Assessment of Delayed Skin Sensitivity Induced by Freeze-Dried Japanese Percutaneous BCG Vaccine

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SUMMARY

Percutaneous BCG vaccination with the freeze-dried Glaxo percutaneous vaccine has been practised in South Africa for some years. In an investigation conducted in the Transvaal region in 1971 it was found that the BCG-induced delayed skin sensitivity (allergy) was very low. After the introduction of the freeze-dried Japanese percutaneous vaccine for routine vaccination in 1973, the allergy induced by this vaccine was assessed in a controlled study on 1 900 Black schoolchildren. They were tested with the Mantoux and Heaf methods simultaneously and the negative reactors* were vaccinated with the freeze-dried Japanese percutaneous vaccine. One-tenth of the children eligible for vaccination were left unvaccinated to serve as a control group. Ten to twelve weeks after vaccination the immune response was assessed by simultaneous testing with Mantoux and Heaf. For the Mantoux test three different strengths of tuberculin were used in different groups: 2 TU, 5 TU, and 10 TU of PPD RT 23 with Tween, respectively.

The freeze-dried Japanese percutaneous BCG vaccine induced a satisfactory, and in a substantial proportion a high level of allergy in the vaccinated children, as measured in terms of mean induration, of increase of mean induration, and 'conversion rate'. The allergic response was commensurate with the test dose used: the stronger the test applied, the larger the reactions elicited by it. The allergy induced by this vaccine was significantly higher than that induced by the freeze-dried Glaxo percutaneous vaccine used previously.

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PLAN AND CONDUCT OF THE INVESTIGATION

In 1971 the authors investigated the degree of delayed skin sensitivity induced in children vaccinated with the freeze-dried Glaxo percutaneous vaccine.[1] It was found that the allergy induced by this vaccine was very low. When the more potent freeze-dried Japanese percutaneous BCG vaccine was introduced in South Africa in 1973 the necessity of assessing the allergy to human tuberculin induced by this vaccine compared with the Glaxo-induced allergy became obvious. In routine field work in South Africa the Heaf test is used to discriminate between individuals eligible for vaccination with BCG or for chemoprophylaxis at a certain age; however, since this test is not well suited for epidemiological studies, it was decided to double-test a group of Black schoolchildren with the Mantoux and the Heaf test simultaneously, before and after vaccination. This procedure would afford an opportunity of accurately measuring the allergic status of those examined before and after vaccination, as well as of determining the degree of correlation existing between the two tests, which both serve as epidemiological indicators in tuberculosis control.

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* The terms 'negative reactor' or 'non-converter', 'positive reactor' or 'converter' are used throughout this study to denote persons whose reactions to the Mantoux test are less than 10 mm (negative) and 10 mm or more (positive) respectively.

METHODS AND MATERIAL

Study Population

This investigation was conducted in 12 primary schools for Blacks in the district of Pietersburg, from May to August 1973. The 8 schools which had already participated in the 1971 trial were again included on purpose. A Sub A school population of both sexes aged 5 - 15 years (90% being 6 - 8 years old), and numbering 1 969 children who had not yet been vaccinated, was registered by the school staff on specially designed forms in duplicate on the first visit.

Tuberculin Testing

Tuberculin testing was carried out on the first visit and 10 - 12 weeks after vaccination to determine the degree of allergy to tuberculin present in the participants at the time of testing. Each child was identified on each occasion, with the help of the class teacher, and given two tests: the intradermal test by one operator, and the percutaneous test by the other.

The intradermal test was done on the upper third of the volar surface of the right forearm by injecting 2 TU of PPD RT 23 with Tween 80[®] with special tuberculin syringes of 1 ml, calibrated 10 × 0.1 ml, and mounted with Luer 26 × ½, long bevel, 45 × 13 mm needles. The percutaneous test was done on the upper third of the volar surface of the left forearm by means of the East Multiple Puncture Apparatus Mark V model with the 6-needle head and one drop of PPD Weybridge 100 000 units (TU)/ml of batch 2/71.

The tuberculin PPD RT 23 was supplied by courtesy of the Tuberculosis Research Unit of the South African Medical Research Council at Onderstepoort. It had been prepared from concentrated RT 23 from Statens Serum-institut, Copenhagen, in ampoules containing 100 TU in freeze-dried form ready for reconstitution, to which 0,05 parts per 1 000 of Tween 80 had been added. Immediately before use the contents of one such ampoule were dissolved by injecting 1 ml of aqua bidist. into the ampoule; then 4 ml of normal saline were added; thus 5 ml of the final solution, ready for use, contained 100 TU, 1 ml 20 TU, and 0,1 ml 2 TU.

After 4 days the tests on 1 893 children were read and recorded by each operator on separate copies of the list. The interval of 96 hours was chosen because it was considered the optimum time for reading the Heaf and Mantoux test simultaneously.

For the reading of the Heaf test the five standard categories were used: grade 0 — no induration; grade I — induration around at least four punctures; grade II — coalescence of indurations to form a ring; grade III — solid induration of test area; grade IV — grade III with vesiculation.

The Mantoux test was read by measuring the largest transverse diameter of induration in millimetres by means of a transparent ruler as used in WHO work.[3]

In deciding which individuals were to be vaccinated, the following method was applied: *(a)* children with Heaf reaction grades 0 - II and Mantoux indurations less than 10 mm were vaccinated, excepting every tenth child with Heaf grade 0 and Mantoux 0, to form an unvaccinated control group; *(b)* children presenting with Heaf grades III or IV or with Mantoux indurations of 10 mm or more were not vaccinated, irrespective of their simultaneous Mantoux or Heaf reaction, but were registered for chemoprophylaxis.

A control group was again included in this test series *(a)* because an accurate estimate of the increase in tuberculin allergy produced by BCG vaccination is more readily obtained, especially when a particular BCG product is being assessed, by omitting vaccination of a fraction of the eligible group and including this unvaccinated fraction later as a control group when retesting;[4] *(b)* to test reader consistency; *(c)* to observe a possible enhancing effect of repeated testing at short intervals; *(d)* to observe the epidemiological behaviour of the unvaccinated group in the interval between the two tests.

BCG Vaccination

This procedure left 1 435 children eligible for vaccination out of 1 893 tested: 298 were eliminated because they presented with Heaf grades III or IV, or with Mantoux reactions of 10 mm or more, or because they had old vaccination marks; a further 160 children were left unvaccinated as controls.

For vaccination a heat-stable, freeze-dried glutamate BCG vaccine for percutaneous administration, manufactured by the Japanese BCG Laboratory, Tokyo, batch KV 144, I.L.No.188, was employed. This vaccine is supplied in powder form in vacuum-sealed ampoules, each containing 10 doses of BCG. The biological contents of each ampoule are given as 240 million bacilli or more, or 80 mg/ml. The vaccine was reconstituted with 0,3 ml of dissolvent supplied by the manufacturers in ampoules each containing 0,3 ml of dissolvent.

Vaccination was carried out with the East Mark V model with the 20-needle head. A large drop of vaccine was put on the upper part of the deltoid region of the right arm with a glass syringe and was evenly spread with the footplate of the Heaf gun, the skin of the area was stretched taut with one hand, and the trigger was pulled under firm pressure. The trigger was then released, the gun slid down about 2 cm, and the trigger pulled again, thus making 40 punctures.

One of the investigators fell ill during the first round of testing, test reading, and vaccination. Heaf testing and vaccination was then done by a Black health assistant of the Department; the other investigator carried on alone with Mantoux testing and test reading until the end of this first round. This unplanned participation of a Black field worker approximates this trial even more closely to routine field conditions than would have been the case without his active involvement.

Tuberculin Retesting

The important final round of retesting and reading 10 - 12 weeks later was carried out by both investigators. In this round a total of 1 187 children vaccinated in the first round presented themselves for retesting and test reading. A further 112 children of the unvaccinated control group participated in this round.

Initially, the group presumed to be naturally infected and which was left unvaccinated, that is, children with Heaf grades III or IV or with Mantoux reactions 10 mm or more at the first test, were also retested; however, when it was observed that a substantial fraction of this group responded with very severe reactions to the second test (vesiculation and even ulceration in some cases), Heaf as well as Mantoux, further retesting of this group was discontinued to spare them further discomfort.

In this round the same testing and reading procedures were applied as in the first round, with one modification: the whole group was divided into three subgroups to be tested with different strengths of RT 23—892 children were retested with 2 TU (as before); 209 children were retested with 5 TU; and 86 children were retested with 10 TU.

It is customary to use the same dose of tuberculin before and after vaccination in routine control programmes although the two tests serve entirely different purposes—the test before vaccination discriminates but does not measure the so-called negative reactions; the test after vaccination measures the allergy but does not discriminate.[4] However, there is another aspect to the dose of tuberculin used in the second test: by varying the strength of the postvaccination test in the same series three points may be demonstrated:

(a) that the vaccine has retained its potency throughout the series if the mean induration of reactions increases proportionately to the strength of the test applied;

(b) conversely, the same tuberculin, used in different dilutions, has retained its potency if the mean indurations elicited by these different strengths in children vaccinated with a vaccine of constant potency correspond proportionately in size to the strength of the tuberculin used;

(c) finally, if the reactions elicited by these different dilutions correspond to expectations, it may be said that, everything else being equal, the vaccination and testing techniques have been constant throughout the series.

RESULTS

Method of Evaluation

Postvaccination allergy should always be considered as a strictly quantitative phenomenon: as something that must always be present to a greater or lesser degree in BCG-vaccinated persons.[4] This point of view has been documented in a number of publications from the WHO Tuberculosis Research Office.[5-7] Furthermore, it has been shown that, with a uniform dose of vaccine uniformly applied in a particular population, the response is practically always uniform. Vaccines of different potency had been used in the 1971[1] and 1973 trials: in 1971 the Glaxo percutaneous, and in 1973 the Japanese percutaneous vaccines were used, and the results obtained in these two trials will be compared later.

In expressing the postvaccination allergy as measured with the Mantoux test, the WHO standard was applied, which assumes the presence of some degree of allergy in weak as well as in negative reactors and includes them in the computation of the allergy level; the sum total of all reactions is divided by the number of tests read, and thus the mean average induration is arrived at. This measurement is particularly useful in comparative studies and should be the main guide in assessments of BCG vaccination programmes. As it is, however, still customary to use the terms 'positive reactor', 'negative reactor', 'conversion rate' etc., these terms are also used in the present context for the sake of mere convenience without imputing any epidemiological significance to them.

Prevaccination Test Results

In May 1973, 1 893 children were tested simultaneously with the Heaf method and with Mx 2 TU RT 23 with Tween 80. The Heaf grades of these children are reflected in Table I, which also correlates them to their respective mean indurations elicited with 2 TU RT 23 before vaccination. Of the total, 1 605 or 84,8% presented with a Mantoux reaction smaller than 10 mm to Mx 2 TU, and 288 or 15,2% with a reaction of 10 mm or more to Mx 2 TU. The mean induration was 3 mm.

TABLE I. CORRELATION BETWEEN HEAF GRADES AND MANTOUX REACTIONS BEFORE VACCINATION

Heaf grades	Number of children	Percentage	Mean induration	Test
0	1 358	71,7	0 mm	2 TU RT 23
I	223	11,8	1,7 mm	,,
II	69	3,6	10,3 mm	,,
III	199	10,5	18,7 mm	,,
IV	44	2,4	21,5 mm	,,
All	1 893	100,0	3,0 mm	,,

According to these results the Heaf test would have earmarked 243 children and Heaf grades III or IV for chemoprophylaxis, whereas according to the Mantoux test the number was 288, a difference of 18,5% in this category, or 2,3% related to the total of tests read, with the arbitrary separation point set at 10 mm. This ambiguous fraction is mainly contained in the Heaf grade II group, which point will be discussed later.

Postvaccination Test Results

According to Heaf test: 10 - 12 weeks after vaccination, 892 children who had been negative reactors, that is, presenting with Mantoux reactions smaller than 10 mm and Heaf grades 0 - II before vaccination, were retested with Mx 2 TU RT 23 and Heaf. Their postvaccination Heaf grades are recorded in Table II. Seven hundred and fifty-one children were Heaf grade 0 at the prevaccination test, and 83% of them converted to Heaf grades I, II, or III after vaccination.

TABLE II. HEAF GRADES AFTER VACCINATION

Heaf grade	No. of children	Percentage
0	140	15,7
I	316	35,4
II	324	36,3
III	112	12,6
IV	0	0

According to Mantoux test: 307 or 34,4% presented with a Mantoux reaction smaller than 10 mm, and 585 or 65,6% with a reaction of 10 mm or more to 2 TU. The mean induration was 11 mm.

Fig. 1 combines the histograms of the frequency distributions of the postvaccination reactions of the three groups of children tested with 2 TU before vaccination, but retested with 2 TU, 5 TU, and 10 TU, respectively, 10 - 12 weeks after vaccination. The prevaccination histograms of these groups are not given because they are of little interest: all children, being eligible for vaccination, had to be negative.

Table III records the test strength, number of children, mean induration and conversion rate. The mean induration and the conversion rate increased with the strength of

TABLE III. RESULTS OF TESTING WITH 2, 5 AND 10 TU RESPECTIVELY AFTER VACCINATION

Units	Children tested	Mean induration (mm)	Rate of conversion
2	892	11	65,6%
5	209	14	74,4%
10	86	19,3	86,0%

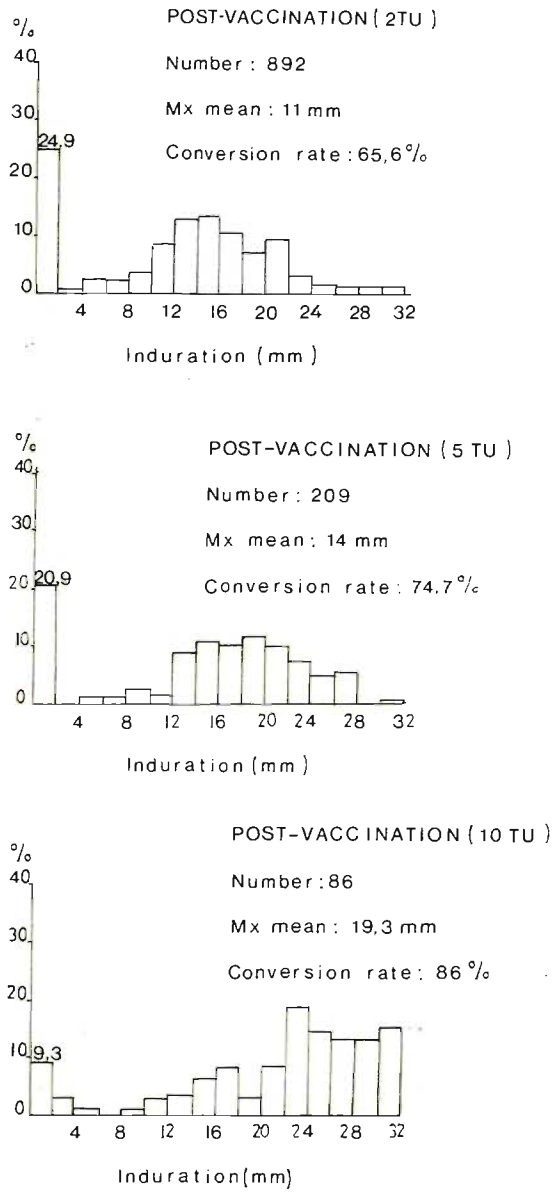

Fig. 1. Frequency distributions of Mantoux reactions elicited by testing with 2, 5 and 10 TU respectively after vaccination.

the test applied in this series. These results fully support the view that these indicators of sensitivity may be manipulated at will by choosing a sufficiently strong postvaccination tuberculin test, and thus have little significance if different test doses are used before and after vaccination in the assessment of vaccination programmes.[3,12] Furthermore, these findings appear to bear out what has been suggested concerning proof of constancy of potency of test material and vaccine, and of constancy of performance: mean induration increased progressively from 11 mm to 14 mm to 19,3 mm, conversion rate from 65,6% to 74,4% to 86%, and the frequency distribution pattern shifted from symmetrical concentration around 14 mm in the 2 TU series, to around 18 mm in the 5 TU series, and to around 25 mm in the 10 TU series.

The histograms of Fig. 2 give, in juxtaposition, the frequency distributions of reactions as obtained after vaccination with Glaxo percutaneous vaccine in 1971 and with the Japanese percutaneous vaccine in 1973 (Table IV).

Observer Agreement in Test Reading

Observer agreement in the reading of the Heaf test occurred in 80,4%. Disregarding a difference of 1 grade, excepting the difference between grades II and III, agreement reached 94%. Regarding the readings of the Mantoux test, 76,6% were within 3 mm and 82% were within 4 mm of each other.

DISCUSSION OF FINDINGS

Correlation between Heaf grades and frequency distributions of Mantoux reactions are shown in Fig. 3.

Heaf Grades Correlated to Mantoux Reactions

Prevaccination: The histogram on the left (Fig. 3, top) presents the Heaf reactions of 1 893 children before vaccination; the two histograms on the right divide them according to Mantoux negatives (reactions smaller than 10 mm) and positives (reactions 10 mm or more). Practically all Mantoux negatives fall into Heaf grades 0 and I, with the bulk, 84,6%, in grade 0. The Mantoux positives are mainly Heaf grades II - IV reactors, with a significant fraction, 15,6%, of Heaf grade II reactors, which will be considered in greater detail presently. The mean induration of the negatives was 0,3 mm, and of the positives 18,4 mm.

Postvaccination: On the left (Fig. 3, bottom) is the prevaccination histogram of the 892 children who remained after the elimination of Heaf grades III and IV, of Mantoux reactions 10 mm or more before vaccination, of the controls, and of the children with vaccination marks, with their postvaccination histogram next to it for comparison. Here, a new phenomenon is to be observed: the appearance of a substantial percentage (12,6%) of Heaf grade III reactions after vaccination with the Japanese percutaneous vaccine—a phenomenon which was hardly ever observed with the Glaxo percutaneous vaccine.

The two histograms on the right show the group again split into Mantoux positives and Mantoux negatives. The latter all presented with Heaf grades 0 - II, the bulk being Heaf grades 0 and I; the mean induration of this fraction is 2 mm. The Mantoux positives are Heaf grades 0 - III, the bulk being Heaf grades I - III; the mean induration of this fraction is 15,8 mm. Of this Mantoux-positive fraction 19% are Heaf grade III, which Heaf grade is completely absent in the Mantoux-negative fraction.

Mantoux Reactions Correlated to Heaf Grades (Fig. 4)

Prevaccination: 1 358 children presented with Heaf grade 0 and Mantoux 0 mm before vaccination. Of the four histograms representing Heaf grades I - IV (Fig. 4),

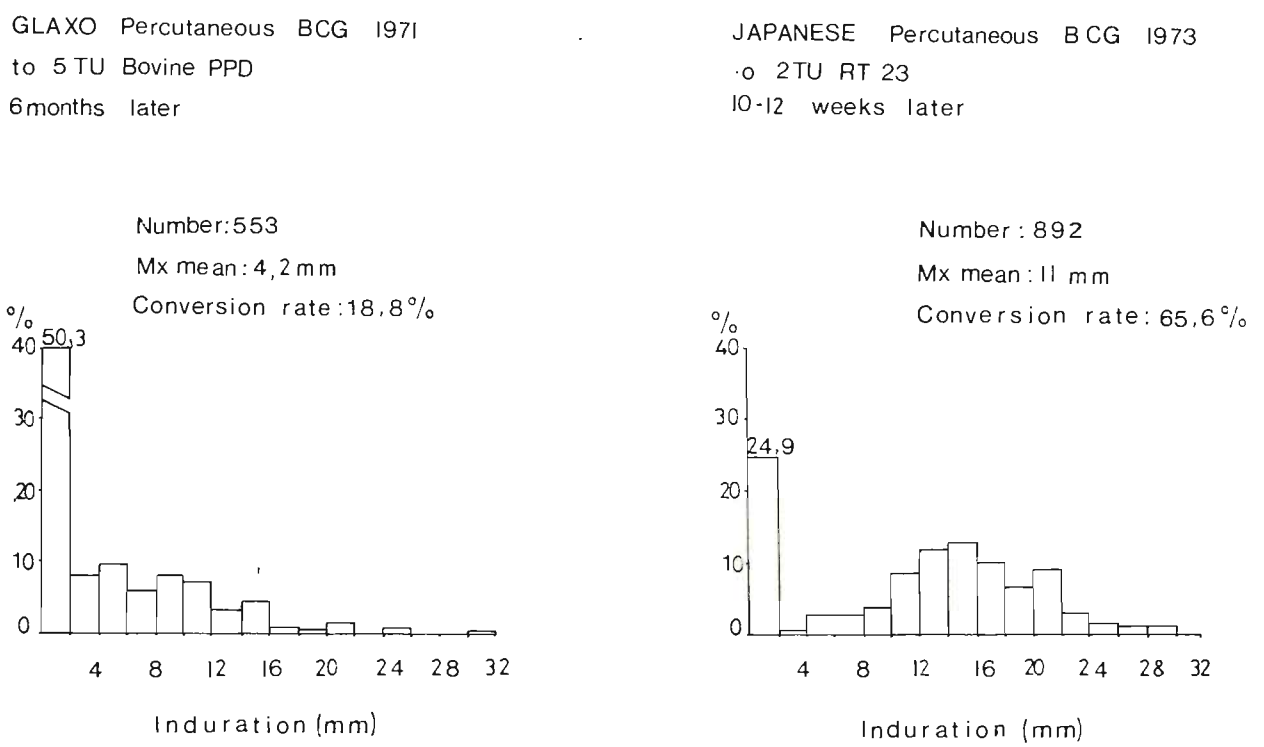

Fig. 2. Comparing frequency distributions of Mantoux reactions obtained after vaccination with Glaxo and Japanese percutaneous BCG vaccine respectively.

TABLE IV. DEGREE OF DELAYED SKIN SENSITIVITY INDUCED WITH TWO PERCUTANEOUS BCG VACCINES

Vaccine	Year	Children studies	PPD used	Mean induration (mm)	Rate of conversion
Glaxo	**1971**	**553**	**5 TU bovine**	**4,2**	**18,8%**
Japan	**1973**	**892**	**2 TU RT 23**	**11,0**	**65,6%**

only the histogram of Heaf grade II is of special interest: 11,6% of this grade presented with reactions of 0 - 3 mm; 23,4% presented with reactions of 4 - 9 mm; and 65,0% presented with reactions ranging from 10 to 25 mm, the overwhelming bulk falling within the 10 - 15 mm range with a mean induration of 13,3 mm; the solid block of 75,75% of reactors is seen to be in the 8 - 15 mm range. The mean induration of the entire Heaf grade II group is 10,3 mm.

The interpretation of these findings presented some difficulties with regard to vaccination policy, since it is not known whether, and to what extent, non-specific infection has to be taken into account. The 1971 trial[1] produced some evidence that cross-sensitivity to avian PPD exists to a certain extent in the Northern Transvaal region which, on the other hand, does not have as high a prevalence rate of specific infection as, for example, the Transkei;[5] however, the fact that a large fraction of the Heaf grade II reactors also presented with Mantoux reactions of 10 mm or more, led to the decision to consider the individuals with a Heaf grade II and a simultaneous Mantoux reaction of 10 mm or more as infected with tuberculosis and due for obligatory chemoprophylaxis. This view is in agreement with that of Australian investigators[9] who concluded from their studies that 60% of Heaf grade II reactions are caused by specific infection, but differs from the findings of the team from the Tuberculosis Research Unit of the SAMRC, in the Transkei.[5] In the Australian trial marked overlapping of some Heaf grades, as judged by the Mantoux reactions, was found; these findings are confirmed by the results of the present investigation. This overlapping is particularly well illustrated by the frequency polygon reproduced in Fig. 5.

The histograms in Fig. 4 all present an unambiguous appearance, with the exception of one. The histogram of Heaf grade 0 (not reproduced) consists of zero reactions only; of Heaf grade I mainly of zero and of some small reactions; these histograms probably represent the uninfected individuals; the histograms of Heaf grades III and IV consist of high and very high reactions only, probably representing the natural specific infections. The histogram of Heaf grade II, in contrast, presents a very different, ambivalent picture: it shows 35% of reactions smaller than 10 mm, and 65% of reactions of 10 mm or more; most of

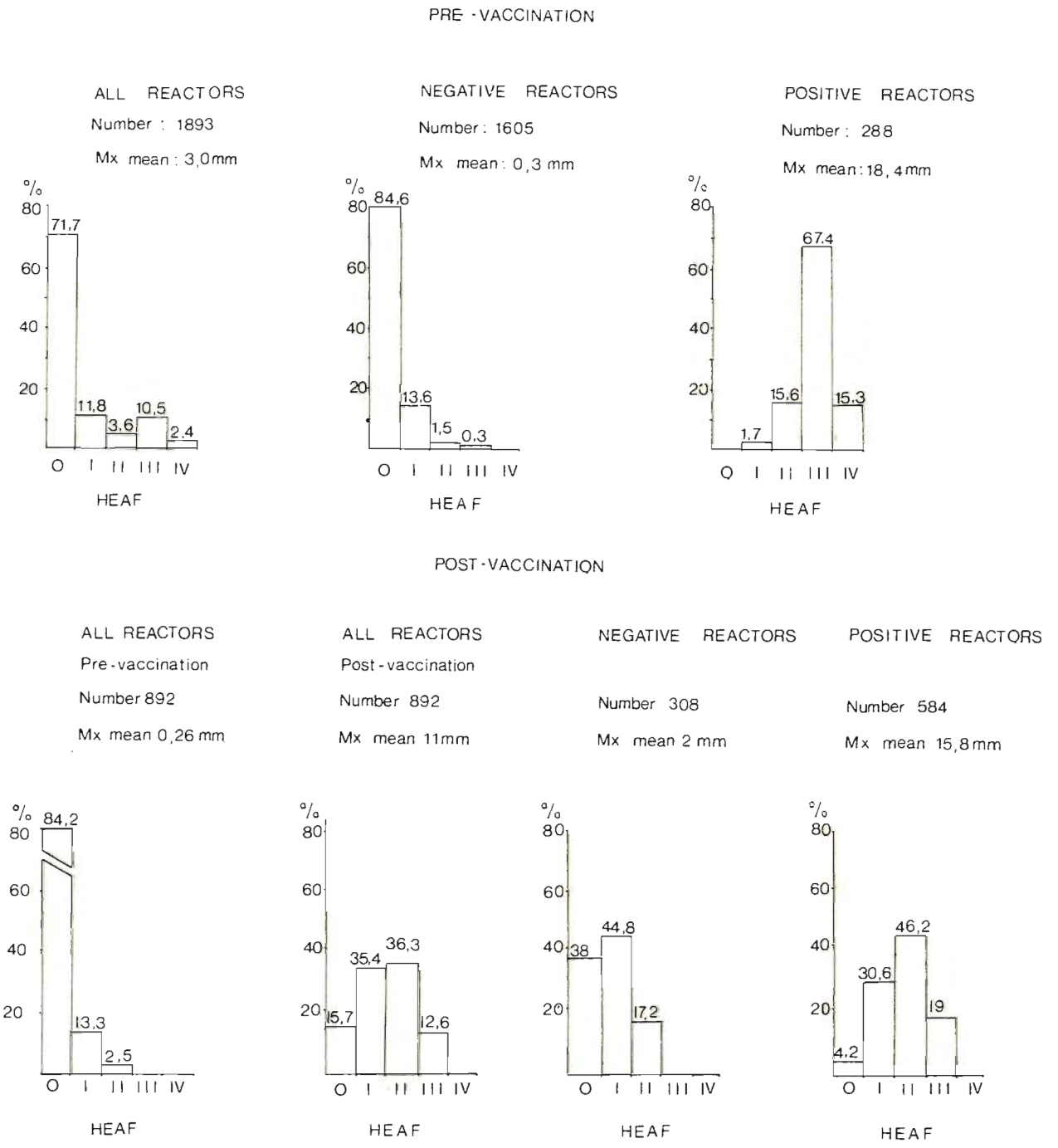

Fig. 3. Correlation between Heaf grades and frequency distributions of Mantoux reactions before and after vaccination.

the latter are, however, not very large, only up to 15 mm, and certainly not as large as those of the naturally infected reactors. The question is: how great a proportion of non-specific or cross-sensitivity is contained in Heaf grade II?

Testing of small reactions elicited by the small-dose (2 TU) tuberculin test with a high-dose test could clarify this problem: surveys in tropical countries with a comparatively high prevalence of non-specific infection have shown that the small reactions (less than 10 mm) to the low-dose test react almost universally strongly to the high-dose test in these countries, whereas small reactions in countries with little or no non-specific infection respond with small reactions to the high-dose test as well.[19] Convincing epidemiological evidence has been presented to support the contention that persons giving weak reactions to low doses of tuberculin and strong reactions to high doses have a

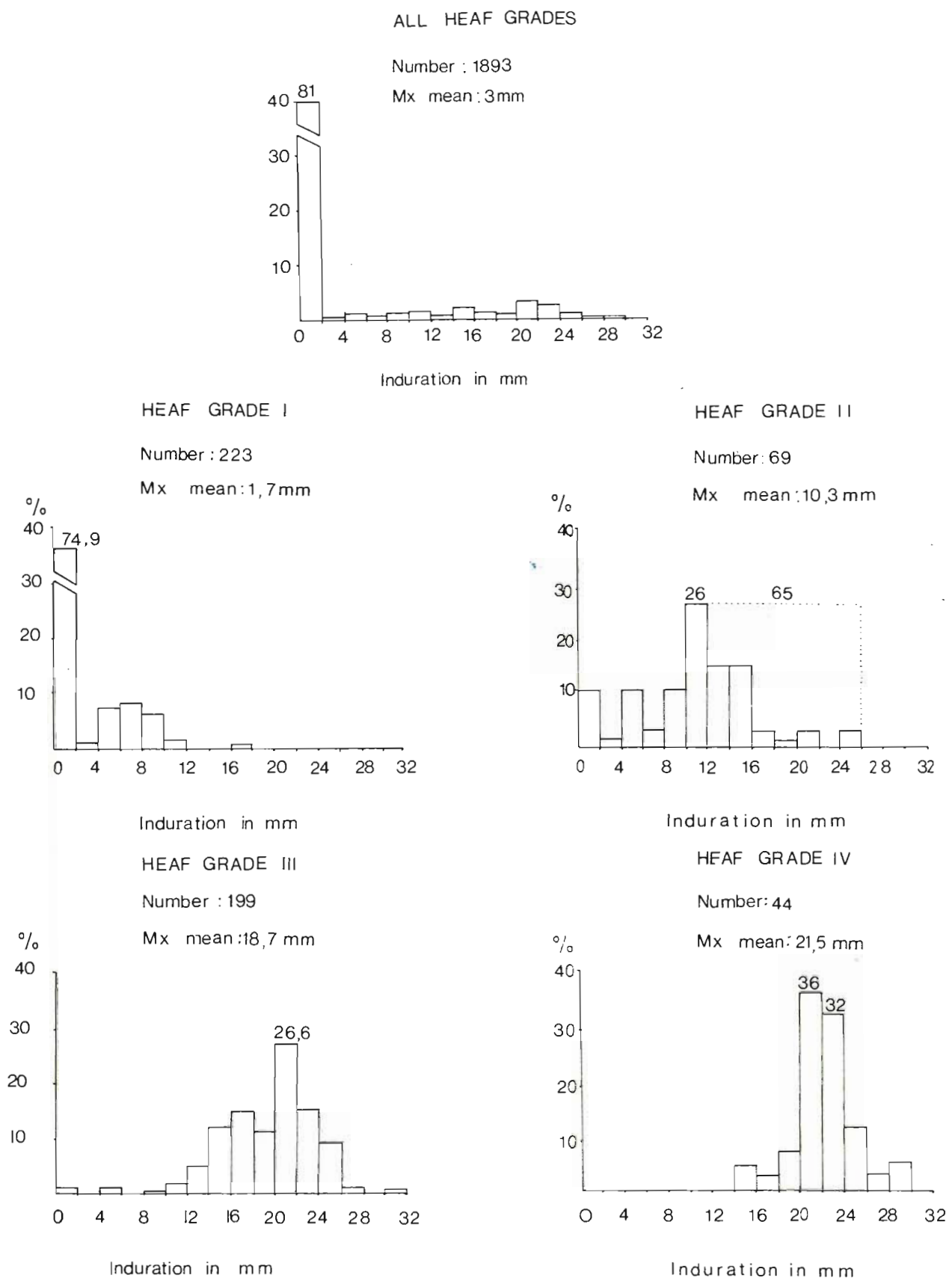

Fig. 4. Mantoux reactions of 1 893 children tested with 2 TU before vaccination, correlated to Heaf grades.

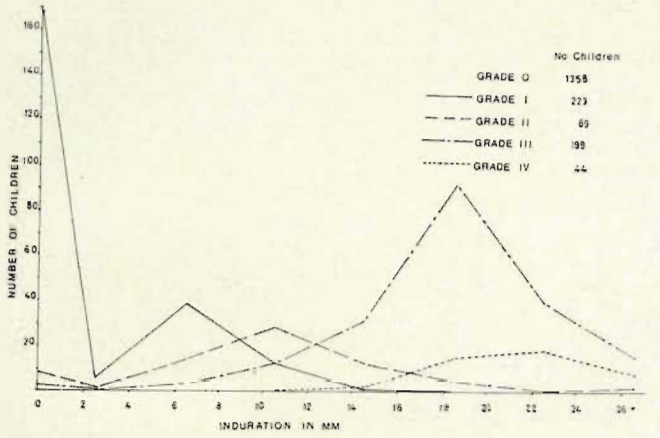

Fig. 5. Prevaccination frequency polygon illustrating overlapping of Heaf grades as judged by Mantoux reactions.

non-specific type of allergy and are, therefore, not likely to be infected with tubercle bacilli." The problematical nature of the Heaf grade II reactions may merit a special study in the Northern Transvaal region.

Postvaccination: The histograms in Fig. 6 present the correlation of the Mantoux reactions to Heaf grades in 892 vaccinated children retested with 2 TU RT 23.

The first four histograms are distinctly bimodal, with the antimode at the 2 - 3 mm point on the induration scale; the mean induration increases rapidly with the Heaf grade. The reactions in the Heaf grade III histogram are clustered around the 20-mm point, with a mean induration of 18,3 mm, practically identical in configuration and scale with those of grade III before vaccination — the presumably naturally-infected children. The over-all mean induration of the entire vaccinated group is 11 mm. The postvaccination histogram of Heaf grade II presents a pattern different from that of Heaf grade II before vaccination: in the latter the reactions of 10 mm or more are nearly all within the range of 10 - 15 mm, whereas after vaccination the reactions of 10 mm or more are about half in the range of 10 - 15 mm, the smaller half being in the range of 16 - 24 mm; in other words, the artificial specific infection by BCG vaccination is expressing itself in the appearance of a substantial proportion of strong reactions; conversely, it may be argued that the absence of such strong reactions in grade II before vaccination indicates that the intermediate reactions may, to a certain degree, be due to non-specific infection.

The frequency polygon of Fig. 7 illustrates the overlapping of Heaf grades as judged by Mantoux reactions after BCG vaccination; however, it should be noted that the curves of Heaf grades 0 and III each represent less than half the number of individuals than represented by the curves of Heaf grade I as well as grade II.

Retesting of Controls

Of this group, 112 children with Heaf grade 0/Mantoux-negative reactions on the first test, presented themselves for retesting and subsequent reading. Of 92 children retested with 2 TU, only 1 reacted with Heaf grade I/Mantoux 8 mm; of 12 retested with 5 TU, 3 reacted with Heaf grade I/Mantoux 16 mm, Heaf grade II/Mantoux 18 mm and Heaf grade 0/Mantoux 20 mm, respectively. These findings probably indicate the occurrence of natural infection in the interval. No enhancing effect of Mantoux tests repeated at short intervals was observed in this group. Reader constancy and agreement for this batch was practically 100%.

Comparison with Other Investigations

In Table V the results of this investigation are recorded, together with the results obtained by the SA Tuberculosis Study Group in their assessment of delayed skin sensitivity induced with different vaccines applied by various methods in White schoolchildren.[12] From the figures presented it appears that the results obtained with the percutaneous Japanese vaccine in the Northern Transvaal trial are more or less on a par with the results obtained with the intradermal Japanese vaccine by the SA Tuberculosis Study Group: testing with 2 TU RT 23 from the same source 10 - 12 weeks after vaccination elicited a near-identical response in the two runs, mean induration being 11 mm and 11,2 mm respectively, and the conversion rate (which is of no significance in assessments) being 65,6% and 76,8% respectively, with the arbitrary limit set at 10 mm in this trial, and at 9 mm in the trial of the SA Tuberculosis Study Group.

TABLE V. DEGREE OF DELAYED SKIN SENSITIVITY INDUCED WITH VARIOUS BCG VACCINES IN THREE INVESTIGATIONS

A. Studies conducted in the Northern Transvaal region in 1971 and 1973

Vaccine used	Glaxo percutan. 1971	Japan. percutan. 1973
Time of vaccination	6 mo. before test	10 - 12 wks before test
Mean induration	4,2 mm	11 mm
'Converters' (10 mm or more)	18,8%	65,6%
'Non-converters' (9 mm or less)	81,2%	34,4%
Mantoux test dose used	5 TU bovine PPD	2 TU RT 23

B. Study conducted by the SA Tuberculosis Study Group in 1972

Vaccine used	Glaxo percutan.	Japan. percutan.	Japan. intradermal
Time of vaccination	10 wks before test	10 wks before test	10 wks before test
Mean induration	7 mm	8 mm	11,2 mm
'Converters' (9 mm or more)	45,1%	52,8%	76,8%
'Non-converters' (8,9 mm or less)	54,9%	47,2%	23,2%
Mantoux test dose used	2 TU RT 23	2 TU RT 23	2 TU RT 23

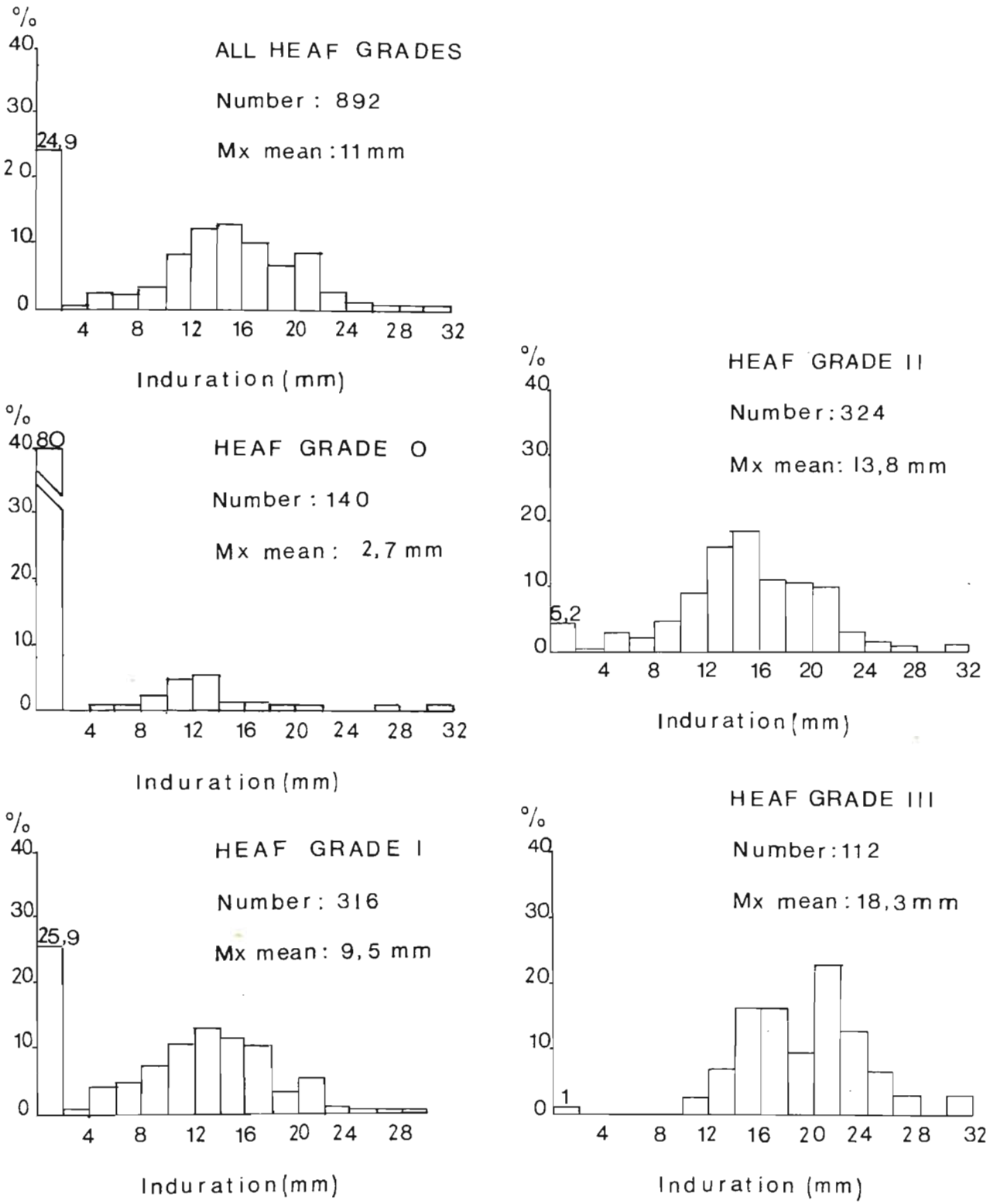

Fig. 6. Mantoux reactions of 892 children tested with 2 TU after vaccination correlated to Heaf grades.

The results obtained in the present trial are better than those of the trial of the SA Tuberculosis Study Group with the same (percutaneous) vaccine, where the postvaccination response was: mean induration 8 mm, conversion rate 47%. It must be borne in mind, however, when comparing these two trials, that the Northern Transvaal trial was conducted under field conditions, and was consequently subject to a wider margin of error than the trial of the SA Tuberculosis Study Group, which was conducted under strictly controlled scientific conditions. Furthermore, attention is drawn to findings by Kleeberg[13] of the Tuberculosis Research Unit of the SAMRC, in which he reported that in a further trial, conducted on Black schoolchildren with the percutaneous Japanese vaccine and the Heaf East Mark IV applying 40 punctures, the immune response elicited was equal to that with the intradermal Japanese vaccine in the first trial, that is, the same response as in the Northern Transvaal trial.

A valid comparison with the results reported by the British Thoracic and Tuberculosis Association in 1971[14] cannot be made, because this report omits to state which PPD was used for the 10 TU intradermal test after vaccination. However, it may be pointed out here that in the present trial children retested with 10 TU RT 23 showed a conversion rate of 86% with a mean induration of 19,3 mm, these results being very similar to those in Britain. In addition, the arbitrary limit between negative and positive reactors was set very much lower in the British trial.

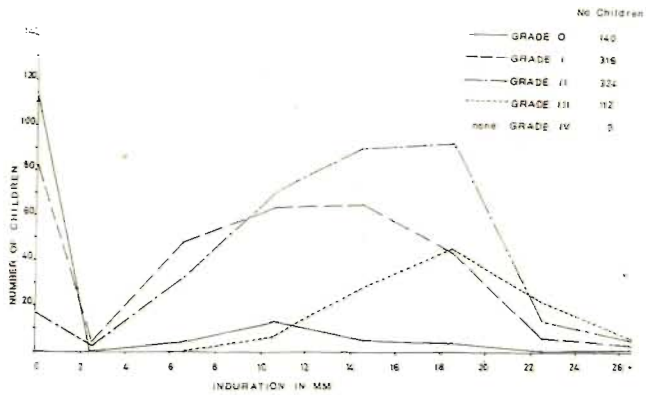

Fig. 7. Postvaccination frequency polygon illustrating overlapping of Heaf grades as judged by Mantoux reactions.

CONCLUSION

The objective of the present investigation was to ascertain the degree of delayed skin sensitivity to tuberculin conferred on children vaccinated with the Japanese percutaneous vaccine under field conditions by double-testing a cohort of unvaccinated children with the Heaf test and with the Mantoux 2 TU RT 23 test before, and 10 - 12 weeks after, vaccination. The allergy thus induced is the only short-term means at our disposal for assessing the efficacy and effectiveness of this tuberculosis control measure. The results of the present investigation indicate that vaccination with the Japanese freeze-dried percutaneous BCG vaccine induces a satisfactory, and in a substantial proportion of those vaccinated, a high level of allergy. The mean induration increased from 0,26 mm before, to 11 mm after, vaccination (though comparisons of pre- and postvaccination allergy levels *per se* are not very meaningful epidemiologically), and the conversion rate was 65,6% with Mantoux and 83% with Heaf. This vaccine did not cause any undue complications, such as severe lesions at the vaccination site, lymphadenopathy, etc. The fraction of complete non-reactors (0 mm) to the Mantoux test after vaccination was somewhat high (23,8%); however, since for intradermal vaccination a 10 - 20% rate of non-reactors is acceptable by international standards, 23,8% is considered acceptable for percutaneous vaccination. Stronger low-dose tuberculin tests of 5 TU and 10 TU reduced this rate to 20,6% and 9,3% respectively, which indicates that a certain degree of allergy is also present in the vaccinated children who did not react to the 2 TU test after vaccination.

The very severe reactions elicited in the original Heaf grade III and IV reactors by retesting with 2 TU, might be interpreted as an enhancing effect of tuberculin tests repeated at short intervals.

The control group served its purpose well without yielding any new information.

The prevaccination Heaf grade II reactions pose a certain epidemiological problem: in this series they presented with Mantoux reactions of 10 mm or more, but mainly in the range of 10 - 15 mm, in 65%. Since a certain degree of cross-sensitivity is present in this region,[1] their epidemiological significance cannot be pin-pointed with accuracy in routine field work. This problem is being investigated at present.

Other studies have adduced evidence that the Heaf test is a somewhat crude tool for epidemiological studies, and unsuitable for exact measurements of degrees of sensitivity for which purpose it was actually never intended, but that it fulfils its purpose for routine field work.[9,16] This view is supported by the information gained in this assessment. The most important fact emerging from this investigation is that percutaneous vaccination with the Heaf method with a potent BCG vaccine produces a very satisfactory level of delayed skin sensitivity to tuberculin in those vaccinated.

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