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SOME ASPECTS OF IMMUNITY IN LEPROSY AND THEIR IMPORTANCE IN EPIDEMIOLOGY, PATHOGENESIS AND CLASSIFICATION OF FORMS OF THE DISEASE. *

Based on 1529 Lepromin Tested Cases

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The influence of the phenomena of resistance in the pathogenesis of leprosy was for a long time studied only with the observation of clinical and epidemiological facts. Hence the theories based on environmental factors and those related to sex, age, eating habits, individual constitution and different debilities, in contradiction to the exclusive action of the germ.

Man, however is a conjunction of varied factors and influences, within with it is almost impossible to follow the track of conditions leading up to resistance to infections. If the study is transferred from that of man to man, to that of human group to group, the difficulties still persist, because we shall never secure the variations of

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one factor and have the others stationary. So, if in order to study the influence of climate, we we could divide populations by different climatic zones, we would also find differences of race, eating habits, general sanitation, as well as different conditions of life and occupation. Because of the impassibility of experimental studies for lack of animals receptive to leprosy, it is not surprising that no theory of resistance to it could be established in its entirety, without discussions, and even contestations. We only remember, as an example, in disaccord with the accepted theories, the cases of initial leprosy in adults, its incidence in individuals who have conserved their bodily vigor, its non obligatory incidence in individuals debilitated in every way and in spite of their intimate contact with patients of open leprosy; and this in such numbers, as not to be thought of as a simple law of average.

A new fact, however, has appeared and opened the way to possibilities of study along this line; that is, the skin-reactions with antigens prepared with materials of leproma. A careful and systematic study of these reactions will be destined to present results of value in the epidemiology and the etiopathology of leprosy, and to establish on a more scientific base the best conditions for contagion or resistance, or the later evolution of the disease in the infected individual.

SKIN REACTIONS IN LEPROSY

The first investigations of skin-reactions had in view the obtaining of a test, capable of constituting a process of early diagnosis, analogous to tuberculin for the infection of the bacillus of Koch.

The attempts of TEAGUES (1), NICOLLE (2), MANTOUX (3), MARCAOUX and PAUTRIER (4), with lepromatous antigens, or with leprolin of ROST, brought no practical results, and were forgotten, as were also the leprin of BABES (5), the glycerine and aqueous extracts of SCHOLTZ and KLINGMÜLLER (6).

In some posterior researches facts were observed which brought attention to the authors, and which value began to be given to their real importance.

> MUCH (7), KULES (8), BERNUCCI (9), FERRARI (52), MARIANI (10, 11), MONTANES (12), NEGRO (13), and AMBROGIO (14), noticed with their diverse intradermic reactions, the greater reactivity of the forms considered resistant, both incipient and neural, contrasting with the weak or non-reactivity of the mixed or nodular forms. Having injected his antigen of leproma into the skin of 403 patients, MITSUDA (15) observed the fugacity of reac-

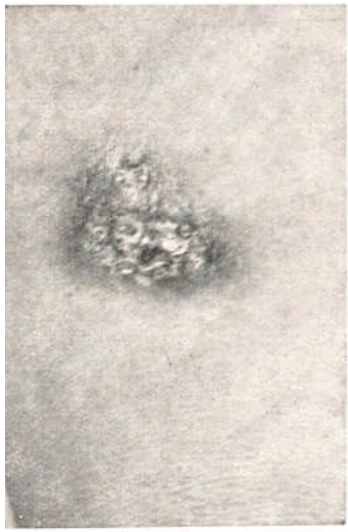


Fig. 1
Strong positive lepromin test, scar formation.

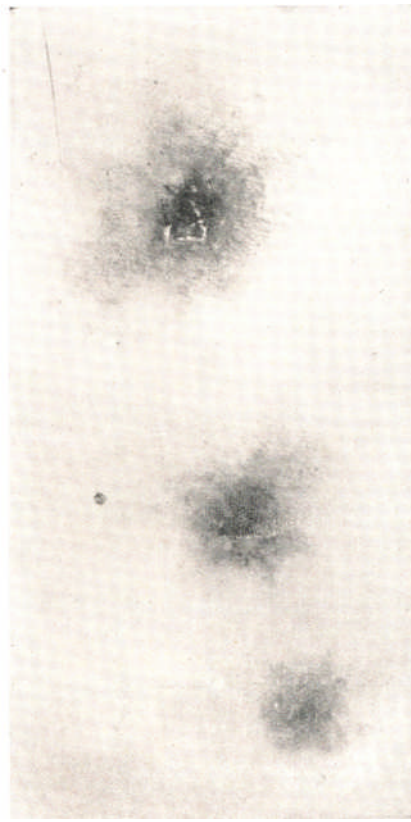


Fig 2
Positive Lepromin tests in a sarcoid type of tuberculoid leprosy Standard antigen and dilutions 1:8 and 1:15.

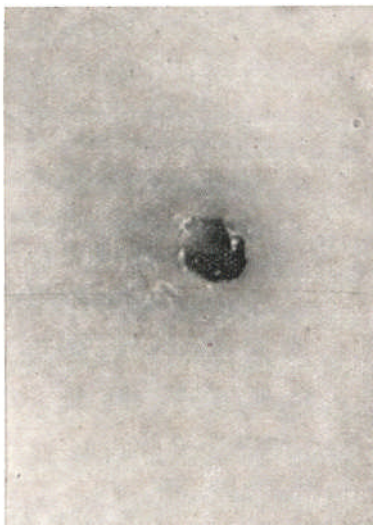


Fig. 3
Strong, ulcerated lepromin test, in tuberculoid leprosy, with 1:10 dilution of the standard antigen.

tive phenomena in nodular cases, while in the neuro-macular an initial hyperemic reaction was observed with papulous infiltration in 2 weeks, persisting for a longer period still. Identical reactions in healthy individuals.

From his observations, MITSUDA, concluded that healthy and the patients with macular and neural leprosy presented great resistance to infection, a resistance which the nodular ones "exhausted" in their struggle against the germ.

The studies of MITSUDA were resumed by HAYASHI (16.17), who, abandoning all attempts of diagnosis, established definitely the divergence between the stage of the disease and the intensity of the reaction, and insisted on its immunitary value, and its importance in classification of clinical forms, preparing the recognition and use which the reaction has in our days.

Similar conclusions, of great clinical and epidemiological value, resulted from the work of BARGEHR (18, 19, 20) and DE LANGEN (25), in which the technique of preparing the antigen varied, being more concentrated, and its application by scarification instead of the intradermic injection.

The reaction to lepromin is, however, sometimes very slow, and may begin 3 or 4 weeks after the application. It is thus understood that a simple deposit of the antigen, even highly concentrated, on the scarification of the skin, from where it is rapidly eliminated, represents a minimum introduction, which could only reveal an exaggerated reactivity of the organism, failing to indicate the medium grades of resistance. Besides this, its dosage being very difficult, there have not been many followers of BARGHER'S and DE LANGEN'S technique.

Modern researches took as a standard the techniques of MITSUDA and HAYASHI, based on the intradermic injection of a fixed quantity of the antigen indicated, as well as the criterion of reading also indicated by these authors.

PERSONAL TECHNIQUE

Preparation *of antigen:* The technique of preparing the antigen adopted by us is based on that of HAYASHI, with some variations. Lepromas collected aseptically in sterile normal saline water are boiled in a water bath for one hour, after which they are relieved of any piece of skin that they may have, cut into small bits with scissors, ground in a mortar and weighed. For each gram of the triturate prepare 20 cc, of the sterile water which served for the first boiling, adding more water of necessary. The mass of leproma is again triturated strongly, with a little of this prepared water. After a short rest, the murky liquid on the surface is sucked up with a fine Pasteur pipette, and filtered through 4 layers of gauze, being received

in a balloon. New quantities of water sucked up will show mediocre turbidity, contrasting with the strong murkiness of the first water.

The mass of leproma may now be discarded. The balloon containing the antigen filtered by the gauze is put into the autoclave for 15 minutes at a temperature of 120°. To the contents is added 0,5% of carbolic acid, then distributed in sterile ampoules or tubes of the insuline type.

Aspect — The material thus obtained presents a cloudy, milk-like aspect, and when in repose it leaves a deposit at the bottom of container. The bacterioscopic examination shows a great number of Hansen's bacilli and globi in all fields. Since the bacillary count is practically impossible, and consenquently also the titration of the antigen, we obtained originally a great quantity of material with which most of the tests were made.

Duration — The antigen has exceptionally conservative qualities. We are even now getting excellent reactions from antigen which we prepared in 1933 and has been kept in dark, rubber-covered glasses, all experiments having been checked by our present antigen.

Denomination — The most varied names have been given to this type of antigen. HAYASHI calls it «vaccine»; MUIR (22, 23) and the authors from India adopted the term «leprolin». As we had occasion to mention, (25) the term «leprolin» is not appropriate, since it brings to mind the «tuberculin» process. Since there is not presently any culture of Hansen's bacilli, such a process could not be followed. A more appropriate term for the material prepared with triturated leproma would be the designation used by BARGEHR, «lepromin», leaving the term «leprolin» to the product of the metabolism process, or to the toxins of Hansen's bacilli, when their culture is obtained.

Application — A fine syringe of 1 cc. and a short needle are used for injecting the lepromin into the skin, preferably in the front part of the thigh, on account of the strong reactions that it may cause, though, in certain cases, we have applied it in the arm. It is advisable, generally, to inject 0,1 cc. This is rather difficult to accomplish with an ordinary syringe, not only because of losses of quantities in the syringe, but also due to accidental introduction into the hypoderma. The most efficient method is to note the diameter of the anemic papule which should measure 1 cm., corresponding approximately with the desired quantity.

Reading — Following the methods of HAYASHI, we begin ours first observations by reading each reaction eight, sixteen and twenty-four days after the injection. After some experiments, we were convinced that the initial readings made on the eighth and sixteenth days were not necessary. The cases of positive reaction to lepromin generally reach the peak of reaction from the third to the sixth week after the injection, this being an ideal period for the reading. A reading taken on the eighth day

may give as positive a populous lesion which may represent a lesion of trivial irritation in involution. We have often observed this even in advanced cases of nodular leprosy. As a matter of fact there is no necessity, usually, of successive readings of the same reactions, as timely readings are quite sufficient to comprehend tardy reactions. Our experience proved that a period of thirty days after the injection is ideal for a routine reading, not overloking, however, a checking-up later, in special cases, such as those presenting very slow reaction, necrosis, etc.

Types of Reaction — The reactive lesion is elementarily a nodule, raising up the skin, which at the surface turns reddish-violet more or less intense. This aspect may vary in accordance with the evolution of the lesion. Crusty formations are frequent as a consequence of the particularly intense suppuration undergone by the nodules of reaction; the scar aspects, from involution of a nodular lesion (photo 1) ; the frankly ulcerous aspects giving emission of serosity during a few months; and the deep nodules, and deep infiltration without erythema on the surface.

Classification of Reactions — The original classifications were made in accordance with HAYASHI: +++ for nodules with more than 1 cm.; ++ for those of one half cm. to 1 cm.; + for the infiltrations of less than half a cm. next the reactions which are doubtful and finally those which are totally negative. Having initiated the work with this criterion of reading and classifying, we have continued it till today. The verification of results, however, and their correlation with the clinical forms and the histopathology, gave us the conviction that a binary classification would be sufficient, in negative reactions (from 0 to 0,5 cm, including the reactions — and + of HAYASHI) and positives above 0,5 cm. including the ++ and +++ of HAYASHI and the ++++ of other authors). The table X and the considerations we expose about it justify our classification. Considering the importance we assign to lepromin in distinction between «anergic» and «allergic» cases, the intermediate dimension exactly of 0,5 cm. should be considered «doubtful».

Involution — A reactive lesion may persist from a few weeks to many months, resolving itself finally into a scar more or less evident, which may sometimes characterize the intensity of a previous reaction.

THE REACTION TO LEPROMIN IS A SPECIFIC REACTION OF LEPROUS IMMUNITY

The clinic and bacterioscopy may affirm that a positive reaction to lepromin occurs only in cases in which resistance of the organism to leprous infection has been proved. As an example, let us take the extremes of approximately 100% of positive reactions in tuberculoid leprosy and approximately 0 % in nodular leprosy, according to our criterion of reading. By this way the results of the anthors, not

always interpreted at the time, are explained and who, in search of a test of allergy for diagnosis, the positiveness of which should be frank in declared cases of leprosy, obtained instead the exact contrary; that is, positive reactions in neural forms and in cases of incipient macules; negative in nodular ones.

On the other hand, only antigens prepared with material of leproma and rich in bacilli, in accordance with the technique of MITSUDA-HAYASHI, MUIR and others, are capable of revealing this state of immunity. Attempts at substituting the original antigen did not give success, neither with other acid-fast bacilli, nor with the very material of lepromas from which have been eliminated all bacilli by filtration (16,17).

In an previous work (24) we have had occasion of reporting what we have observed with the intradermic reactions to tuberculin in healthy persons and in lepers, in which we have searched previously for the reactivity to lepromin. Using the synthetic tuberculin of Dorset, diluted to 1:10000, we observed the results condensed as follows:

1. — Among healthy infants, lepromin + : 75,5 % negative tuberculin reactions.
2. — Among healthy infants, lepromin — : 77,8 % negative tuberculin reactins.
3. — Among lepers, lepromin + and —, identical indifference to tuberculin reactions.

It becomes evident that the reactivity to tuberculin depends in no way upon the reactivity to lepromin neither interferes with it in any way. The anergic forms to lepromin present good coefficients of positive tuberculin positive reaction, which proves that existent anergy is not "general" for all the antigens, as BERNUCCI wishes; inversely, among the lepromin-positives, numerous cases did not react to tuberculin, which is contrary to AMBROGIO, for whom the allergic reactivity of leprosy is a form of "general" hypersensitiveness to all external stimulants.

The substitution of antigens by cultures of acid-fast germs obtained by various authors and announced as being Mycobacterium leprae, or by the material of rat leprosy, rich in the Stefansky bacilli, gave clearly positive reactions in the majority of individuals tested. The mechanism by which these reaction was produced is not explained, the authors generally thinking of local irritations produced by the germ. It is known, however, that these positive reactions, more precocious and of shorter evolution than the real lepromin test,

are constantly observed in all forms of the disease, even in lepromatous cases. These reactions are other proofs of the specificity of the antigens of leproma, which only exceptionally give positive reaction in cases of bacillary leprosy.

THE REACTION TO LEPROMIN IS A SPECIFIC REACTION OF ALLERGY

Admitted, with facts of observation, the immunitary nature of the reaction to lepromin, some authors refuse to see in this reaction an "allergic" response of the organism to the bacilli of Hansen. By the definition, on account of allergic proofs can be taken only those which are dependant on organic modifications caused by previous relations between the organism and the causing agent which the antigen represents.

Lacking a receptive animal to this proof, we cannot prove experimentally that positive lepromin tests results only in a previously infected organism. This forces us to conduct our reasoning with the clinico-epidemiological observations.

An adult healthy man of endemic areas reacts generally positively to lepromin. It is not within our reach to discover the initial lesion of leprosy which will justify this reactional capacity and its allergic nature. If this phase of primary inoculation exists, it escapes, at present, at least, the known processes of investigation. Nothing analogous, therefore, exists here to the initial anatomical and radiological lesion of tuberculosis, which causes the allergic reactivity to tuberculin.

There still remains the resort to research into the reactivity to lepromin in individuals in whom the epidemiological inquiry reveals diverse conditions of contact with the bacilli of Hansen.

1*st.* — The observations of stronger and more frequent positive reactions among healthy individuals living in leprosariums than among the general healthy population in minor contact with the bacilli of Hansen, make one suspect a prior infection which aborted and produced an alteration in the manner of cutaneous reaction; that is, allergy.

> It was already noted in the original observations of MITSUDA that the healthy, even without known contact with lepers, react to lepromin. This reaction, however, was more intense in three nurses who worked for ten years in the leprosarium. The studies of BARGEHR are more suggestive from this point of view. The reaction is negative in the healthy, who never had contact with a leper. The positive reaction of the «contacts» is due, according to BARGEHR, to the formation of specific antibodies by

virtue of minimum previous infections. De LANGEN obtained identical results, and gives the same interpretation. MUIR observed in healthy children of lepers stronger reactions than among boys without contact, which «may be taken as an index of augmented resistance against leprosy». In the children of Oshima, MUNEUCHI (26) accentuated the existence of reactions, the stronger, the longer the duration of the previous contact with the sick parents. STEIN and STEPERIN (27) present very interesting and elucidative results. In 49 healthy adults working in leprosariums the frequency and intensity of positive reactions were directly proportional to the intimacy of contact with the patients, varying according to the professions — the doctors having the strongest reactions: in the same profession the frequency and intensity of reactions were directly proportional to the length of service. Healthy individuals, free from contact with leprosy and with lepromin negative reactions. after a certain time of service in the leprosarium became lepromin-positive and this positiveness became more defined and increased with the time of habitation.

2*nd.* — The final and probably decisive argument would be the verification of the reactivity to lepromin in countries securely free from leprosy. The allergic nature of the L. T. (lepromin test) would be confirmed in these countries by a frequent negative result in contrast to that observed in endemic countries. This is the condition which MUIR imposes for considering, allergic the L. T.

A research of this nature is not within our reach, and could, for example, only be done in certain European countries. But this research has already been done, even though in a very small scale in proportion to the importance of the subject, and from this we can get certain data of value, whilst awaiting more extensive and informative studies.

CUMMINS and WILLIAMS (28) inoculated with lepromin furnished by MUIR 25 psychopaths hospitalised in London without any admissive contact with leprosy. The peak of reaction was always observed on the 8th day, reaching in but 6 times the maximum of 9,5 mm., declining soon after till the 22nd day, the diameter being then 3,5 to 4,5 mm. in 19 cases, and 6 mm. in the 6 cases above. In these 6 cases referred to having reached 6 mm. on the 22nd day, an intradermal reaction with bacilli of Koch, made at the same time, gave lesions of much greater diameter.

Comparing these results with the reactions which we call “positive”, nodular, late and always superior to 5 mm. we are forced to believe that in no case did CUMMINS and WILLIAMS obtain positive reactions.

DUBOIS (30) gives results obtained with a lepromin furnished by VAN BRESEGHEM in 29 individuals who had never left Belgium. Of these, 14 reacted with 0-2 mm., and 10 with 3-5 mm. In only 5 were observed reactions of 6-10 mm., sometimes with suppuration.

Based on these results, DUBOIS opposed the allergic nature of L. T. because he encountered "numerous positive reactions". In accordance with our method of reading (negative up to 5 mm.) only in 5 cases were the reactions positive.

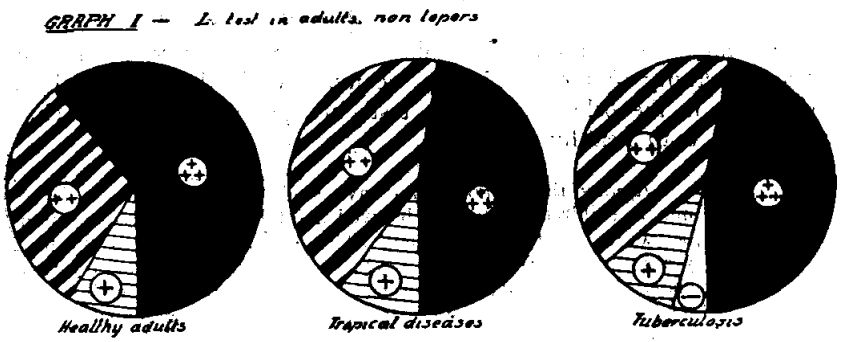
> In his recent work BONCINELLI (31) protests against the hypothesis of the allergic nature of L, T., presenting 44 individuals, healthy and coming from zones not endemic of leprosy in Italy, and in them, positive reactions were observed in 22 cases.

We are again in a position caused by disagreement in the methods of reading the reactions by different authors. BONCINELLI includes among "clear positive reactions", 9 reactions of the type which he calls "pompho-papulous", with aspects analogous to the tuberculin reactions and lasting on an average half a week-and which we would call negative. We doubt still further in admitting as positive 9 other reactions which the author calls "papulous", persisting 2 to 3 weeks (he does not give dimensions). There remain 4 nodular reactions, identical to our real positive reactions.

Now, let us compare these results with those verified in healthy inhabitants of endemic countries:

> We have already seen that adults always react with «nodular» lesion to the intradermic injection of lepromin. Let us add now the observations, to the same intent, of MUIR (9 strong reactions in 10 cases); TAJIRI (32) 100%; MITSUDA 10 in 13; FERNANDEZ (33) 75 to 77%; ADANT (35) and CHIYUTO, 67% in children and 9 in 10 adults (36).

Our Observations in regard to reactions to lepromin in individuals not affected by leprosy were made in healthy children of lepers.



isolated in the Preventories of São Paulo State, and in 144 adults, 55 being contacts of leprous patients, 19 suffering from various tro-

pical diseases (leishmaniosis, blastomycosis) and 70 from pulmonary-tuberculosis without known contact with cases of leprosy, according to a previous work (51). Not including children, that will be studied apart, we have the following graph according to the reading of HAYASHI. (See tables at the end of work).

We shall point out that our reactions ++ and +++, refer to large nodular formations, often with supuration and permanence of lesion for several months before involution.

These results, as those of other authors who have worked in endemic countries, contrast clearly with the weak and transitory reactions, and in reduced number, of the non-endemic countries, and bring a new contribution to the allergic nature of L. T.

APPLICATION OF THAT KNOWLEDGE TO EPIDEMIOLOGICAL FACTS

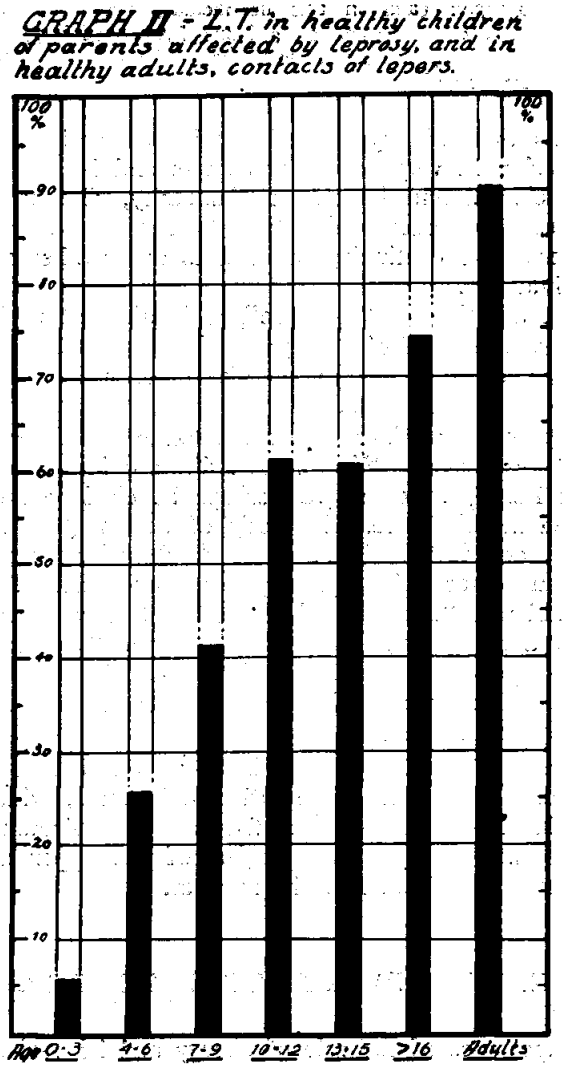
Once proved the necessity of contact with the germ in order to determine the positive L. T., we fall by analogy, into the same order of ideas that gave to tuberculin the value of allergic and diagnostic test of primary infection of tuberculosis, in spite of JADASSOHN's (37) admitting that the allergy in leprosy may be produced by bacillary protoplasma, without pathogenicity.

As BARGEHR had supposed, with DE LANGEN and others, the positiveness of the reactions seems to signify infection, to which the organism reacts, with the immunity, and which manifests itself with an allergic reaction. In leprosy the allergic reaction is equal to a reaction of immunity. From this point of view leprosy approximates closely to trichophytosis, in accordance with the animal experiments of BRUNO BLOCH.

Granted the analogy with tuberculosis in reference to the general infectivity of the adult man, we must see if there is equally a difference in the behaviour to the tests in leprosy between the child and adult, both healthy.

> Among the authors who have studied the reaction to lepromin in children, CHIYUTO observed a totality of negative reactions below the first year of age; 52,9 % positive reactions up to 2 years; 66,6 % from 2 to 3 years, and 100 % positive reactions above 3 years. MUIR observed positive reactions in children of lepers, proportionally more frequent as the age increased. Identical results were observed by TAJIRI (negative below 5 years; positive above that age). FERNANDEZ observed 5,26% of positive reactions in children of less than 2 years and 25 % in children less than 3, who had had contact with lepers.

Our observations refer to 323 healthy infants, children of lepers, isolated in the "Preventories" of the State of Sao Paulo. The distribution of these infants in groups of 3 to 3 years provided us



the table 2, on which is based the graph above n. 2. (As previously, we call negative reactions, those of less than 0.5 cm. in the 30th day of reading).

The analogies with tuberculosis are evident; but not all authors believe that the positiveness of the reactions signify “infection”.

> KLINGMULLER (38) studying and condensing the existing bibliography (and in this he includes first JADASSOHN) shows that it could depend on a banal hypersensibility, or an allergy produced by the simple «presence» of the germ, without any pathogenic action.

It seems that this hypersensibility is not so banal, because it presents itself with very particular aspects and is intimately correlated with clinical and histological immunity, disappearing totally in even precocious cases which tend to bacillary impregnation, in spite of these cases continuing to react to many other antigens and external stimulants.

As to the action of “presence”, it is difficult to believe that by itself it is capable of effecting a profund modification of tissular reactivity so as to show an allergic response of such prolonged evolution as that to lepromin.

For these considerations we are inclined to admit the existence of *primary leprous lesions.* We cannot indicate evidently the type and location of lesion, which might perhaps be elucidated by observation directed in this sense. The study of SERRA (39) revealed the presence of acid-fast bacilli in the glands of numerous healthy individuals in contact with open leprosy. SERRA holds that they are leprosy bacilli in a “saprophytic” state: latent leprosy, as in the rat, waiting for a predisposing cause for eclosion. The introduction of the germ would be through the tonsils, where the germ would find a surrounding for permanence and resistance, passing later to the general lymphatic system.

The general infectivity of leprosy, we admit, would be in perfect accord with the observations of SERRA, with the introduction of bacilli of Hansen from the dust of environments of bacillary cases into the lymphatic organs of the upper air passages and consequent allergization of the receiver.

ALLERGY AND RELATION TO LEPROSY

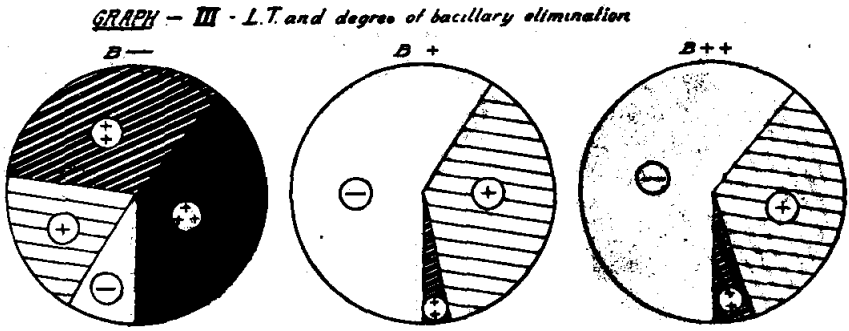
The importance of the role of allergy and its variations in the pathogenesis of leprosy, and in the mutations of its clinical forms has been accentuated by many authors, among whom we may cite ARNING, LIE, WADE, ROGERS, MUIR, RABELLO JR. We shall study here the conceptions of MITSUDA and JADASSOHN.

In the original work of MITSUDA there is the following interpretation of anergy found by him among nodular patients: "The nodular patients have lost their immunity in the struggle against the germ". Trerefore, MITSUDA admits that the anergy to lepromin is a "consequence" of the aggravation of the disease. Generalized natural immunity would be overcome, in the cases, by infection, which would determine, with breaking of resistance, the negative reaction to lepromin.

This hypothesis is in disagreement with the high prognostic value which is attributed to L. T. in our days, since HAYASHI.

Our observations will contribute to the examination of the MITSUDA hypothesis. If we admit this hypothesis we must expect that the more advanced the disease, the smaller will be the individuals reacting positively. Therefóre, if we allow 100% of positivity to lepromin among non-bacillary cases, and 0 % in strongly bacillary cases we shall have, for example, 50 % of positive reactions as an average among slightly bacillary patients. Or, again, 100% of reactions progressively weaker, from non-bacillary to strongly bacillary.

Let us see the distribution of these cases according to the degree of bacillary elemination (negative —, weak + and strong ++) (See table III).



Conclusion — There is no difference in reactivity between weak and strong bacillary cases. One cannot accuse a slightly bacillary macular case of having "caused" the almost total anergy, which is seen in the graph. Then, anergy preceeds bacillary leprosy; it is not caused by leprosy. Anergy is already present before any clinical manifestations; the nodular leprosy will not anergize an individual, just as cannot anergize him a simple bacillary macule, which is the majority of our cases. The opposite seems to be the real evolution: in an anergic

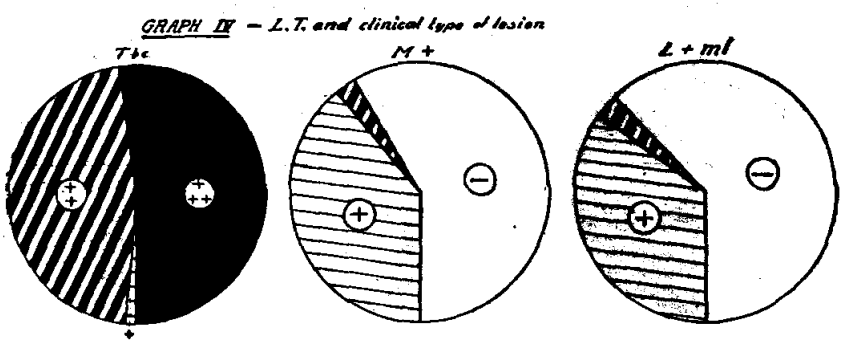
case the infection is revealed, for example, by the macule, sooner or later bacillary, and perhaps even evolutive into leproma.

It remains to be seen if this anergy preceeds immediately the declaration of bacillary leprosy; that is, if a case which is allergic, lepromin-positive, may turn into anergic before the invasion by the bacilli of Hansen. The theories of the JADASSOHN school are all based on the variability of allergy, conditioning clinical eventualities.

But once we come into contradiction with the accepted observations of the prognostic value of L. T. and which assure that an individual who is allergic is one, who is immune to disease at least to the bacillary types.

We are firmly convinced that a positive lepromin reaction is one of a considerable stability. Even the patients debilitated by tropical diseases, open tuberculosis, did not seem to be influenced in any appreciable manner in the reactional capacity to the antigen of leproma. (Table I, Graph I).

The best proof, however, of allergic stability, and which approximates the most of the experimental conditions, is the verification of the evolution of tuberculoid forms. If the anergizations were possible in adults, they should be also in cases of tuberculoid leprosy, recognized allergic; it would be then verified the more or less frequent



transformations, of tuberculoid leprosy into bacillary forms. However this transformation is very rare, doubtful and controverted. Let us see now another division of our cases, not now by degree of bacillary elimination, but by the type of lesion. The table IV refers only to three types: the tuberculoid lesion, the erythematous or erythemato-hypochromic bacillary lesion, and the leproma and macula-leproma.

By the above graph we see there is no difference between the allergic reactivity in No. 2 and No. 3 circles, which is another proof that there is no gradual passage, which we should suppose if allergy was caused by the advance of the disease.

We further see that the passage from a tuberculoid lesion to a simple macule is extremely sharp and does not seem to indicate a gradual passage from one type to another, with slow elimination of allergic reactivity.

Conclusion — The anergy of a bacillary patient is not produced "during" the sickness; as we also see it is not produced "before" the illness, in an individual who has already been allergic.

CONGENITAL ORIGIN OF ANERGY

For what reason is the leper, even slightly bacillary, totally anergic? If the allergic individual, lepromin-positive, does not turn anergic, lepromin-negative, neither before nor after the appearance of the disease, we are forced to admit that the *anergic individual was always so, even from birth,* in spite of the contact with the bacillus, as infection shows. *Leprous anergy is the resultant of congenital incapacity to react with an immuno-allergic condition to the infection by the bacillus of Hansen.*

What are the conditions connected with this incapacity to react to the bacillus, we do not know, and probably will not be known for some time. It is already present at birth and seems to depend on *exclusively hereditary factors.*

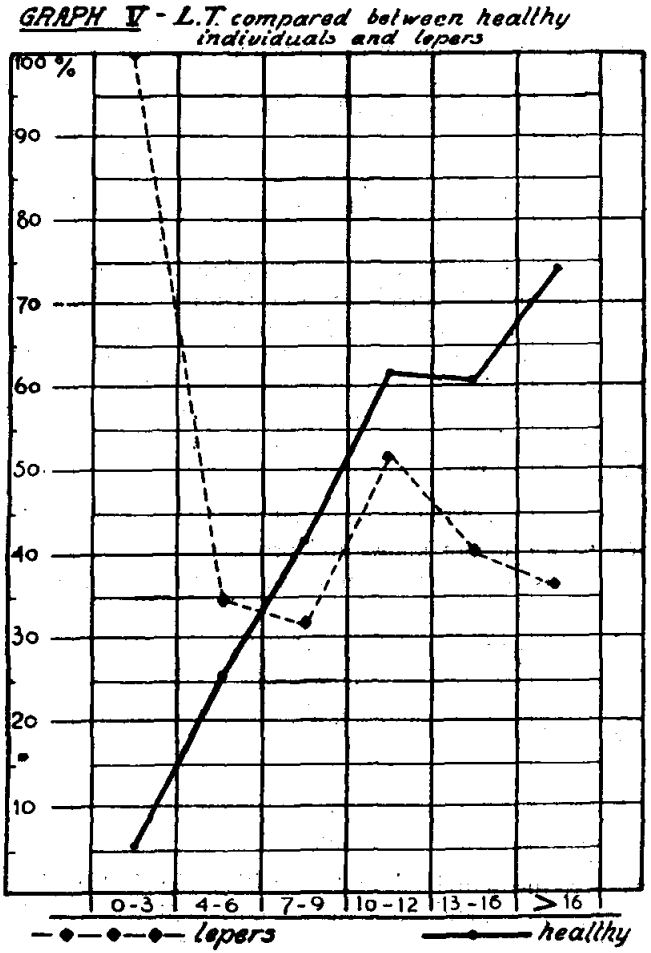
The controverted inheritance of predisposition takes on thus a new objective aspect, which was already suspected by JADASSOHN, when he stated: "there is undoubtedly an individual difference in the capacity of allergization in contact with the bacillus of Hansen."

To avoid repetition we shall give this factor, or the conjunction of factors, which gives capacity of allergization the name of *"natural factor"* abreviated to *Factor* N.

Therefore, the individual *not inheriting the factor N* will not develop allergy in contact with the bacillus, and will *remain always anergic.* Among these anergic cases are the candidates to the bacillary forms of leprosy, once there are accessory factors, as superinfections, organic debilities, bad environment, etc. We will return to this point when we deal on the pathogenesis of clinical forms.

THE QUESTION OF PREDISPOSITION OF INFANCY

When there appeared the first results of lepromin tests in infancy, showing a large number of negative reactions (almost a totality below 3 years of age) the authors valorized this negativity in



order to corroborate the frequency of infantile contamination with leprosy. In fact, they said: negativity to lepromin is equal to receptivity to leprosy.

We think that this wiew must be modified.

Let us look at Graph II. The dark parts of the columns indicate an infection to which the organism answered with allergy. The corresponding white parts *do not indicate receptivity,* but do indicate "absence of infection", and tend to diminish in proportion to the increase in age and probability of infection, exactly as in tuberculosis. The truly receptive cases, or rather those, without the factor N., definitely anergic, are confused in these white parts with the anergy of "non-infection", and in extremely small proportion.

The examination of this table or graph, from another aspect; that is, considering the dark parts as a sign of infection, shows that a majority of infections are acquired in endemic countries before 16 years of age. This does not mean "receptivity", but is simply the evidence that leprosy finds facility in contaminating the new generations as they come up. The adult who comes from non-endemic zones is affected with the same constancy as in infancy, reacting or refusing to react with the immuno-allergy according to his possession of factor N.

As to the greater frequency of "declared" leprosy in infancy, it might be explained by the fact that latent leprosy generally finds sufficient conditions to eclose in the period before adult age.

The graph V shows allergy compared in healthy individuals and lepers of the same age. (Tables II and V).

While the line of positivity goes up rapidly with the age in healthy infants, it is irregular among the sick children due to the existence of allergic cases (tuberculoid in general) and anergic ones, (cases without factor N., in which latent leprosy became external).

TYPE OF DISEASE AND AGE OF INFECTION

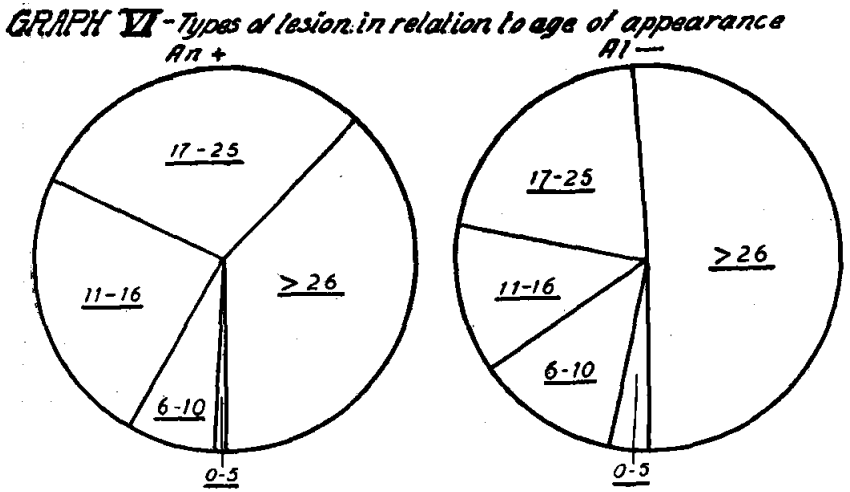
This confusion between "definite" anergy, due to lack of factor N; and "accidental anergy" due to lack of opportunity to infection, was the reason for MUIR's suggestion.

> MUIR observed that as the lepromin test is weak or negative in infancy and strong in adults, we might logically expect the leprous infection of children to tend always to cutaneous bacillary forms, while the adult would give only the forms of resistance, as for example neural negative leprosy. He proposed the confirmation of this fact or its rectification.

This would be confirmed if in fact anergy in infancy was a definite anergy, but we have seen that this is not the case. If a

child inherits factor N. which is generally the case, and sooner or later has contact with leprosy, it will develop allergy, remaining totally immune, or giving "allergic forms" of the disease, tuberculoid, etc. On the contrary, in the adult with "definite" anergy, latent leprosy acquired in infancy may exteriorize it self by any motive, assuming the characteristics of bacillary leprosy.

Our cases may serve as a demonstration. On one side we place the resistant forms to leprosy (tuberculoid and Boeck's sarcoid type) and on the other side the more severe ones (lepromatous, macula-leproma), investigating in each group the approximate age, in which the initial lesion appeared. (Table VI).



We see that the older the age, the more frequent were the allergic types of lesions that appeared but they exist equally in infancy (14,9% below 10 yars). The bacillary lesions increased in the same manner, even if less apparent, that above 26 years such bacillary lesions are shown in 27.4 % of the cases (against 50.7 % allergic). In infancy below 10 years we have, however, 8.1% of bacillary forms against 14.9% of allergic forms.

STUDY OF NATURAL FACTOR N

The factor N guarantees allergy and immunity. Any condition which is seen to be related to the presence of this factor will

have extraordinary reach in the study of leprosy. At present we content ourselves with admitting its congenity and heredity.

We will, nevertheless, attempt to correlate factor N with some data of our cases.

AGE

There is no correlation between factor N and age. The common anergy of infancy is not derived from lack of factor N but from lack of infection. We have already established the distinction between these two types of anergy.

COLOR

Nearly all our cases belong to the white race. It not possible to make a statistical study comparing such diverse totals. We will say only that in 9 cases of colored patients we found 3 positive reactions (2 tuberculoids and 1 pre-tuberculoid). In general lines it seems that factor N has no relation to race.

SEX

The division of cases into sexes has been made separately.

1st. — among lepers in general.

2nd. — among lepers between 0 to 9, and 10 to 15 yars (to eliminate errors due to difference of ages).

3rd. — among healthy children of lepers.

4th. — among tuberculous, non-lepers.

From this, table VII resulted.

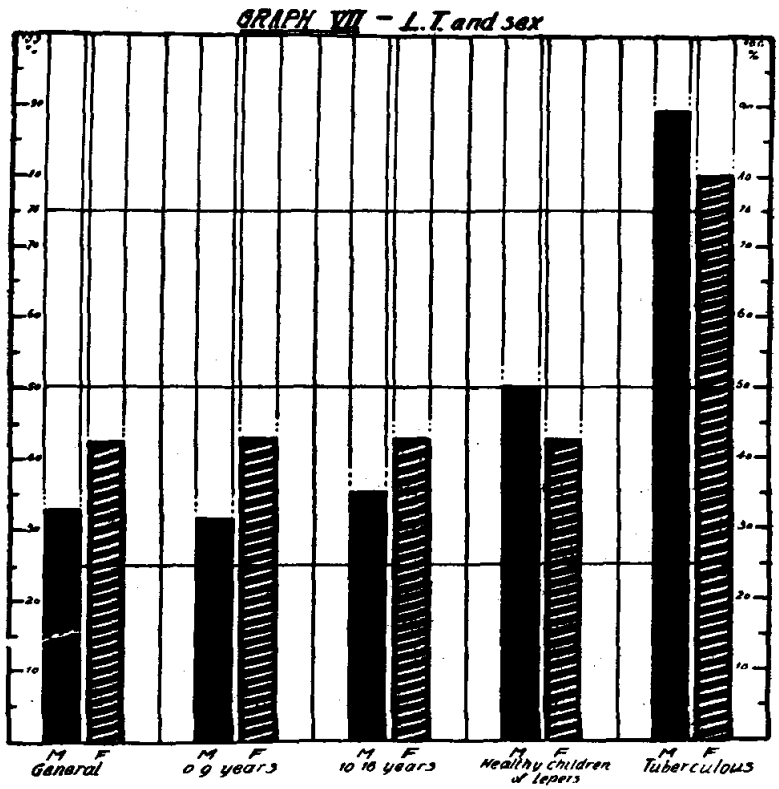
Conclusion — There is no difference in sex as to conditions of resistance and immunity to leprous infection.

NATIONALITY

Brazil is a country of immigration, continually receiving immigrants from European countries. The influx of these elements from regions where leprosy does not assume an endemic character has been pointed out as one of the causes of increase of intensity of leprous foci in Brazil, for lack of an atavic immunity which the

native of the country possesses to a high degree. The same is said of descendants of these immigrants, though born in this country.

The discrimination of our cases by nationality presents thus a particular interest. On one side were considered all individuals born in European countries, on the other those born in Brazil (a large majority in the State of São Paulo). Among these was made a new subdivision according to the nationality of the parents, if Brazilians, foreigners or Brazilian and foreigner. This division is:

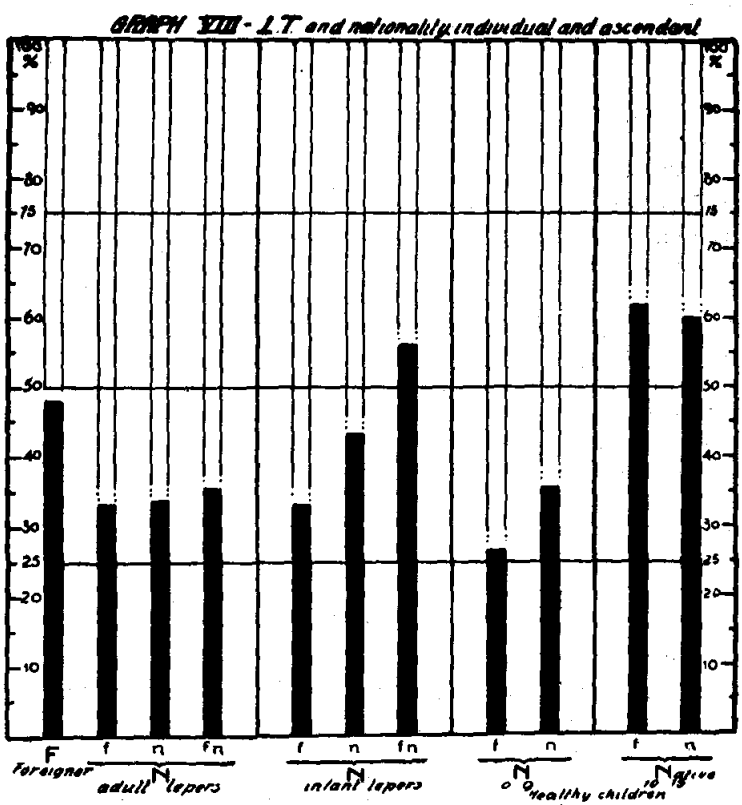


1st. — among adult lepers;

2nd. — among minor lepers, under 15 years.

We have added a subdivision between healthy minors, children of lepers. All being Brazilians we considered only the ascendency according to family name (Table VIII).

Conclusion — There is no difference worth noting as to allergic reactivity between natives and foreigners, or, considering natives, between the descendants of the one or the other. The elevation of the column of descendants of marriage of national with foreigner is paradoxical, but refers to percentages based on relatively small quantities, and so liable to error.



DEBILITATING DISEASES AND IMMUNITY TO LEPROSY

Debilitating diseases are generally accused of preparing the field for the breaking out of leprosy or the unfavorable evolution of it this action operating, according to some authors, as a perturbating influence on the immunitary equilibrium, this should be reflected clearly in the allergic response to lepromin. Ideal conditions of experimen-

tation would be the performance of L. T. in an individual securely allergic as soon as this individual suffered any depression whatever in health. In the impossibility of presenting observations of this type we must limit ourselves to showing the reaction in adults, non-lepers, and suffering various affections, preferably debilitating ones.

Our observations: These refer to 19 cases, 1 being lupus vulgaris (reaction +++), 3 with malaria (all ++), 8 with leishmaniosis (1 +, 2 ++, 5 +++). More illustrative are the 7 other cases, all of "blastomycosis", a disease of Brazil produced by the "Paracoccidioides", highly consumptive and of a fatal prognosis in a relatively short time. Of these cases only once there was a weak positive reaction (+). In the others it was frankly nodular, 3 times ++ and 3 times +++. The sedimentation index of these 3 cases +++, was 87, 96 and 107, in one hour, by Westergreen's technique.

We publish apart (51) the seventy results of reaction to lepromin in open cases of pulmonary tuberculosis, hospitalized. We found 3 negatives reactions and 7 weak reactions. In the 60 remaining there formed typical nodules, sometimes ulcerated, 27 ++ and 33 +++ (Table 1). Though lacking a greater number of cases and sufficient control with totally healthy individuals, we are led to believe that the allergy to lepromin is resistant to debilities and organic modifications produced by various intercurrent diseases, whose role in the breaking out and development of leprosy seems should be reserved to anergic cases.

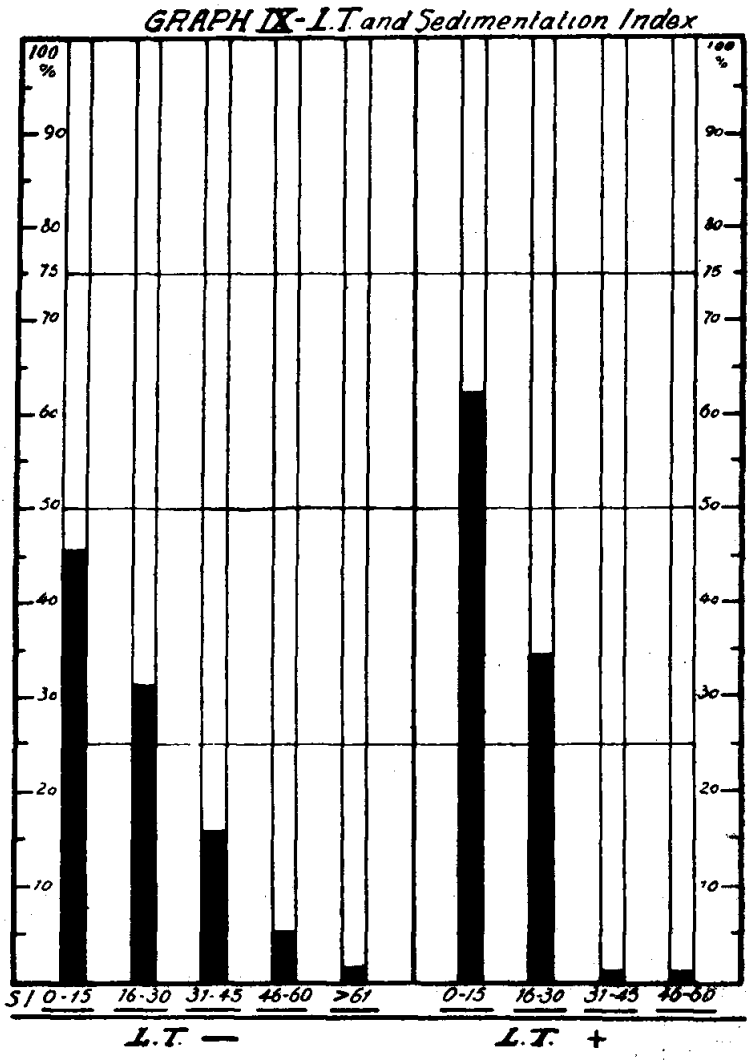
VELOCITY OF SEDIMENTATION OF RED CELLS AND REACTION TO LEPROMIN

In 448 of our cases hospitalized in the Sanatorio "Padre Bento", we could accompany the sedimentation index of the hematias, which in that Sanatorium is taken weekly in the routine of the control of treatment, according to the technique and reading of MUIR. For each patient there were made 4 readings around the L. T. performance date.

The table IX will show S. I. in allergic and anergic cases to lepromin. The average readings above 31 are observed almost solely in the anergic group, and this is logical, for, in this group, are the most bacillary cases, and the nodular forms.

We are interested especially in the high percentage of readings below 30 (77.3 % of the total), and better yet below 15 (45.7 % of the total) among allergic cases. The low S. I. is considered an index of a good organic disposition and humoral equilibrium. Neither of the two necessitates, therefore, alteration for the case becoming anergic to lepromin.

We see thus, that the positive lepromin reactions occur in even greatly debilitated individuals, non lepers, and that the negative reactions may occur in cases of leprosy, bacillary or not, even when the bodily vigor is intact.



The leprous anergy does not seem to be correlated closely with the state of weakness of general health.

EPIDEMIOLOGICAL AND PROPHYLACTICAL CONSEQUENCES

The base of natural resistance to leprosy is the factor N, the essential of which has not yet been demonstrated. On the variations of this factor one can build up theories which refer to the diffusion of leprosy among diverse peoples and at different periods of history.

The paralization of leprosy in Europe, for example, should be due to isolation, progressive elimination, and sterilization of cases without the factor N, and who were victims of evolutive leprosy, as well as to the lack of a favorable environment to its diffusion. Thus, the present population of Europe would be composed, in our opinion, of a majority of "resistant" individuals, and possessing the factor N. In contact with leprosy the immuno-allergic condition is cleary developed. There is, however, a minority without this factor, whose ascendants were also anergic but that for whatever motive were neither infected nor sterilized. These cases remain healthy whilst they are not in contact with leprosy. If contact occurs, there is infection, without development of immunity. The infection remains latent and awaits accidental causes for breaking out.

RECEPTIVITY OF FOREIGNERS

It is possible that these accidental causes of eclosion of latent leprosy in anergic individuals may be more frequent among foreigners, less adapted to the climate and environment than the native, justifying thus greater incidence of "declared" leprosy among immigrants.

LEPROSY IS A HIGHLY CONTAGIOUS, BUT A HIGHLY IMMUNIZATING DISEASE

The contagion of leprosy is very much more frequent than is generally admitted. As with tuberculosis, the infection is general to the population, where it is not recognizable except by the positivity to lepromin. The clinically declared cases are due to unknown disturbances of the biological equilibrium, in which probably debilities and superinfections have their part, and may be bacillary or persistently negative, in relation to allergic reactivity.

The guarantee of the human organism against the infection of leprosy is assured by a ready and efficient immunitary response, which will restrict the leprosy within the reduced limits of its known present incidence.

INTIMATE AND PROLONGED CONTACT

The axiom of necessity of intimate and prolonged contact with a leper for infection must be re-checked. The sporadic cases of leprosy which do not present the usual existence of contact with open cases, can be explained in that way. Such prolonged contact, however, seems to have an important role as the cause of superinfections, acting principally on anergic cases.

INFECTION IN ENDEMIC COUNTRIES OCCURS BY PREFERENCE IN INFANCY

We have already seen, by the graphs, that infection is made in 70 % of the cases before 16 years of age.

> These data refer to children of lepers. That the same observation can be made in general is proved by the works of CHIYUTO and of MUIR, who observed a totality of positive reactions in healthy children above 3 years of age, without known contact with leprosy.

THERE IS NO GREATER SUSCEPTIBILITY IN INFANCY

This infection of children does not, however, represent any biological susceptibility whatsoever, and depends only on the accidental fact of its being the candidate to contagion, because the adult had been already contaminated in his turn. The adult who did not receive his infection in infancy, as those who come from European countries, are infected and immunized with the same facility as infants.

HEREDITARY PREDISPOSITION

If the infection is so generalized how might we explain the greater incidence among "contacts", compared with sporadic cases? There are three plausible reasons, which frequently combine:

1st. — Consanguinity, with probability of inheritance of predisposition; that is, absence of factor N, base of immunity.

2nd. — Superinfections, straining the weakened defences in anergic cases (acting also in allergic cases tuberculoid lesions).

3rd. — Identity of social environment.

THE BACILLUS OF HANSEN IS THE AGENT OF INFECTION

The presence of the bacillus of Hansen in the lepromatous antigen of MITSUDA-HAYASHI was considered, by the experiments of filtration, as essential for the manifestation of positive reaction in allergic cases: it is therefore, equally the cause of this allergy and of the infection. It does not matter that it could be proved some other day that there is another cause for the allergic reaction together with the bacillus and eliminated with it by filtration: such other cause existing beside the bacillus in the antigen, will exist also in the living leproma and in the nasal mucosa of the bacillary case. If the bacillus is not the cause of infection, it is at least an indicator of the presence of the infecting agent, and this is sufficient for prophylactic guidance.

THE SUCCESS OF PROPHYLAXYS IN LEPROSY

The bacillary case, the "open case", is the case which should be isolated. If we can imagine that in a determined region we could isolate all the bacillary patients in one day we must admit that new cases would continue to appear for a certain time. In effect the whole population of a region is constituted in reality of individuals already infected, with latent leprosy. The immune cases are protected. Among the anergic cases, however, for different motives, leprosy may externize itself and assume bacillary characteristics, and this at a very near or more remote period of their lives.

The following generation, free from all infectious cases, already isolated or dead, would be free from contagion and would return to the conditions of virgin people to leprosy. The curve of incidence, so long a plateau, even after isolation of all infectious cases, would tend to drop, by virtue of absence of superinfections and would reach zero in another generation.

THE SO-CALLED PERIOD OF INCUBATION

Another subject for verification would be the "time of incubation". Lacking experimentation with animals or humans, this period of time was determined by clinical-epidemiological observation, giving as initial and final terms those moments when the individual had contact with a known case of leprosy and the moment of eclosion of clinical or bacteriological symptoms. However, both

of these terms are, in our opinion, subjects of criticism. The real moment of infection, almost always in man, is before the supposed moment, and may date from infancy, in endemic countries, in spite of the non-existence of open cases of leprosy in the immediate environment of the individual. The final term, the eclosion, clinically or bacteriologically manifested, is dependant on disturbances which do not represent in any manner the true term of a "biological" incubation, Thus, for example, if the individual is infected without immunization, leprosy may declare itself in the first year or 2 or 3 yars later, by any intercurrence, this not signifying "variations" of the period of incubation. The proper expression would be *"period of latency"*.

The observations of cases of leprosy in children under one year, the existence of strong lepromin reactions reactions in such cases, since of the tuberculoid form, as it was observed by SOUZA CAMPOS (40), leads us to believe that the infective and immunitary "movements" of leprosy are not so dilated as it is generally supposed. In these children we would admit that the primary infection, the allergization and the eclosion of tuberculoid manifestation are a process of months only.

LEPRA REACTION AND LEPROMIN TEST

It has been already attempted to explain lepra reaction as a phenomenon of immunitary nature, representing the effort of the organism against the infecting agent. The eruptive nodule would be thus a real endogenic lepromin reaction, provoked by the resistance of the skin to the bacillus thrown into circulation.

We will not enter into the discussion of lepra reaction; we merely mention that erythema nodosum is a syndrome with occurs in numerous infectious disuses where sepsis does not occur as explanation of the phenomenon. Besides this, the interval wich goes from the administration of a provocative, as iodine, to the appearance of the eruptive nodule is much shorter than necessary for the formation of a real positive lepromin reaction.

We shall mention finaly that out of our cases, 220 patients were in L. R. the moment of the test or had already suffered it. The distribution of the cases according to their allergic reaction to lepromin provided us the table XI, the examination of which will show that a lepra reaction can not be considered a process of "specific" defense against leprosy. It is possible that we deal with a phenomenon wich

is allergic, or better parallergic, but the relation of this allergy to the true specific allergy to lepromin cannot be demonstrated, at least by our present methods of research.

FERNANDEZ observed 11,28% of positive reactions in cases of L. R. and 53,93% in cases which never had L. R. We suppose that the small percentage of positive L. T. in the L. R. could be still further reduced if they had been considered negatives under 0,5 cm.

ALLERGY AND PATHOGENESIS OF LEPROSY

The relations of cutaneous tuberculosis to allergy, well studied, from the clinical as well as from the experimental point of view, principally by JADASSOHN's school revealed general biological facts which were applied immediately to other infections. We have already seen that JADASSOHN foresaw their application to the special pathology of leprosy.

Let us note rapidly the experiments of LEWANDOWSKY, which are the homatogenous reproduction of Koch's phenomenon.

Injecting the bacillus of Koch into the heart of a normal Indian pig we obtain in two weeks a papulo-squamouss eruption which does not delay in transforming it self into a diffuse dermatitis. Histopathology: diffuse infiltrations of polymorpho-nuclear leucocytes. No giant cells. Numerous bacilli in every field.

The reinfection of this animal by hematogenous way gives in 24 hours a follicular tumefaction with erythema in the skin of the abdomen, in 2 days a diffuse desquamation, in 10-14 days red papules with clear centers with strongly adherent scales. Histopathology: clearly circumscribed infiltrations, with many epithelioid and giant cells. Caseosis and necrosis around the arteries. Bacilli, very rare.

«Whenever bacilli grow unhindered in the body the organism responds with non-specific inflammation. If, on the contrary, the antibodies desintegrate the bacilli, reducing them to bacillary albumen, there is produced tubercular or tuberculoid structure» (Law of LEWANDOWSKY–JADASSOHN).

A Tuberculoid lesion is therefore a lesion of resistance to re-infection or superinfection, resistance coincident with the allergic condition produced by the primary infection.

PATHOGENESIS OF FORMS OF LEPROSY

We admit that the contamination by leprosy in endemic environments is as prevalent as that by tuberculosis, and that this contamination is revealed only, at least till today, by the positivity of the intradermic reactions to lepromin. By analogy with the phenomena of KOCH and LEWANDOWSKY, we shall admit that a re or superinfection of these individuals already infected and allergic will produce a tuberculoid lesion. *Tuberculoid leprosy is the leprosy of re or superinfection of an allergic individual.* This reinfection may be exogenous, and determine the isolated tuberculoid lesions at the level of the skin; the propagation through nerve branches, always encountering an allergic resistance, will continue to produce the manifestations of the tuberculoid type in the nerves, sometimes with caseosis. They can also be endogenic, by hematogenic or lymphogenic route, and determine the disseminated lesions of tuberculoid structure, and the so-called "tuberculoid lepra reaction" recently described by WADE (41), SCHUJMAN (42), FERNANDEZ (34).

> FERNANDEZ referred recently to have found usually the bacilli of Hansen in the recent lesions of «tuberculoid lepra reaction». In agreement with RABELLO's JR. opinion (43), we see that these «tuberculoid reactions» resemble thus very much an endogenic, hematogenic, lepromin-reaction.

A banal and bacillary inflammation would be, on the contrary, an infection of a virgin case of leprosy; and this is the probable structure of the supposed primary lesion. The allergy developed at the cost of this has as immediate effect a "cure" of these same primary lesion and general immunization of the organism, which passes now to react with a tuberculoid lesion to new infections. But the first infection does not always give origin to allergy, because, as we have seen above, there seems to lack in certain individuals a basic element for the formation of the immuno-allergic condition, and which we denominate the factor N. The primary focal lesion will remain latent until the causes usually given as favouring the breaking out of leprosy (exalted bacillary virulence, debility, mal-nutrition, fatigue), and the bacillary overcharges, determine the objective manifestations to the clinician or to the bacteriologist.

Thus we have by endogenic super-infections by the hematic or lymphatic routes, the *erythematous and erytheznato-dyschromic bacillary macules, the diffuse leprosy* (which is a general dissemination of bacilli through teguments without the formation of identifiable lesions), the *exhantenuvtic-edematous and urticariform macules, the*

brownish - yellowish, fulvous macules (macula-leproma) and the *lepromas.*

Our cases will illustrate what we have just delineated. We will not divide them by forms of disease in accordance with this or that classification, but by "type" of lesion, on which there cannot be theoretical discussions. In case of concomitance of several types of lesions, the case was classified by the most severe lesion, the most bacillary. Below are the types into which we have distributed all the cases studied, and of which we will not make the systematic, but give only some identifiying characteristics.

1. — Leproma (of any type); L.

2. — Macula-leproma, Macules of yellow to chestnut tones, generally infiltrated, lepromas "en nappe"); Ml.

3. — Diffuse leprosy. Leprosy of the skin without formation of visible lesions. Even erythema may not be evident, and diagnosis is made by finding habitually bacilli in scattered points of the tegument. Ed;

4. — Bacillary erythematous macule. Infiltrated or not, with in general diffuse margins, sometimes figurated, of uniform color or with tendency to form rings. Me +;

5. — Bacillary hypochromic macule. Non-pigmented macules with more or less visible back-ground of erythema. Bacilli, present Mh+;

6. — Edematous urtificariform macule, of in general rapid appearance, Bacilli, present Mu +;

7. — Same without bacilli. Mu --;

8. — Erythematous macule without bacilli. As in 4 without bacilli. Me -- ;

9. — Hypochromic macule without bacilli. As in 5, without bacilli Mh -- ;

10.— Involuted macule, which nature and characteristics, present or anterior, are not possible of determination. Faded. Mi;

11. — Clinically tuberculoid macule. Tbc. cl.;

12. — Tuberculoid macule with histological confirmation (lupoid type, pure tuberculoid) Tbc. hist.;

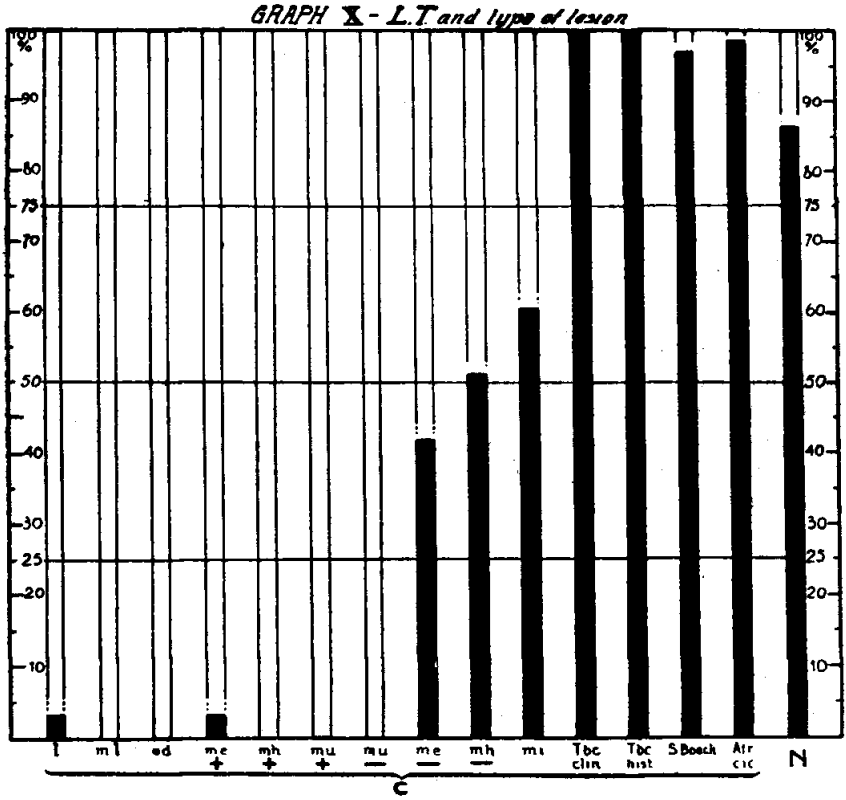
13. — Tuberculoid macule with histological confirmation (type sarcoid of Boeck) Tbc. S. B.;

14. — Atrophic macule, spontaneously scarred. M. atr. cic.;

15. **— Lesions in nerve trunks** (amyotrophia, thickening) without apparent lesions nor bacilli on the skin. N.

The division of these types of leprosy by lepromin reactivity in accordance with HAYASHI's method of reading, provides us the Table X.

Examination of this table shows at once an interesting fact. The types classified from 1 to 7 are represented among the ++ and +++ reactions, only in very small quantities; they are anergic cases. This signifies that the reaction + (under 0,5 cm.) behaves more or less like the negative reaction, in regard to the frequency among anergic and bacillary cases and does not seem to signify, at least at present, appreciable immunitary defense. Between the reaction + and ++ we observe



an evident barrier. This barrier becomes more evident when we observe the inverse phenomenon, in the types 11 to 14. The reactions are distributed more or less equally in ++ and +++, falling practically to zero in the column of weak reactions (+).

This is the motive for giving as "anergic" the reactions +, which were tabulated as negative reactions, and "allergic" the reactions ++ and +++, without destinction between them. This division was adopted in several graphs of this work.

This graph justifies the considerations which we made in regard to pathogenesis of the lesions of leprosy. There are, however, cases which prove that it is not only allergy that governs the clinical modality of all cases of leprosy.

ALLERGY DOES NOT ENTIRELY GOVERN THE CLINICAL MANIFESTATIONS OF LEPROSY

1st. — There is among the healthy population of endemic zones a proportion, though small, of individuals who, in spite of constant contact with lepers, and probable infection, do not succeed in developing allergy, because of hereditary factors, in our opinion. In spite of this, we cannot say that these individuals will all become declared lepers. There is evidently a natural non-allergic resistance, or such conditions of health, vitality and resistance, as to hinder the efflorescence of the disease.

2nd. — The examination of columns 1 to 7 of the graph X will show that between equally anergic cases, one may remain in a state of simple bacillary macule, while another may reach the state of advanced nodular leprosy. In column 10 (involuted macules) there are cases of anergy as well. The same general non-allergic resistance, enters here into action, paralysing or rendering undeveloped such clinical manifestations.

3rd. — The observation of columns 12 to 14 will show that a pure tuberculoid case of leprosy, one of the Boeck's sarcoid type and one with atrophied macules are not distinguished from one another by variations in allergy.

4th. — The infection of the nerves does not depend on allergy. Some authors consider the neural form of leprosy to be eminently allergic because the bacilli, encountering an allergic resistance at the skin, tend to take shelter in the nerves. This interpretation does not explain:

A. The numerous anergic cases, lepromatous or not, with flagrant infection of the nerves.

B. The numerous allergic cases, tuberculoid or not, without invasion of the nerve trunks.

This part deserves a chapter by itself.

INVASION OF THE NERVES

The clinical examination of our cases revealed the existence of characteristic lesions of the nerves or of the neurotrophic type (amyotrophies, thickening of nerves, perforating ulcer) in 221 patients, which represents 20,7% of the total studied. Of these, 99 were among the allergic and 122 among the anergic, in the proportion of 24.9% and 18.3% respectively. There is, therefore, a high percentage of anergic cases in which the infection attacked the nerves, a proportion which represents 3/4 of the proportion of nerve infection among the allergic cases and does not appear to indicate that there is a dominant question of allergy in the formation of the neural complications. The high allergic reactivity in pure neural leprosy is explained by the frequent disappearance of the skin lesions in allergic cases becoming uncharacteristic or unrecognizable; the disturbances produced by the nerve lesion, though inactive are, however, conserved.

PATHOLOGY OF PURE NEURAL LEPROSY

Leprous immunity concerns not only the skin but also the nerves. Cutaneous lesion of an allergic case is benign and tends to tuberculoid and atrophic lesions. If for any motive there is infection of the nerves, allergy manifests itself in the same form, with tuberculoid structure, caseous degeneration, or simple infiltration tending to cicatricial fibrosis.

The consequences of the fight against the germ are, however, unequal. While at the level of the skin the destruction of the germ may proceed in unobjective manners, in the case of the nerves it is difficult not to feel the effects of the destruction or the compression of the fibres, even when there is an organic victory against the infectious agent.

This is the motive of the pure neural allergic forms.

In anergic cases, on the other hand, the infection attaining the nerves by the same motive (therefore non-allergic) encounters the same anergy which it encountered at the surface of the skin and a lesion results, as in the skin, of bacillary type, with leprous infiltration, with Virchow cells, and secondary compression of the nerves, with its consequences. It is possible to admit that in a determined case, though anergic, the cutaneous manifestations reduce to the most difficult recognizable state for the reason of other non-allergic conditions of the determination of the clinical forms, as we have seen above (bacillary overcharges, natural resistance, environment etc.,). Clinically the case

presents itself as a pure form of neural leprosy, without lesions or bacilli in the skin. The anergy, indicated by the antigen of MITSUDA-HAYASHI, will reveal the true condition of the patient, demonstrating the bacillary infiltrative neuritis.

Therefore pure neural leprosy can occur just as much in allergic cases (the great majority) as in anergic ones.

PATHOGENESIS OF NON-BACILLARY MACULAR LEPROSY

The graph X of the relations between the types of leprous lesions and the degree of allergy, reveals that between the allergic group constituted by tuberculoid macules, sarcoids and scars, and the anergic one including the lepromas, bacillary macules, diffuse leprosy, etc. there is a group of lesions which presents a certain allergic indifference: there are the simple erythematous or erythemato-dyschromic, non-bacillary macules. The existence of many identical clinical types in anergic and allergic cases makes one suspect immediately that such types represent an initial aspect of lesions, the evolution and the latter aspect of which will depend, in great measure, upon the reactive condition of cutaneous allergy.

In case of persistent anergy, the macule infiltrates, becomes bacteriologically positive, lepromatous, once there appears the contributing and unknown factors already cited (bacillary overcharges, fatigue, illness, etc.). In case of allergy these macules become definitely abortive, assumming either the cicatricial aspect or not, or presenting the clinical and histological characteristic of pure tuberculoid lesions, or the sarcoid of Boeck type, as we have observed.

ALLERGIC REACTIVITY AND HISTOLOGY

The evolution we have just outlined has its histological representation.

The tuberculoid structure has been recognized, since LEWANDOWSKY, as the histological representation of allergy. All tuberculoid lesions of leprosy occur in allergic cases. The common bacillary lesion or the frank lepromatous structure exists only in anergic cases. The apparent exceptions of these rules will be studied apart. (see "some doubts")

It now remains to investigate the reciprocal, that is, to see whether in every allergic case the lesion is tuberculoid, or whether in every anergic case the lesion is banal or bacillary.

As it would be expected, in view of the initial evolution outlined above, this is not the case.

If we study the histology of two absolutely equal clinically and bacteriologically macules, (hypochromic negative initial macules) one from an allergic case and the other from an anergic one, we will observe in the latter, banal infiltrations without any characteristics, whilst in the former we will perceive a tendency to follicular disposition of the infiltrations, sometimes even a frank pre-tuberculoid structure.

Often, however, there is no possible distinction between the histological picture of an allergic case and an anergic one. The histological identily accompanies the clinical. It is the *neutral lesion* from which the pre-tuberculoid and tuberculoid lesions will originate if there is allergy; bacillary lesions and leproma if anergy.

This study of histological evolution in function of allergy was but recently begun by us and we cannot present definite results yet. It is an open field for investigations.

SOME DOUBTS

The study of the reactions lo lepromin is recent and its technical preparation, application, time for reading and interpretation of results, are not fixed with uniformity, rendering comparison difficult between the different authors. Variable are also the methods of classification of the clinical forms, the appreciation of evolution, the interpretation of the histological pictures, which together complicate the study of the question still further. Therefore, there are sufficient motives for the appearance of doubtful points.

1st. — The existing literature on the coexistence of bacillary lesions and tuberculoid structures appears to be a contradiction to the conclusions of studies like ours, where the tuberculoid structure is considered as a form of high allergy. It is necessary to note in the first place that those cases are extremely rare, and that in them the allergic reactivity was not investigated; any explanation of these rare cases would have to be based on their lepromin reaction, present and future, in their evolution, summing up, in their biological sense.

For example: Among our cases there are two whose lesions reveal a sarcoid structure and which, in spite of this, react slightly to lepromin. We cannot yet say if these sarcoid lesions are the histological aspect of weak and useless resistance of an organism almost anergic which will soon succumb to the bacillary invasions *("passage"* to the lepromatous form, and, at a determined moment "coexistence" of lesions of both types"), or if they represent the beginning

of resistance for belated appearance of allergic reactivity (infection and invasion on the ante-allergic period?) or even still a small allergy, but "sufficient" for definite resistance.

In cases of real tuberculoid leprosy, passing to the bacillary and anergic form, there must be documents with complete studies of reactivity to lepromin.

2nd. — The technique of application and reading of lepromin reactions could be made uniform, with a conventional base. But the uniformization of the antigens would be difficult because it would depend upon the bacillary content, which is practically impossible to determine because of the more or less enmeshing of the bacilli in globi. Perhaps one could make the titration of the antigen by the provoked reaction in an individual with previous known allergic reactivity.

We may note however that such differences, generally, slightly marked, of antigens prepared accordingly to a certain technique, would not have great inconvenience in practice, due to the very similar response of the organism.

Thus, we have rarely secured a positive reaction with antigens purposely concentrated in individuals with bacillary leprosy, already recognized anergic by negative results to the standard antigens. On the other hand, a highly allergic individual, continues generally to react strongly to dilutions of the standard antigens. The photograph 2 shows reactions in a case of sarcoid leprosy with the standard antigen and dilutions of 1: 8, and 1:15. Even with the last we obtained a reaction of 10 mm. In a case of tuberculoid leprosy with particularly intense lepromin reaction, a new test with dilution of 1:10, gave the ulcerous lesion as a result, as shown in photograph 3.

The question of uniformization of the antigen is brought out for the need of a solution, to cases of intermediary grades of allergy, in which the small differences of concentrations of the antigen could cause erroneous classifications of a determined case. We have the impression that in the eleven cases of table X of positive reactions (++) among bacillary patients, the reaction could be reduced to + from using an antigen a little more diluted, without altering the conjunct.

While this question is not solved, cases which react around the borderline size from anergy to allergy (about 5 mm) should be estimated with great prudence.

3rd. — We spoke a little while ago about the ante-allergic period, which is the interval between infection and the appearance of allergy. We have no idea of the duration of this period in leprosy,

nor of its pathological importance in this disease. We can possibly admit the following: a child becomes infected, and the bacillus of Hansen encounters such conditions in this organism that the infection shows itself rapidly by the usual clinical or bacteriological symptoms, in less time than necessary to the constitution of an allergic state. The appearance, after, of the allergic state should bring modifications in the aspect of the lesions (scaring or passing to a tuberculoid lesion of macules already bacillary, perhaps even those observed cases of acute fusions of lepromas (?)).

LEPROMIN REACTION AND CLASSIFICATION OF CLINICAL FORMS

All authors who have studied the reaction to lepromin in leprosy, have related their results with various clinical forms of the habitual classifications.

> Reviewing the bibliography, we can say that the lepromin reactions were found positive in a large percentage of the pure neural, macular, and incipient forms and negative in the bacillary, cutaneous, nodular, mixed ones. Such were, for example, the results of MUIR, HASHIMOTO, KOMATSU, NITTO (44), MUNEUCHI, DUBOIS, DEGOTTE (29), BHATTACHERJI (45), RAO (46), BONCINELLI, STEIN and STEPERIN, MONTANÉS, SOUZA ARAUJO (47), NEGRO, AOKI (48), CUMMINGS-LYLE (49), TISSEUIL, (40), FERNANDEZ, and our own (25).

Our first proposal would be to study, as the above authors and ourselves did, the results of the experiments with lepromin in the various clinical forms of the disease, and search, for the stable factor, which would be a clinical classification of cases, the fluctuations of this variable factor represented by allergic tests.

However, this factor, which we have desired to suppose fixed, constitutes, as we know, exactly one of the most discussed problems of leprology. The classifications diverge from author to author and often on essential points, causing great difficulty in the study of comparison and bibliographic research. Still further, even if adopting a determined classification, it will not always be easy to include all the studied cases in it, even with the aid of the laboratory.

On the other hand, the constant handling of experiments with lepromin in patients of leprosy since 1933, and continued observation of these cases from the point of view of clinical evolution, histology and bacteriology, have made the value of the L. T. so im-

portant to us that we have come to mentally classify these patients according to their allergic reactivity. We have thus gone, personally, contrary to the initial proposition, tending to consider as a fixed factor the allergic reactivity, the clinical manifestations varying in accordance with it.

A primary division into the groups of *Allergic* and *Ancrgic* could not be, however, the basic classification of the forms of leprosy, since we would have to place side by side in the same allergic group a case of tuberculoid leprosy of the skin, and another of pure neural leprosy with mutilations, and, still further, a healthy adult.

Biologically there is nothing extraordinary in this fact, since there would remain together only those non-bacillary forms of resistance; however, it seems to us an exaggeration to force in any way a classification which must be clinical at first. We suppose we should thus conserve the binary division into cutaneous leprosy and neural leprosy, dominantly based on clinical manifestations, adding also mixed leprosy.

Leprosy
- Cutaneous . . C
- Neural . . . N
- Mixed . . . CN

HELP OF ALLERGY

As indispensable and necessary complement for a subdivision of clinical forms, let us now also add the grade of allergic reactivity specified in each case. This does not imply that the lepromin test should be made obligatory in all patients. The nodular cases, lepromatous, those with fulvous macules and the clearly bacillary ones, are all considered at once as anergic. A possible allergic reactivity, exceptional in these cases, would have merely a scientific value, and not classificative. The tuberculoid forms, diagnosed clinically or histologically are evidently classified as allergic cases.

The detailed study of allergic reactivity is necessary only in the macular cases, as this is the critical point of the classifications. We pretend having demonstrated that the group of erythematous and erythemato-dyschromic macules occur equally with anergy as with allergy, and that this reactivity influences greatly the evolution of the lesion and the prognosis of the case. The study of this reactivity is undoubtedly more important than the research of bacilli, very aleatory and variable in these cases, and therefore not serving as a basis for classification. Still further, the allergic re-

activity always dominates the bacillary impregnation; an allergic case is generally negative to bacterioscopy, and when positive, we can be sure that we are dealing with rare bacilli, energetically fought and candidates to the destruction (bacilli of tuberculoid lesions, etc.). Inversely, an anergic case is generally bacillary; and if not, it is a favorable soil for the spread of bacilli, which will not delay in appearing under the influence of various factors (bacillary overcharges, fatigue, debility, etc.). The bacterioscopical negativity, present in these anergic cases, could be still due to hidden germs in internal tissues.

Therefore, as long as the clinical and bacterioscopical manifestations are not *clearly* indicative of a reactive-allergic state, the research of this state will be necessary with a L. T.

CUTANEOUS LEPROSY

Cutaneous leprosy includes all cases presenting specific manifestations at the surface of the skin, characterized by the present methods of research, clinical, histological and bacteriological. Thus the term, "cutaneous leprosy" will not give the idea of gravity such as obtained by the reading of the existing classifications. It merely expresses the aspect of leprosy from the point of view of dermatology, and includes as well the strongly bacillary lesions of the leproma type, as the simple macules, whether bacillary or not, as well as the lesions practically uninhabited of the tuberculoid type.

These various types of cutaneous lesions, their histological structure and bacillary content, are dependant on the allergic reactivity of the cutaneous tissues.

The disturbances of sensibility at the surface of these lesions are considered as the consequence of leprous processes at the local terminations of the nerves, and do not influence the classification. In the same way the manifestations of initial neuritis, which are not characterized in any perfect manner (slight nerve thickenings, doubtful amyotrophies) would not take out such cases of the cutaneous form.

SUBDIVISION

The so-called macular form is included in the cutaneous. The term "macule", is, however, too much extensive and needs discrimination, because there are macular lesions which represent the degree next to leproma, macular lesions, of extreme resistance, as the atropho-cicatricial and tuberculoid, and the intermediate forms

(erythemato-dyschromic, etc.). The "macular" form expresses nothing from the point of view of biology, because it represents the more widely separated allergic conditions.

Therefore, we, have, in the cutaneous form: the type of "leproma", which needs no description, the "macula leproma" type (ml) which is the fulvous macule, strongly bacillary, prelepromatous; and the several types of the various macules, "erythematous macule" (me), "hypochromic macule" (mh) ; "diffuse leprosy" (ed).

The type *me* includes edematous macules which we described above. Diffuse leprosy has no appreciable clinical characteristics and identification is made by searching for the bacilli on various points of the skin, healthy in appearance. The lepromin test revealing anergy in cases suspected of leprosy and without visible lesions often gives trace of a case of diffuse leprosy, which bacterioscopic examination should confirm, even if one has to persist in them.

In case of erythematous and erythemato-dyschromic macules, if bacilli are found, the anergic condition is "ipso facto" proved, and the lepromin test may figure as complement. In case of bacillary negativity (or an examination not being, possible) a L. T. is imperative, because negative macules of this clinical types occur both in the allergic cases as in the anergic ones (table X). We already know that sometimes the histological examination, presenting a slightly different picture in the one or the other, can be helpful. One cannot always have resource, however, to biopsy, which, furthermore, does not give certainty in many cases. The allergic reactivity is the only appreciable difference, and here the study takes on the greatest interest because it is the only index of probable later evolution of the lesion.

The following group within the cutaneous form is that of highly allergic macules: the lepromin test is dispensable for the purpose of classification, since these are the clinical and histological characteristics of tuberculoid lesions (tb) or of spontaneous cicatricial lesions of leprosy (ac).

ABSTRACT

The division of the cutaneous form into sub-types is made directly into "elementary" types (leproma, hypochromic macule, etc.) adding thereto the cutaneous reactivity (al-allergy, an-anergy). If there are difficulties in classifying the subtypes, the indication of reactivity is sufficient.

Examples:

Lepromatous leprosy, though with not clear neuritis:

Cl (allergy dispensed)

Erythematous macules. Here the indication of reactivity is necessary.

C me } al
     } an

Tuberculoid macules

C tb (allergy dispensed)

Macular case, in which it is difficult to distinguish clearly the clinical type of lesion.

C m } an
   } al (indication of allergy)

The occurrence of various types of cutaneous lesions, will be represented by combinations of small letters.

A case of lepromas and erythematous macules

Cl me (allergy dispensable)

General outline:

C { l, ml, ed } an
  { me, mh, mi } an al
  { tb, ac } al

MIXED LEPROSY

In case the infection has attained the nerves in such a manner that its lesions became clinically unelusive (specially clear lesions of nerve trunks, amyotrophies, lagophtalmus, perforating ulcer, etc.), the patient is considered of mixed form, if the cutaneous lesions persist. In these cases it is sufficient to add the letter "N" to the symbol of cutaneous leprosy, and finally the allergic condition, if necessary.

Examples:

Case of tuberculoid lesion, with neuritis

C tb N (allergy dispensable)

Case of lepromas with amyotrophies

Cl N (allergy dispensable)

Case of erythematous macules with nerve thickenings

C me N { al / an (indicate the allergy)

NEURAL FORM

Supposing now that the cutaneous manifestations are absolutely absent, the case would be classified by its frank nerve lesions, or by its disturbances of typically neural origin (especially neuritis, amyotrophies, perforating ulcers) in the neural form.

We have no cutaneous manifestation to lead us objectively in the perception of organic reactivity to the infection. The L. T. again acquires its importance here, principally because we can not institute as processes of routine the bacteriological or histological examination of the nerve trunks.

In case of neural leprosy, the positive lepromin test, will indicate a suspicion of *a structure of resistance,* the nature of which only biopsy will solve (tuberculoid, colliquative, fibrous). If the test is negative we must admit a *structure of invasion* (leproma of the nerves, bacillary infiltration). The prognosis becomes unfavorable, and it seems that we are authorized to believe that the lesions on the skin can appear under various circumstances and with the characteristics of the anergic lesions. The fact also may happen that repeated bacterioscopic examinations of the apparently healthy skin will show that we are dealing with a case of diffuse leprosy.

N { al / an

NOTE: These are all simple suggestions based on the importance of allergy, and which can he adapted to a more complete classification. We think that one only classification cannot include all cases that appear in practice, without sacrifice of simplicity, and it will be sometimes necessary to indicate a case by a whole term (lepra bullosa, secondary neural case, arrested case, etc.) and perhaps by its degree of allergic specific reactivity (lepromin positive, lepromin negative).

ABSTRACT AND CONCLUSIONS

The author describes the technique employed in the preparation of lepromin, the types of reaction found, the criterion of reading, etc. He considers as positive reactions those with more than 5 mm diameter in the 30th day of reading.

Reactions were studied in 1529 individuals, both lepers and healthy, with or no contact with leprosy; and the results are correlated with age, sex, race, nationality, degree of bacillary elimination, types of disease, debility of the body through various diseases, speed of sedimentation of the red cells, lepra reaction, (present or prior to the test).

Analyzing his results, together with the works of various authors, about lepromin, in endemic and non-endemic zones, and comparing the data with those of general pathology, in particular with tuberculosis, he arrives at the following conclusions:

Epidemiology — Leprosy is a highly contagious but also highly immunizating disease. The bacillary leper it the propagator of the infection. However, close or prolonged contact with such bacillary cases is not necessary to acquire the infection. Hence, in endemic countries a large part of the population have been contaminated and immunized. Infection occurs naturally at younger ages, not because of special receptivity in infancy, but rather because adults were already contaminated in their turn. (The author makes a distinction in childhood between "real" anergy and anergy of "non-infection").

A predisposition to leprosy exists, which is represented by an incapacity to react with the immuno-allergy to the bacillary invasion, and which has no relation to age, sex, race, nationality or general conditions of health. The greater ratio of cases of "declared" leprosy in familial foci is due to probable inherited predisposition, to superinfections and to identity of environment.

Clinic — The expression, "period of incubation" seems erroneous, and should be substituted by "period of latency". A tuberculoid, sarcoid or atropho-cicatricial leprosy is a manifestation of re-infection at the level of the skin or of the nerve of an already infected and allergized individual. A primary infection, with allergy, may possibly be made through the upper air passages, in the regional lymphatic organs. An endogenic re-infection of this same individual, through hematogenic or lymphogenic dissemination from the primary focus,

will have the so-called "tuberculoid lepra reaction" and the other cases with multiple tuberculoid lesions as consequence.

In a definitely anergic case; that is, in the so-called "predisposed", incapable of reacting sufficiently with allergy against the bacillary invasion (not to be confused with the anergy of infancy, often due to the absence of such invasion) the primary focus will remain latent. The transformation into declared leprosy is made under conditions, yet unknown, entering possibly into action the role of superinfections, debility, various illness, inadaptation to climate and environment (foreigners!) etc.

In the anergic individual the clinical manifestation may be a simple macule, bacillary or not, or an acute and extensive lepromatization. Therefore the distinction between the one and the other is no longer made by the action of the allergic condition, but rather by the influence of another kind of resistance, probably connected with the above mentioned conditions of superinfections, debility, inadaptation, etc. In the same way the degree of allergy does not distinguish the cases amongst the allergic groups, the tuberculoid, the sarcoid, the cicatricial and abortive lesions. Also the invasion of the nerves seems to occur independently of the allergic condition of the individual.

The existence of typical tuberculoid lesions is not probable in bacillary cases. The cases mentioned in bibliography refer perhaps to "lesions of tuberculoid structure", "en passage" to frank bacillary lesions, and produced by a resistance lacking in completeness, and useless therefore to the organism.

The lepra reaction (erythema nodosum) is a phenomenon independant of specific leprous immunity.

Histology — The cutaneous lesion, absolutely incipient, presents an uniform histological structure, just as much in allergic cases as in anergic ones. However the evolution differs. In the first case, there will be observed a gradual tranformation to a pre-tuberculoid lesion, or a simple paralysation. In the second case, a gradual infiltration, a bacillary invasion, a lepromatization, depending on the non-allergic factors just mentioned. The same facts can happen by analogy in the nerve tissues.

Prophylaxis and therapeutics — Admitting general contamination, the cases of declared leprosy will continue to appear even after isolation of all bacillary patients, diminishing gradually by the inexistence of possibility for superinfections. The following generation will be, however, in the conditions of a virgin people of leprosy.

Therapeutics has no probability of altering the specific allergic reactivity, but may guide by having in view the non-allergic factors of resistance (involuted macules in anergic cases!). The question resolves itself into studying and remedying the causes which, in determined anergic cases, make a simple macule transform itself into a leproma; if superinfection is one of the causes, as it seems, the consequences are obvious and pertain to, prophylaxis.

Classification — The author, emphasing the importance of allergy in the evolution and determination of the types of the disease, suggests its employment in the classification of the forms of leprosy. He presents for discussion a plan of classification with the following principal characteristics:

1st. — Primary division into the large classic types: cutaneous, neural, and mixed. He would include in the cutaneous types *all cases with lesions in the skin,* from the leproma to the tuberculoid macule; in the neural type, all the cases with *appreciable lesions in the nerve trunks.*

2nd. — Secondary division into *elementary* types (leproma, hypochromic macule, diffuse leprosy, tuberculoid leprosy, cicatricial macule).

3rd. — Characterization of the allergic condition in doubtful cases, and in types of lesions, which may exist both in allergic and in anergic cases: (erythematous macule, erythemato-hypochromic macule, involuted macule).

TABLE I

L. T. IN ADULTS, NON-LEPERS.

	—	+	++	+++	
Contacts	0	5	17	33	55
Tropical Diseases	0	2	8	9	19
Tuberculosis	3	7	27	33	70
		11,8 %		88,1%	

TABLE II

L. T. IN HEALTHY CHILDREN OF PARENTS AFFECTED BY LEPROSY.

AGE

	0 — 3	4 — 6	7 — 9	10 — 12	13 — 15	16 or more
L. T. +	1	18	33	43	28	29
L. T. —	18	52	46	27	18	10
% positive tests	5,7 %	25,7 %	41,7 %	61,4 %	60,8 %	74,3 %

TABLE III

L. T. AND DEGREE OF BACILLARY ELIMINATION

	—	+	++	+++	
B ++	189 (60 %)	116 (36,8 %)	10 (3,1 %)	0 (0 %)	315
B +	89 (59,9 %)	58 (38,4 %)	4 (2,6 %)	0 (0 %)	151
B —	47 (9,5 %)	94 (19,1 %)	160 (32,6 %)	190 (38,7 %)	491
			—		957

TABLE IV

L. T. AND CLINICAL TYPE OF LESION

	—	+	++	+++	
Mac. tbc.	0	2 1,3 %)	68 (46,5 %)	76 (52 %)	146
Mac. +	121 (58,7 %)	80 (138,2 %)	5 (2,4 %)	0	213
L. ml.	133 (62,4 %)	74 (34,7 %)	6 (2,8 %)	0	206

TABLE V

L. T. AMONG LEPERS, DISTRIBUTED BY AGES

	0—3	4—6	7—9	10—12	13—15	16 or more
Mits + ...	4	8	14	38	39	304
Mits —	0	15	30	36	58	526
% of positive tests ..	100	34.7	31.8	51.3	40.2	36.6

TABLE VI

TYPE OF LESION IN RELATION TO AGE OF APPEARANCE

	0—5	6—10	more	17—25	26 or 11—16	
Leproma and macula-leproma	2 (0.4%)	35 (7.7%)	107 (23.7%)	138 (30.5%)	169 (37.4%)	451
Tuberculoid & Sarc. Boeck ..	6 (3.1)	23 (11.8%)	25 (12.9%)	41 (21.2%)	98 (50.7%)	193

TABLE VII

L. T. AND SEX

		M	F
Lepers in general	L.T. +	194 (33.1%)	203 (42.5%)
	L.T. —	391	274
		585	477
Lepers 0—9 years	L.T. +	13 (31.7%)	13 (43.3%)
	L.T. —	28	17
		41	30
Lepers 10—15 years	L.T. +	31 (39.7%)	36 (43.3%)
	L.T. —	47	47
		78	83
Healthy children of lepers .	L.T. +	90 (50.2%)	58 (42.6%)
	L.T. —	89	78
		179	136
Tuberculous, non-lepers	L.T. +	35 (89.7%)	25 (80.6%)
	L.T. —	4	6
		39	31

TABLE VIII

L.T. AND NATIONALITY, INDIVIDUAL, AND ASCENDANT

		Foreigners	*Natives Children of foreigners*	*Natives Children of natives*	*Natives Children of foreigners and natives*
Adult lepers ..	L.T. +	81 (48.2%)	132 (33.3%)	75 (33.9%)	14 (35.8%)
	L.T. —	87	264	146	25
		168	396	221	39
Infant lepers ..	L.T. +	0	34 (33.3%)	46 (43%)	13 (56.5%)
	L.T. —	0	68	61	10
			102	107	23
Healthy children 0 — 9 years .	L.T. +		26 (27%)	26 (36.1%)	
	L.T. —		70	46	
			96	72	
Healthy children 10 — 15 years.	L.T. +		36 (62%)	35 (60%)	
	L.T. —		22	23	
			58	58	

TABLE IX

L.T. AND SEDIMENTATION INDEX

S. I.	L. T. —	L. T. +
0 — 15	172 (45.7%)	45 (62.5%)
16 — 30	119 (31.6%)	25 (34.7%)
31 — 45	60 (15.9%)	1 (1.3%)
46 — 60	19 (5%)	1 (1.3%)
61 or more	6 (1.5%)	0
	376	72

TABLE X

L. T. AND TYPE OF LESION

	—	+	++	+++	*Total*
L	120	68	6	0	194
Ml	13	6	0	0	19
Ed	23	31	0	0	54
Me +	97	64	5	0	166
Mh +	16	11	0	0	27
Mu +	8	5	0	0	13
Mu —	3	9	0	0	12
Me —	22	24	21	12	79
Mh —	13	21	16	20	70
Mi	11	25	30	30	96
Tbc (cl)	0	0	23	31	54
Tbc (hs)	0	0	20	18	38
Tbc (SB)	0	2	25	27	54
M. a. C.	0	1	7	37	45
N	3	4	26	19	52
					993

TABLE XI

L. T. AND LEPRA REACTION

L. R.	125	89	6	0	220
	—	+	++	+++	Total

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