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STUDY OF THE IMMUNO-ALLERGIC RELATION BETWEEN TUBERCULOSIS AND LEPROSY BY THE CORRELATION OF THE MANTOUX AND FERNANDEZ REACTIONS^{1, 2}

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SUMMARY AND CONCLUSIONS

The objective of this study was to investigate the cross-sensitization between tuberculosis and leprosy by correlating the reactions of Mantoux and Fernández (early lepromin reaction). Given this co-sensitization, the material studied would lead to the following observations:

1. The Fernández reaction (FR or rF) should be more frequently positive among tuberculous patients than in healthy individuals;
2. The frequency of a positive Fernández reaction should be higher in urban than in rural areas because in the latter the tubercularization is usually less;
3. In healthy persons the percentage of a positive FR would be higher among the tuberculin-positives than among the tuberculin-negatives;
4. Among BCG-vaccinated persons the FR should be more frequently positive than in nonvaccinated control groups.

These were the items which I tried to study in this thesis, though Item 3 constitutes its chief objective; the others are correlated and were considered to allow a better general approach to the subject.

In view of the investigation undertaken, the study would also allow consideration of another aspect of the co-sensibilization: once proved the cross-sensitization between tuberculosis and leprosy, what would be its degree? Limited or extensive? Would the tuberculosis infection have as much importance as leprosy in causing a positive FR?

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² Summary and conclusions of the thesis presented in December 1960 for appointment to the Chair of Dermatology at the School of Medicine at Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil.

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To verify these premises, several groups of individuals were given lepromin and tuberculin tests:

A. Patients with tuberculosis:

- I. In an area where leprosy is endemic: São Paulo, 165: FR + 6.7%.
- II. In an area where leprosy is nonendemic: Cleveland, Ohio, USA, 129: FR + 0.8%.

B. Individuals without tuberculosis:

- I. In a leprosy-endemic area:
 1. Contacts:

Educandario (Preventorium) Jacarei:	246,FR + 60.6%
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 2. Noncontacts:

Asilo Anjo Gabriel (S.P.)	199,FR + 10.6%
Creche de Jacarei	50,FR + 0%
Educandario D. Duarte (S.P.)	413,FR + 13.3%
Gota de Leite (S.P.)	187,FR + 0.8%
Holambra, Dutch (Mogi-Mirim)	125,FR + 0%
Holambra, Brazilian (Mogi-Mirim)	99,FR + 1.1%
Nitroquimica, workers from Bahia (S. Miguel)	157,FR + 1.9%
Nitroquimica, excluding those from Bahia (S. Miguel)	533,FR + 0.9%
Pirapora, Parnaiba, Cajamar	574,FR + 3.6%
Pirapora (adults)	85,FR + 17.5%
Serviço Social de Menores (S. P.)	46,FR + 0%
- II. In a nonendemic area:

Cleveland (Ohio,USA) university students	19,FR + 5.3%
" " " patients with psychosis	45,FR + 2.2%
The New York Skin & Cancer Unit, skin cases	50,FR + 12.0%

C. Leprosy patients:

Lepromatous, up to 18, Sanatorio Padre Bento	46,FR + 0%
Lepromatous, adults, Sanatorio Padre Bento	208,FR + 1.4%
Lepromatous, arrested, Ribeirão Preto	31,FR + 3.2%
Indeterminates, Sanatorio Padre Bento	15,FR + 20.0%
" " " " (to 18)	27,FR + 11.1%
Tuberculoids, Sanatorio Padre Bento	10,FR + 66.6%

The study was made on men and women of different age groups, babies, children, adolescents, adults and old people. The groups from nonendemic leprosy areas were the best for the investigation, since the positivity of the FR could not be attributed to previous exposure to leprosy but to the influence of *M. tuberculosis* or other mycobacteria. Furthermore, in the nonendemic areas the best material would be the group of tuberculous patients; it is in these patients that the cross-sensitization should be observed to its maximum degree.

In leprosy-endemic areas the groups of individuals with a high proportion of tuberculin-positive reaction coming from areas where leprosy rates are lower (for instance, people from Bahia working for the Nitroquímica Company), could provide more useful data. Patients with tuberculosis constitute interesting material comparable with similar groups of individuals without tuberculosis and equally, without known exposure to Hansen bacilli: we should see in the former a higher proportion of positivity of FR.

Another group in which we may note the association between tuberculosis and positivity of FR is that of children from 0-1 year old, not exposed previously to tuberculosis and leprosy; the tuberculosis and the early lepromin reaction are, as a rule, negative. Positivation of FR in a great number of these children after the use of BCG vaccine would indicate the influence of tuberculosis, provided that the same thing is not also noted in the control group.

The material was considered separately in relation to each of the four above-mentioned premises. The results obtained in the groups can be summarized as follows:

1. The percentage of a positive FR in tuberculous patients of the nonendemic leprosy area (Cleveland, Ohio, USA) was only 0.8 per cent, i.e., so low in the material considered most adequate for the correlation study, that the hypothesis of co-sensitization remains seriously in question or very much attenuated in its importance. This deduction is confirmed by the fact that, in tuberculous patients of leprosy-endemic areas, the proportion of positivity reached 6.7 per cent and because, in individuals supposedly healthy (excluding contacts) of endemic and nonendemic areas, the results were practically the same.

2. Among the groups of endemic or nonendemic areas, there was one—that of child contacts of leprosy patients—in which the positivity of FR was very high (60.6%) differing sharply from the others, in which the positivity varied from 0-17.5 per cent. This leads to the deduction that, in general, exposure to Hansen bacilli would sensitize the organism in such a way as to cause a positive FR, while the influence of previous tuberculinization would be practically nil, reduced, or inconstant.

3. The results of FR in urban areas (where tuberculosis infection is more frequent) and in rural areas, were usually similar and the percentage of positivity was low (contacts excluded); in the rural

areas, positivity was 0–3.6 per cent; in the urban area, the higher proportion of tuberculin positivity (85.4%) was found in workers from Bahia in the Nitroquímica factory and only 1.9 per cent of them had a positive early lepromin reaction. Comparison of these results does not favor the hypothesis of cross-sensitization.

4. The study of correlation between Fernández and Mantoux reactions in patients with tuberculosis in the endemic leprosy area (São Paulo), or the nonendemic area (Cleveland), shows that the frequency of positive FR was very low.

5. In the individuals supposedly free from tuberculosis, contacts or noncontacts of leprosy patients, there was an association between positive Fernández and Mantoux of 1:1,000 and 1:10 in the groups of Pirapora, Parnaíba and Cajamar, with Mantoux up to 1:100 in the Educandário Dom Duarte; and in contacts only with Mantoux 1:10. The positivity of FR tended to be associated more frequently to the strong tuberculin reaction. There was no association in other groups, i.e.: Pirapora adults, Serviço Social de Menores, Asilo Anjo Gabriel, Creche de Jacarei and the New York Skin and Cancer Unit. In the light of these results the co-sensitization could be considered in some groups but not in others. They show that, even if demonstrated a casual relation between tuberculinization and positivity of FR, the cross-sensitization would occur in a limited range and inconstantly. On the other hand, the association of FR to Mantoux 1:10 could depend also on the eventual influence of other mycobacteria or of other affinitive germs which could have the capacity to cause, according to Palmer's theory, nonspecific tuberculin and early lepromin reactions.

6. Children, adolescents and adults with or without tuberculosis who reacted positively to tuberculin, presented positive FR in a percentage which varied from 0 to 37.9 per cent in the several groups (in the child contacts of leprosy patients it reached 63.9%). The differences observed make it difficult to admit that tuberculosis has induced the positivity of FR to a significant degree or that it acts in a constant manner.

7. In lepromatous patients there was no correlation between the two reactions; the result of early lepromin reaction, almost always negative, has not depended on the positivity or negativity of the tuberculin test. Only 10 tuberculoid patients were given the tests and so no conclusion could be drawn on the existence of association or not. In lepromatous and tuberculoid patients exist—it seems independently of tuberculosis—peculiar immuno-allergic conditions which are responsible for the almost constant negativity of FR in the former, and frequent positivity in the latter, which caused the appearance of these polar types of the disease. In patients with indeterminate leprosy, not yet clearly defined in their immuno-allergic behavior, we would be better able to observe the effect of the cross-sensitization; the group had only 42 patients and association between the two reactions was not seen.

8. Investigation of the eventual effect of BCG in the FR, undertaken in some groups of the Creche de Jacarei (10-12 months old) and Asilo Anjo Gabriel, has shown that with BCG and lepromin retesting there was a very low proportion of positivity of early lepromin reaction or even an absence of same. The inconstancy of the results and the low frequency of positivity obtained have confirmed the opinion expressed in previous items.

Taking into account the above data, we arrive at the following conclusions:

1. The percentages of positivity of Fernández reactions were definitely much higher in contacts, tuberculin negatives or positives, indicating that, in individuals with the capacity to react, the reaction would depend essentially on sensitization to *M. leprae*.

2. Observation of positive Fernández reactions in individuals of a nonendemic area of the USA, where previous exposure to *M. leprae* would have been extremely improbable, suggests the possibility of cross-sensitization with tuberculosis bacilli or other antigenically related germs. However, as the positivity of Fernández reaction in one group of tuberculous in the USA was almost nil (0.8%), this cross-sensitization would occur only within a very limited range.

3. The frequency of positivity of Fernández reaction in one group of tuberculous individuals of an endemic area (S. Paulo) and a non-endemic area (Cleveland, USA) was practically similar to that of individuals apparently nontuberculous living in the same areas, and would constitute an unfavorable element to cross-sensitization.

4. The similarity of results of Fernández reactions in urban areas (with a higher rate of tuberculization) and in rural areas, does not favor the hypothesis of cross-sensitization.

5. In some groups there was association between tuberculization and Fernández tests and it was observed higher frequency of positivity of Fernández reactions in connection with tuberculin positivity; further, it tended to be associated more with the strongly positive tuberculin reaction. In other groups, slightly more numerous, the association was not apparent. With these data there is evidence that, once proved the causal relation between tuberculization and positivity to Fernández reactions, the cross-sensitization would occur within very limited range and inconstantly.

6. In several groups of tuberculin positive individuals, the percentage of Fernández positivity varied from 0 to 37.9 per cent, making it difficult to admit that tuberculosis had induced such positivity to any significant degree.

7. Association between positivity of tuberculin and Fernández reaction was not observed in a small number of cases of indeterminate leprosy, the form of the disease in which the immuno-allergic behavior is frequently not well-defined as in lepromatous and tuberculoid leprosy. In the lepromatous cases, the results of Fernández reactions did not depend upon tuberculin positivity and it was almost always

negative. In lepromatous and tuberculoid cases, there exist—it seems independently of tuberculosis—peculiar immuno-allergic conditions which guarantee the almost constant negativity of Fernández reactions in the former and the frequent positivity in the latter, and determine the appearance of the polar types of the disease.

8. Evaluated on the Mantoux and Fernández tests, the hypothesis of cross-sensitization had in our material only few favorable elements while others were contrary in such a way as to hinder it seriously or to reduce very much its importance. If confirmed in the future—and it is possible that it be true, along the lines of the Palmer hypothesis—the overall review of our data leads us to admit that the cross-sensibilization would occur inconstantly and within a limited range.