CORRESPONDENCE

This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.

CONCERNING CONVIT'S REPORT ON BCG convittent.

TO THE EDITOR:

In the paper by Dr. Jacinto Convit entitled "The morbidity rates in BCG-vaccinated and unvaccinated groups during five years," published in THE JOURNAL some time ago [24 (1956) 269-274], we find to our knowledge for the first time in the current literature the statement that in the vaccinated group the "great reduction in the morbidity coefficient can thus be attributed, with all certainty, to the effect of the BCG vaccination" (italics ours).

The extraordinary importance of this statement with respect to the prophylaxis of leprosy induced us to analyze the paper carefully. In doing so we were confronted with serious doubts, which we should like to submit to Dr. Convit and your readers.

At the beginning of the discussion Convit states clearly the basis for his conclusions with the words, "We consider the two groups studied to be practically comparable. There were differences as regards the numbers of persons in the different age groups, but they are not very important, especially in the younger groups." Is it really so? Let us see:

Both groups immediately showed, in 1950-1951, a substantial loss of persons whose lepromin reactions were not read. According to Table 2 of the article these were 175 of the original 584 to be vaccinated (30.0%), and 162 of the 522 not to be vaccinated (31.1%). This fact suggests that there was a certain degree of unintentional selection of persons who were the easiest to control and perhaps the more educated.

In a study regarding the immunologic behavior by means of the lepromin test, the age groups are of paramount importance. The general positivity rates are influenced by the results particular to each age and therefore by the proportions of the different ages among the examined persons. Age data are given in Table 2—a regrettable feature of which is that the 10-19 years group was not divided into two (10-14 and 15-19), to give a better division between children and older persons.

The figures for those who were read show that the two observation groups were composed differently. Among the people to be vaccinated the first three age groups comprised 73.3 per cent of the whole, whereas in the control group the individuals of those ages were only 42.2 per cent, persons more than 20 years of age or more thus constituting a majority. It is natural, therefore, that the total lepromin positives at that time were more in the control group (94.2% vs 77.1%), a fact which the author himself noted.

We are extremely surprised at the high percentage of lepromin positivity in the 0-4 age group of the controls, 89.4 per cent. That condition has never been observed in Brazil, although it is a country with a high prevalence of leprosy. Here we find a discrepancy between the two lots in that the children of the same age group who were to be vaccinated were only 57.8% positive. We are at a loss to explain this difference, if the two samples were composed of elements of the same community selected at random.

Another point to be noted is the degree of the reaction among the positives. Calculations from the data in Table 2 give the following results:

Degree of positivity, 1950-1951		
3+		
6.0%		
24.2%		

Therefore, the group not to be vaccinated had a considerably higher average degree of reactivity than the other, as well as a materially higher frequency of reactions. The author noted this fact, also, but we still cannot agree with his affirmation that the two samples studied are practically comparable.

Some objections must also be raised regarding the interpretation of the final (1954-1955) results shown in Table 3. At that time, the same persons that had been enrolled in 1950-1951 were listed, without regard to whether their initial tests had been read or not. For the same reason a further loss of material might be expected in the final readings, and consequently the comparability of the two groups must be seriously impaired by the reduced information.

Although there exists no special reference, we assume that the age groups of Table 3 are composed by the same individuals as in the corresponding age groups of Table 2. Would it not be reasonable to assume an influence of the age factor on the results of the lepromin test, made five years later, as is common in every collectivity, independently of BCG vaccination?

What importance are we to attribute to the positivity percentage of 95.8 after BCG vaccination, when in the control group, without vaccination, the initial tests already showed a percentage of 94.2? Also, in 1954-1955 the degrees of positivity in the two groups were nearly identical, without significant superiority of the vaccinated group: Correspondence

Group	Degree of positivity,		1954-1955
	1+	2 +	3+
Vaccinated	24.7%	43.2%	32.1%
Not vaccinated	30.9%	43.2%	26.0%

Initially, Table 4 impressed us deeply, despite our regret that it did not refer to age groups, and our astonishment that it should be possible to encounter so many lepromatous cases in such a well- and constantlycontrolled group.

Later, on re-examining Table 3, we noticed that in the vaccinated group there existed 23 persistently lepromin-negative cases, *versus* 33 in the unvaccinated group. Yet, according to Table 4, there had appeared not a single lepromatous case among the 23 (only 3 tuberculoid cases, these being the only cases in the entire group), whereas the 33 of the unvaccinated group contributed—as could be expected—heavily to the morbidity: 12 of the total (25), and all but 1 of the 6 lepromatous cases that occurred in the study.

We have maintained the thesis that all lepromin negatives, vaccinated or not, are in the same precarious immunological situation. Should we radically change this motion? Could it be that BCG protects against leprosy "with all certainty" even without producing positivity to the lepromin test?

Convit stated (footnote of Table 4) that "no case of leprosy has been found among the total of 177 persons whose final lepromin reactions were not read." We note in Table 3, in the not-vaccinated group, 142 persons not read *versus* 380 read. Now, as there appeared 25 cases of leprosy among the persons who were read we could, proportionally, expect 9.4 cases among those not read. But there was not one—by chance!

Without questioning the influence of BCG vaccination upon the results of the lepromin test, we wish to ask if Dr. Convit really has proven by his study, as published, that "the great reduction in the morbidity coefficient can be attributed, with all certainty, to the effect of BCG vaccination."

Rio de Janeiro Brazil DR. ALFREDO BLUTH¹ DR. JOIR FONTE

[In acknowledging the above letter from the late Dr. Bluth and Dr. Fonte, the editorial prerogative was exercised in commenting on it from the point of view of one nonstatistician reader. The gist of that comment follows, for what it may be worth.]

I am interested in your questions about the report of Dr. Convit to whom a copy is being sent for reply, because I have not been too happy about certain of his data. To me, not a statistician, it has seemed that

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the features pointed out in your inquiry indicate some sort of selection, suggesting that the allocation of the individuals had not been actually random—even by family groups. However, as I see it the differences between the two groups are in favor of Convit's conclusions rather than against them.

First, the proportions "not read" at the outset in the two groups were practically the same, so not much can be made of that point. They were not dropped from the experiment, and so they must have been retested at some later time.

Second, there are the facts that the unvaccinated group contained substantially fewer children (the most susceptible subjects), and that the lepromin percentages were higher. Both facts would make for greater natural resistance to infection in that group. If neither group had been vaccinated or otherwise treated for protection, one would have expected the higher infection rate in the group which was later vaccinated. The results as reported, however, indicate that something happened to make things very different, and the only thing that we know of is the BCG vaccination.

About one point I have heretofore been completely at a loss. That is the failure of any case to develop among the persons whose reactions were not read at the time of the last testing. However, it is possible that the explanation may lie in the fact that all but two of the individuals who developed the disease did so before 1955. Now, those infected persons would naturally be under much closer supervision than the general run of the population concerned. So, the people at the time of the last testing who were "not read" would presumably be of the lot as they were constituted after the leprosy cases which had developed in the previous four years had been separated. There may be no statistical value in this apparent interpretation of Convit's Table 4, but it would seem that only 2 cases developed in the 522 (less 26 infected) in 1955, so it would not be so strange a bit of chance that there were no cases in the 177 who are shown as "not read."

Personally I am glad that these questions have been raised, for it will give Dr. Convit a chance to discuss further a report which in reality is excessively brief compared with its importance, and to clarify some of the questions.

[At the same time that the foregoing letter was written, copies of the correspondence were sent to Dr. J. M. M. Fernandez, chairman of the International Leprosy Association's Panel on Immunology, for his information. The following is the gist of his comment.]

What you say in your letter to Dr. Fonte is exactly what I would have said if my opinion of the matter had been asked. Perhaps from the statistical point of view their criticism is correct, but I think that in spite of their objections Convit's conclusions are valid. I agree that his experiment has produced the most important evidence yet put forth indicating that BCG actually does have real value.

TO THE EDITOR:

With reference to the comments by Drs. Bluth and Fonte on my paper, Studies of Leprosy in the German Ethnic Group of Colonia Tovar, I wish to thank them for the interest they have taken in this work. In the following reply I shall review their observations point for point. I am greatly indebted to Prof. R. Shelly Hernandez for his valuable help on the statistics involved in both the original work and the present review.

1. When your correspondents are confronted with serious doubts about the validity of my statement that the great reduction in the morbidity coefficient can be attributed with all certainty to the effect of the BCG vaccination, it should be recalled that the percentages of individuals "not read" at first are practically the same—about 30%—in both groups. Here cannot be the basis for an idea that there was "a certain degree of unintentional selection of persons who were easiest to control and perhaps the more educated." If such a selection really existed it would be the same for both groups.

2. It is certain that the general percentage of positivity in Table 2 of my report is influenced by the percentages of positivity attributable to age, and consequently by the proportions of persons examined that make up these age groups. It is also certain that the number of persons in each group of the two general groups is not the same.

Now, this is no obstacle from the statistical point of view, as specifically equal values, as functions of age, can be calculated for both groups to obtain a general corrected percentage for each, and it will be seen that the two are technically comparable.

The corrected percentage of increase of the second group over the first is 23.3 per cent. The percentage of increase on basis of the crude, uncorrected figures of Table 2 (77.1 and 94.2) is 22.2 per cent. The difference is so small that it was not deemed necessary to call attention to it.

3. The high percentage of lepromin positives (89.4%) in the age group 0-4 years, of which nothing similar has so far been observed in Brazil, might be the result of the very high index of prevalence in the leprous focus studied, this index being 100.4 per 1,000 (THE JOURNAL **20** (1952) 185-193, Table 1). For a focus of such high prevalence the findings should not be considered extraordinary.

Regarding the difference in the percentages of lepromin positives in the two groups aged 0-4 years (57.8 vs 89.4%), this is explained by the fact that a group of 110 lepromin-negative persons, who were the subjects of the investigation published in the fourth paper of the series, were added to the group later to be vaccinated. Among these there were 23 of the 0-4 years group.

4. Concerning the specific percentages of different degrees of positivity shown for each age group in Table 2, the general percentage proportions for each of the three degrees of reactions (1+, 2+ and 3+) as obtained from the table are the following:

Crude or uncorrected percentages:

	1 +	2 +	3 +
Group later vaccinated	46.0	29.8	24.2
Group not vaccinated	81.6	12.4	6.0
Percentages of variation	+77.4	-58.4	-75.4

When calculated for comparable age groups, the following specific, corrected percentage proportions are obtained:

Corrected percentages:

	1+	2 +	3 +
Group later vaccinated	50.4	27.8	22.6
Group not vaccinated	79.3	13.6	7.1
Percentages of variation	+57.3	-49.6	-68.6

Small differences are observed between the crude specific and the corrected specific percentages, but they do not affect the general meaning of the results. This may be seen from the corresponding percentages of variations. There is a high percentage of increase in 1 + reactors in the unvaccinated group in comparison with the group later vaccinated, but the inverse condition is observed when we come to the 2 + and 3 + reactors.

5. Considering the influence of the age factor over a period of five years, our criterion for attributing importance to the percentage of positivity of 95.8 in the vaccinated group is based on the fact that 110 Mitsudanegative persons, dealt with as already mentioned in our fourth paper, were added to the group later vaccinated. This fact also explains the high initial percentage of 94.2 positives in the unvaccinated group. From our point of view, the influence of age in the vaccinated group is quite secondary compared with the influence of the BCG, because the capacity for positive reaction within the group had been acquired long before 1954-1955.

6. I do not share the surprise expressed by your correspondents about the high number of lepromatous cases found in a group so well controlled. We have similar findings in many other rural foci under continued observation. Work in such areas is admittedly more difficult than is the case in cities, and less accuracy may be expected.

7. Your correspondents are unable to reconcile the results of our work with their thesis that all lepromin-negative persons are in the same precarious situation as regards immunology, whether they have been vaccinated or not. Our opinion is entirely different, because the Mitsuda reaction, when negative, does not at all measure the profoundness of the

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immunological situation. The immunological condition of Mitsuda-negative contacts may be potentially different, and this may explain how some turn out lepromatous and some tuberculoid; while others become Mitsuda positive without presenting any clinical signs of the disease, and others still remain Mitsuda negative without showing any signs of the disease either.

The negative Mitsuda reaction in contacts thus indicates an immunological condition the potentiality of which can differ completely from one person to another. This should be carefully considered in connection with the evaluation of the data in Table 3, which show 23 vs 33 lepromin negatives for the vaccinated and unvaccinated groups respectively; and also in connection with Table 4, which shows no lepromatous cases as appearing among the 23 vaccinated persons and only 3 tuberculoid cases, while 6 lepromatous cases appear in the unvaccinated group.

If more could be known of the immunological conditions of the 8. vaccinated group with unknown Mitsuda reactions, it would be easier to explain how no cases of contagion were observed in that group.

In conclusion, I must accept the criticism that the groups studied were not strictly comparable, due to the fact that there was a greater number of children-considered more susceptible-in the vaccinated group, and due also to our having added to that group the previously mentioned 110 lepromin-negative persons. However, these circumstances give added strength to the conclusion we reached, namely, that the reduction in the morbidity rate as regards leprosy can be attributed with all certainty to BCG vaccination.

It is our concept at present that BCG vaccination in leprogenic foci is an important prophylactic measure. This vaccine adds its immunologic, synergic effect to the specific defensive phenomena induced by the Hansen bacillus in the inhabitants of leprogenic foci. It would be interesting to get data on the question whether or not BCG vaccination, when used in nonleprogenic foci, would prevent them from becoming endemic.

In my opinion BCG vaccination is a weapon of far-reaching potentialties in the fight against leprosy, but there is urgent need for coordinating results obtained by different workers using the same methods and the same manner of administering a standardized BCG preparation.

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