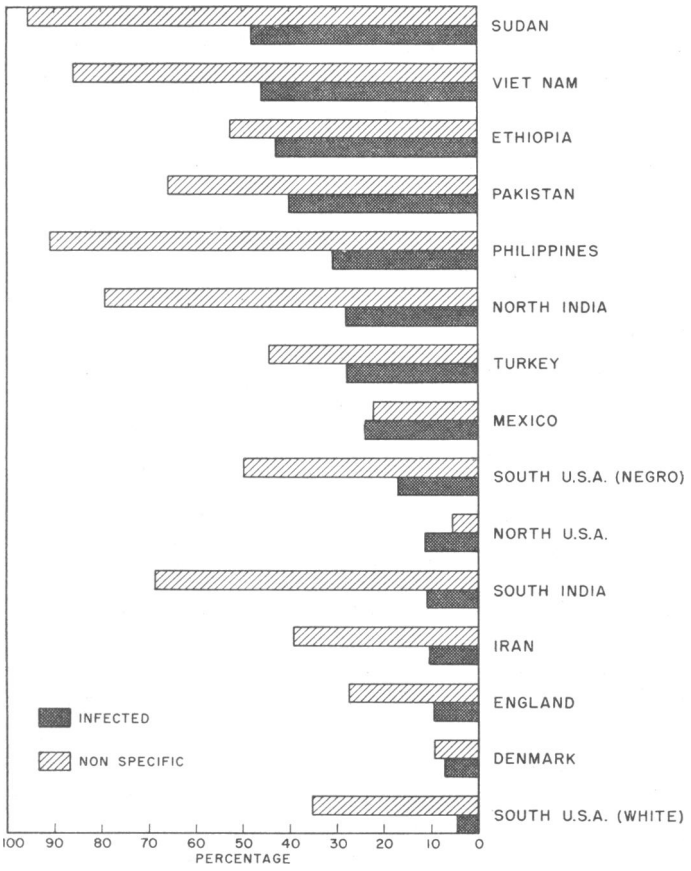
The relation between the prevalence of specific and non-specific sensitivity in the different geographic areas is shown in fig. 7, based on the estimates used for fig. 5. The black bars in fig. 7 give the estimated prevalence of specific sensitivity; the lightly-shaded bars show the estimated total prevalence of non-specific sensitivity, based on the assumption that the prevalence of non-specific sensitivity is the same among those who do and do not have specific sensitivity.[f] This assumption is justified, we believe, from the distributions (not shown in this paper) of 5 TU reactions when the children are separated according to age (see page 101). In areas where non-specific sensitivity is highly prevalent, we find that practically all the children have non-specific sensitivity at a very early age. As the children grow older, a gradually increasing proportion of them transfers into the group with specific sensitivity. After this transfer, of course, their non-specific sensitivity is obscured by the higher degree of sensitivity resulting from specific infection.

As seen in the figure, the estimated total prevalence of non-specific sensitivity ranges from less than 10% in Denmark and North USA to over 90% in the Philippines, the Sudan, and Viet Nam. It is relatively high, 70%-80%, in India, and relatively low, between 20% and 30%, in England and Mexico. The prevalence of specific sensitivity exceeds that of the non-specific in only two localities, Mexico and North USA. In all the other localities, the non-specific exceeds the specific, and sometimes to a pronounced extent, as in South USA and South India. Perhaps the most striking contrast is seen in the USA where non-specific greatly exceeds specific in the South and specific greatly exceeds non-specific in the North.

In a general way, these findings suggest that the prevalence of non-specific sensitivity tends to be highest in the countries lying in the more tropical regions. As the prevalence of specific sensitivity also tends to be high in some of these regions, it might appear that similar conditions favour both kinds of sensitivity. There is little indication, however, that non-specific and specific sensitivity are causally related.

[f] The total prevalence of non-specific sensitivity was calculated by setting the observed percentage of children showing non-specific sensitivity (i.e., the cross-hatched and lightly-shaded portions of the bars in fig. 5) in relation to the percentage not showing specific sensitivity (100 minus the black portions of the bars in fig. 5).

FIG. 7. ESTIMATED PREVALENCE OF SPECIFIC TUBERCULIN SENSITIVITY AND ESTIMATED TOTAL PREVALENCE OF NON-SPECIFIC TUBERCULIN SENSITIVITY AMONG SCHOOLCHILDREN IN VARIOUS COUNTRIES



Practical Implications

The prevalence and intensity of non-specific tuberculin sensitivity create a serious practical problem because, with the tuberculin products in use today, we are unable to distinguish the smaller specific from the larger non-specific reactions. Most of the overlapping apparently occurs in the range of 6 mm to about 12 mm with the 5 TU intradermal test. Thus, reactions in this range may belong to either the specific or the non-specific group: they must be considered " doubtful ", not because they are equivocal in character, but because their interpretation is doubtful.

No entirely satisfactory solution for this problem can be suggested at the present time, though there would certainly seem to be advantages in using different criteria for defining a " positive " reaction in different circumstances and for different purposes. In general, this would involve raising the criterion above 6 mm as the prevalence and intensity of non-specific sensitivity increase, particularly when the prevalence of specific sensitivity is low. The consequences of doing so would be that the higher the criterion is placed, the larger would be the proportion of persons with specific infection contained in the group designated as " negative " and the smaller the proportion of uninfected persons contained in the group designated as " positive ". In BCG vaccination programmes, for example, this would mean increasing the proportion of infected children who would be vaccinated, but, at the same time, it would also mean decreasing the proportion of uninfected children now being excluded from vaccination.

For purposes of estimating the prevalence of tuberculous infection in some communities, a better estimate can probably be obtained with criteria of 8 mm or perhaps 10 mm than with the currently used 6 mm criterion. Whether or not similar criteria would be desirable for BCG programmes would seem to depend on whether the possible dangers and disadvantages of vaccinating some persons already infected with tuberculosis would outweigh the advantages of vaccinating a higher proportion of uninfected persons.

The problems discussed in this paper are not very different from those the veterinarians have had for many years in using tuberculin tests to distinguish between specific and non-specific tuberculin sensitivity in cattle. In England, for example, the incidence of non-specific sensitization varies in different areas, but in a sample of tuberculosis-free herds from a single county (Berkshire) about 15% of all animals reacted non-specifically to mammalian tuberculin and about 35% to avian tuberculin (A. B. Paterson—personal communication). Although only some of the possibly many causes of non-specific sensitization have been identified, the use of tuberculins prepared from avian and mammalian strains of tubercle bacilli, together with a consideration of the history of the herd, has enabled veterinarians to distinguish the specific from the non-specific sensitivity in animals with a fair degree of certainty. Similar methods may be useful for separating specific from non-specific sensitivity in human beings, and a preliminary field investigation along this line is reported elsewhere in this number (see page 85). While a few of the causes and effects of non-specific infections with mycobacteria in man have already been described,[2, 4, 6] it may be many years before the full implications of non-specific sensitivity are well understood.

RÉSUMÉ

On a soumis à des tuberculino-réactions 3.600 tuberculeux hospitalisés et près de 34.000 écoliers dans des régions très éloignées les unes des autres, où l'on avait pu prendre les dispositions nécessaires pour qu'un personnel spécialement formé employât un matériel et des techniques uniformes. On a administré aux malades une dose intradermique de 5 UT; les enfants ont également reçu la même dose, ceux chez lesquels le diamètre de l'induration consécutive était inférieur à 5 mm étant soumis à une nouvelle épreuve avec 100 UT.

Certaines conclusions précédemment publiées sont confirmées par les résultats qui ont été obtenus. Il en ressort que, chez de nombreuses populations humaines, l'on rencontre au moins deux différentes sortes de sensibilité à la tuberculine naturellement acquises : une forte sensibilité, tenue pour *spécifique* de l'infection tuberculeuse virulente, et une faible sensibilité, considérée comme *non spécifique* ou comme n'étant pas spécifique de l'infection tuberculeuse. La sensibilité spécifique est celle que l'on a rencontrée chez les malades tuberculeux et chez certains des écoliers, quel que soit le lieu où l'épreuve avait été pratiquée. Chez les sujets des deux catégories, les dimensions des indurations consécutives à l'injection intradermique de 5 UT étaient comprises entre 6 et 25 mm environ, avec une distribution à peu près normale, la moyenne se situant aux alentours de 16-18 mm. La sensibilité spécifique se présente donc d'une façon remarquablement uniforme partout où elle se rencontre et paraît, suivant le lieu, changer de fréquence mais non pas d'intensité. Quant à la sensibilité non spécifique, sa fréquence varie également, mais, au contraire de la sensibilité spécifique, son intensité n'est pas uniforme. On dispose, maintenant, d'une documentation plus étendue montrant que la sensibilité non spécifique n'est pas en corrélation avec la sensibilité spécifique et semblant indiquer en outre que, selon le lieu, elle peut être due à des causes différentes.

Du point de vue pratique, il se pose de graves problèmes à mesure que s'accroissent la fréquence et l'intensité de la sensibilité non spécifique, car les tuberculines utilisées aujourd'hui ne permettent pas de différencier les grosses réactions non spécifiques et les petites réactions spécifiques. Sans atteindre la perfection, on pourrait sans doute procéder de façon plus satisfaisante à la séparation des sujets infectés d'avec les sujets indemnes, dans une population donnée, en faisant varier, suivant les régions géographiques, les critères applicables à ce que l'on doit appeler une réaction positive à l'injection de 5 UT. En modifiant le critère courant, on parviendrait sans doute à estimer avec plus d'exactitude la prévalence de l'infection dans certaines collectivités : la proportion de sujets indemnes tenus pour positifs serait plus faible mais, en revanche, quelques sujets infectés seraient considérés comme négatifs.

En procédant à des tests comparatifs avec des tuberculines provenant de différents types de mycobactéries, les vétérinaires ont résolu, de façon provisoire, le problème analogue qui consiste, pour eux, à distinguer entre les bovins qui présentent une sensibilité spécifique et ceux chez lesquels la sensibilité est non spécifique. On étudie actuellement des méthodes similaires, susceptibles d'être appliquées dans la lutte antituberculeuse chez les populations humaines.

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