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Some Remarks on the Genetics of Leprosy Resistance *

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Introduction

For a long time it has been thought that susceptibility to leprosy involves a hereditary component. However, only recently, some investigations trying to analyse the genetic basis of the mechanism of leprosy susceptibility have been carried on.

The assumption of a genetic causation for leprosy resistance has been favoured by the following observations: 1) the disease fails to manifest itself in the majority of the exposed subjects, even when submitted to intimate contact (Quagliato, 1957); 2) the empirical risks for leprosy among relatives of index-cases are higher among consanguineous than among the non-consanguineous subjects (Do Pateo and Pereira, 1936); 3) different racial stocks living in the same area show racial differences in the susceptibility to leprosy (Humphry, 1952; Gehr and Munder, 1954; Bechelli, 1956); 4) the concentration of leprosy patients in sibships is not random even in populations where the disease has a high prevalence (Beiguelman et al, 1968a); 5) environmental agents are not capable of changing a polar form of the disease into another, i. e. typical lepromatous (malignant) into typical tuberculoid (benignant) form of leprosy and vice-versa; 6) distribution of the polar forms is not at random among affected sib-pairs (Beiguelman et al, 1968b).

Different approaches have been recently applied to the problem (Beiguelman, 1965b). Associations between leprosy and genetical markers such as blood groups (Beiguelman, 1962a, 1963, 1964c; Verma and Dongre, 1965; Yankah, 1965; Povey and Hornton, 1966; Vogel and Chakravartti, 1966; Singh and Ojha, 1967; Salzano, 1967; Vogel, 1968), taste sensitivity to phenylthiourea (Beiguelman, 1962b, 1964a; Beiguelman and Marques, 1964), haptoglobins (Schwantes et al, 1963; Povey and Hornton, 1966), transferrins (Povey and Hornton, 1966), and G-6-PD deficiency (Pettit and Chin, 1964; Beiguelman et al, 1966, 1968), have been explored in order to look for pleiotropic effects in leprosy susceptibility or resistance.

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Another line of investigation has been represented by the study of the familial distribution of the early and the late lepromin reaction (Beiguelman, 1962c; Beiguelman and Quagliato, 1965), as well as the mechanism of clinical expression of the late lepromin response (Beiguelman and Quagliato, 1964; Beiguelman et al, 1965, 1967; Pinto Jr. and Beiguelman, 1967). These investigations have attracted the Author's attention to a central problem represented by the possibility of recognizing the genetical mechanism of leprosy resistance at a tissular level.

The Lepromin Reaction

Lepromin is a suspension of triturated lepromatous tissues rich in *Mycobacterium leprae* in an isotonic solution of sodium chloride, sterilized by heating. When 0.1 ml of lepromin is intradermally injected, people may disclose a late reaction which is clinically recorded from 28 to 40 days, and/or an early reaction which is macroscopically read from 24 to 48 hours. While the early lepromin reaction (*Fernandez reaction*) is considered as an allergic response to leproproteins present in lepromin (Beiguelman and Quagliato, 1965), the late lepromin reaction (*Mitsuda reaction*) has a prognostic value, since the strong positive reactions are considered as a demonstration of resistance, from the clinical and epidemiological viewpoints, at least, as concerned to the lepromatous type of leprosy. As a general rule, lepromatous patients do not respond to lepromin, while individuals having the tuberculoid form of the disease disclose strong positive reactions. As it is commonly known in clinical practice, the tuberculoid patients show frequently a spontaneous recovery and manifest clear response to therapy.

Usually the early and the late lepromin reactions are classified in five groups, according to their intensity, as it can be seen in Tab. I.

When the late lepromin reaction is analysed histologically, two main groups are distinguished. One group includes subjects displaying a granulomatous infiltrate with tuberculoid structure in the place of the inoculation, composed chiefly of epithelioid cells with absence of, or rare AAR bacilli (*positive reaction*). The other group is composed by those whose biopsies exhibit the presence of lepra-cells, i. e., histiocythes plenty of AAR bacilli (*negative reaction*).

The histological positive reaction derives from the macrophages ability to lyse the leprosy bacilli and their consequent transformation in epithelioid cells. The clinical positive responses appear to be a consequence of both the ability to lyse the bacilli and the influence of sensitizing agents (as primary infections of *M. tuberculosis* or *M. leprae*, BCG vaccination or repeated lepromin injections) which stimulate the lysogenicity of the macrophages (Souza Campos et al, 1962; Beiguelman and Quagliato, 1965; Beiguelman et al, 1965; Furtado and Schultz, 1965; Beiguelman et al, 1967). This dependance of sensitization for disclosing the clinical reaction would explain the decrease of response types when the late lepromin test is read

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Tab. I. The early and the late lepromin reaction classified according to the intensity of the clinical responses (cf Bechelli and Rotberg, 1956)

Class	Early lepromin reaction	Late lepromin reaction
—	Presence of an erythematous halo smaller than 5 mm or absence of an observable erythematous area	Absence of an observable or palpable element
±	Presence of an erythematous halo with 5 to 10 mm diameter	Presence of a perceptible element with a diameter smaller than 3 mm
+	Presence of an erythematous halo infiltrated, with 10 to 15 mm diameter	Presence of a conspicuous element infiltrated with 3 to 5 mm diameter
++	Presence of an erythematous halo infiltrated, with 15 to 20 mm diameter	Presence of a conspicuous element infiltrated with a diameter larger than 5 mm
+++	Presence of an erythematous halo infiltrated, with a diameter larger than 20 mm	Presence of an ulcerated nodule

microscopically. It also would explain why a fraction of clinically lepromin-negative subjects are able to manifest positive Mitsuda reaction after BCG vaccination or lepromin reinoculation (Souza Campos et al, 1962; Beiguelman et al, 1965, 1967).

The Familial Pattern of Mitsuda Reaction

It was demonstrated that the late lepromin reaction, as analysed clinically, is a familial trait (Beiguelman, 1962c; Beiguelman and Quagliato, 1965). In families free of leprosy, the distribution of the lepromin responses in the offspring depends upon those observed in the parental generation; children born to Mitsuda negative parents are more prone to exihibit negative Mitsuda reactions. This situation raised a tentative genetic hypothesis to explain the familial distribution of this reaction by assuming homozygosis for a gene responsible for the inability of the macrophages to lyse *M. leprae* (Beiguelman, 1965a).

Since the macroscopically positive late reaction to lepromin is considered to reflect both the histological ability for lysing *M. leprae* and the influence of sensitizing factors, the above hypothesis was tested in a sample of families which included at least one parent affected with leprosy. Among them, the clinical reactions are supposed to be strongly correlated to the histological responses because these families are often exposed to sensitizing agents.

In two groups of families, the expected and observed numbers of those with all children exhibiting positive reactions and including at least one child with a nega-

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tive reaction, were in accordance with the genetic hypothesis of dominant inheritance for the positive reaction provided that Fisher's statistical analysis for monogenic inheritance has been applied to the data (Fisher, 1939). Those families were composed of couples in which a healthy subject disclosing a +++ Mitsuda reaction was married to a leprosy patient. Among them, 41 were married to patients with the tuberculoid form (Mitsuda +++) while 65 were married to lepromatous subjects (Mitsuda —).

In a third group of families, those composed of 24 lepromatous couples (Mitsuda — × Mitsuda —), the expectation for only lepromin negative subjects in their offspring was not confirmed. A proportion of 30.9% among 81 children born to those couples was found to exhibit strong Mitsuda reactions (++ and +++). This discrepant result was ascribed to the influence of the following factors (Beiguelman, 1965a):

1) high frequency of illegitimate children in the offspring of leprosy patients;
2) influence of BCG vaccination;
3) incomplete penetrance of the genes.

Although the theoretical frequency of illegitimate children is not extremely high (4.5%) in the offspring of leprosy parents who are not living in sanatoria, the estimate for the offspring of lepromatous couples living in leprosaria of the State of São Paulo (Brazil) is three times higher (31.2%) than those calculated for normal populations with the highest frequencies of extramarital children (Pinto Jr. and Beiguelman, 1967).

The second assumption, i. e. the influence of BCG vaccination, was analysed in a sample of 28 children born to lepromatous parents whose paternity was investigated (Beiguelman et al, 1967). Among them, 7 (25%) disclosed strong positive Mitsuda reactions after BCG vaccination. This frequency was significantly lower than that observed in a control group of 43 children (25; 59.1%) born to healthy parents ($\chi^2 = 7.52$; 1 d. f.; $P<0.01$). The latter results support both the hypotheses: 1) that a possibility exists for stimulating positive reactions in the offspring of lepromatous couples; 2) that BCG administration is less efficient for enhancing lepromin reactions among those who are supposed to have an inborn inhability for disclosing positive responses to lepromin inoculation. These hypotheses become more attractive when some observations in susceptible and resistant strains of rabbits to tuberculosis are focused. According to Lurie et al (1952) the natively resistant rabbits reacted rapidly to BCG injection by disclosing a nodule at the site of inoculation. Among the susceptible strains the nodule both grew and healed slowly. In the former group the lysis of the bacilli was rapid, while in the latter the destruction of the bacilli and the development of allergic sensivity was slowly produced.

Objections to the Monogenic Hypothesis

The hypothesis of monogenic inheritance causing Mitsuda reaction, as described above, while attractive, is open to several objections. Some observations favour the assumption of genetic causation in lepromin late reaction (Rotberg, 1957a; 1967b),

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but no conclusive evidence is known on the hereditability of this trait. Studies in twins will probably supply such proof but, up to the present, data on the subject do not seem to have been collected yet.

Other criticisms are concerned either to the methodological approach and to the environmental influences on the macroscopical expression of the Mitsuda reaction, or to the technical difficulties. They will be briefly discussed.

It may be argued that the same factors supposed to distort the results in the offspring of lepromatous couples, may be assumed to affect the other groups of families. Then, the fitting between the observed and expected family data for the latter could be fortuitous. Obviously, it may be answered that the influence of the alleged distorting factors should be of minor degree in the family groups agreeing with monogenic hypothesis. Usually, children belonging to lepromatous couples are more frequently submmited to BCG vaccination and to repeated lepromin injections. Moreover, these couples are usually from sanatorial extraction and, as it was stressed, a high rate of non-paternity is found there (Pinto Jr. and Beiguelman, 1967).

The non-significance of the deviations between the observed and expected numbers of sibs, all of them with positive Mitsuda reactions and with at least one sib exhibiting a negative response, in the offspring of Mitsuda $+++ \times$ Mitsuda $+++$ and Mitsuda $- \times$ Mitsuda $+++$ couples (Beiguelman, 1965a), could merely be a result of the postulate that the frequency of negative reactions among partners of lepromatous patients should be accepted as an estimate of recessive homozygotes. Moreover, concerning these Mitsuda negative subjects, it may be wondered why some healthy partners of lepromatous subjects, in spite of their long time of intimate cohabitation, neither react positively to lepromin nor show signs of leprosy. Of course, it may be supposed that among them, leprosy has not developed due to a longer incubation period of the disease, but other hypotheses cannot be rejected:

1) Among the Mitsuda negative healthy partners of lepromatous patients, all of them or, at least, a fraction, produce positive tissular late reactions which are not expressed clinically because of the absence of appropriate allergic sensitization.

2) It is well known that the administration of cortisone, while stimulating the macrophages' activity, depresses their lysogenic ability against ingested bacilli. The administration of this hormone suppresses nonspecific and allergic inflammation by opposition to factors which increase capillary permeability. In this sense cortisone has been compared to estrogen, since the latter hormone reduces connective tissue and vascular permeability. Otherwise, periodic chorionic gonadotropin administration increases both connective tissue and vascular permeability (Lurie et al, 1949; 1951).

It may be supposed, therefore, that subjects who have an inborn ability to lyse *M. leprae*, under a proper balance of adrenal and other hormones, for instance, an excess of cortical hormone, would exhibit neither macroscopically nor histologically positive-late lepromin reactions. The injected bacilli would accumulate in the macrophages without producing allergic inflammation.

Some facts from animal experimentation can be added in favour of that hypoth-

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esis. When cortisone and chloropromazine-prometazine are injected in guinea pigs in the site of the inoculation of *M. leprae* or *M. lepraemurium*, their macrophages which are usually able to destroy these bacilli, become unable to perform that lysis. A lepromatous-like lesion develops, instead of a tuberculoid structure (Hadler et al, 1965).

3) Among the Mitsuda negative healthy partners of lepromatous subjects or, at least, among some of them, another unknown type of resistance to leprosy would exist, which would not be revealed by Mitsuda's test.

If any of these hypotheses, except the first, would hold true, then the estimation of the frequency of Mitsuda negative subjects in the population, from their proportion among those married to lepromatous partners, would depend on the frequency of false Mitsuda negatives among the healthy ones.

Another observation deserves some comments. Some subjects may exhibit macroscopically positive late lepromin reactions without a corresponding active participation of the macrophages (Bechelli et al, 1959). Such individuals are believed to be hypersensitized. On the other hand, positive Mitsuda reactions may be observed among lepromatous patients when the injected lepromin contains damaged *M. leprae*; their macrophages' lysogenic inability is only towards unhurt leprosy bacilli. In this situation it may be expected that even individuals whose macrophages are unable to lyse *M. leprae*, when hypersensitized by *M. tuberculosis*, after injected with lepromin containing an excess of damaged bacilli, would disclose strong clinical positive reactions with a histological correspondance. The same situation could probably occur by hormonal influence. Thus, among rats, of which macrophages do not have lysogenic ability for *M. leprae* or *M. lepraemurium*, under the action of desoxycorticosterone show in the lesions some macrophages transforming themselves in epithelioid cells, after the lysis of the phagocytized bacilli (Hadler et al, 1965).

As it can be seen, the objections to the monogenic interpretation of the Mitsuda reaction neither destroy the possibility that the late lepromin reaction is genetically determined by a gene pair, nor they discourage the Author's belief that this is the only and main trait which can be used as a clue to the understanding of the genetical mechanism of resistance to leprosy. While multiple influences may contribute to manifest resistance or susceptibility to leprosy, the essential process that determines these behaviors, is the ability of the macrophages of the host to lyse the phagocytized bacilli or the incapacity of his macrophages to destroy them and consequently, not preventing the multiplication of the injected bacilli. The prognostic value of the Mitsuda reaction has been sufficiently proven on clinical and epidemiological grounds. All other influences, although important, would act as modifying factors of the lysogenic ability of the macrophages. In this situation it may be supposed that the macrophages' lysogenic ability to *M. leprae* would depend on a major gene pair and that the modifier factors would confer thresholds for this lysogenicity, causing their bimodal distribution when analysed at a population level. But, for investigating the validity of this assumption, it is necessary to avoid all *in vivo* interferences on the

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macrophages' activity related to *M. leprae*. Such an ability seems to exist, starting from a recently proposed (Beiguelman, 1966) technique for evaluating the individual resistance to leprosy.

The Possibility of *in vitro* Demonstration of Resistance to Leprosy

If blood monocytes are maintained in tissue culture medium, they develop into macrophages with apparently all the capacities of the tissue wandering histiocytes. On this basis, a test that can be considered as an improvement of Mitsuda's reaction was proposed. The procedure can be summarized as follows:

Specimens of 10 ml of venous blood are withdrawn into sterile syringes containing a drop of heparin and injected into sterile 12 ml tubes. The tubes are left to stand for 60 minutes at room temperature for sedimentation of the erythrocytes. When only a small amount of plasma is separated, the tubes are centrifuged gently at a low speed (300-500 rpm) and checked every 3 minutes to avoid excessive sedimentation of white cells. The samples are no longer centrifuged after a sufficient amount of plasma is fairly free from red cells. The plasma of each blood sample is then aspirated and transferred into conical sterile tubes which are centrifuged in order to concentrate the leukocytes at the bottom. The supernatant plasma is then discarded, the leukocytes washed in sterilized saline solution and resuspended in about 6 ml of the final medium, for distribution in five Leighton tubes. Each tube is provided with a coverslip of 8×30 mm. The composition of the medium used is as follows:

Hanks balanced salt solution . . .	80.0 %
Lactalbumin hydrolysate	0.5 %
Calf serum	19.5 %
Penicillin	100 I. U. / ml
Streptomycin	100 μg / ml

The tubes are maintained for 24 hours at 37° C. By this time the *in vitro* blood monocytes have developed into macrophages that resemble the wandering histiocytes of the tissues and have become attached to the coverslip. Afterwards the coverslips in the tubes are washed with sterile Hanks balanced solution in order to remove other types of leukocytes, some erythrocytes and cell debris. Finally, new culture medium containing dead leprosy bacilli in suspension is added to the tubes which return to the incubator at 37° C. The medium is renewed twice a week.

When maintained *in vitro* the macrophages of both lepromatous and tuberculoid patients actively phagocytize the dead leprosy bacilli from the first day of incubation. After this phase, a striking difference between the two types of cultures is apparent. The macrophages of the lepromatous patients transform themselves into typical lepracells with their cytoplasm plenty of bacilli and droplets of lipids easily stainable by Sudan Black, while those of the tuberculoid patients completely lyse the phagocytized bacilli becoming free of lipids. It is noteworthy that when damaged

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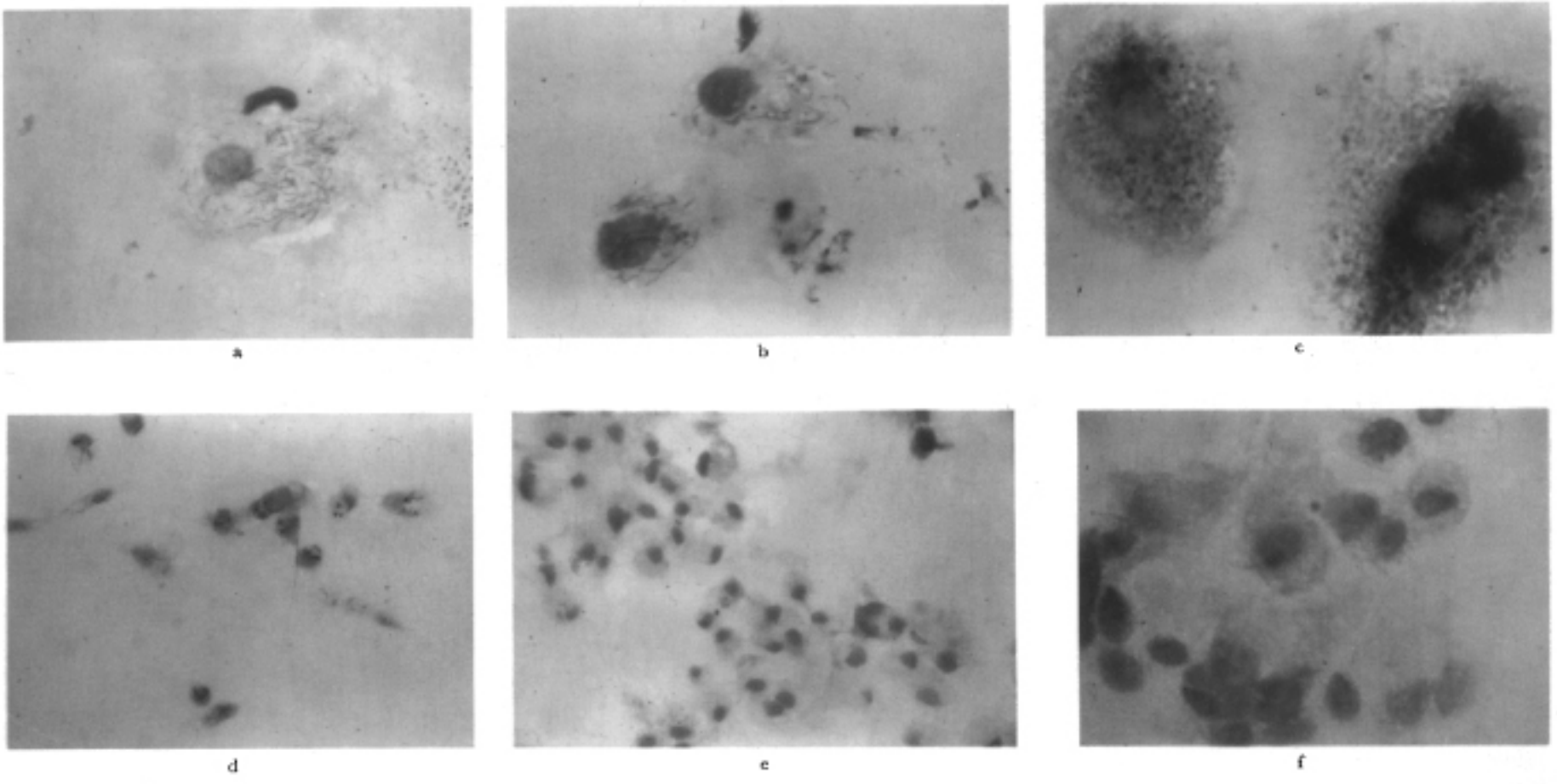

Fig. 1. Some aspects of the differentiation of macrophages in tissue culture medium containing dead leprosy bacilli.

a, *b*, *c* - Lepra-cells developed from macrophages of lepromatous patients; *a*, *b*: lepra-cells stained with methylene blue and bacilli stained with fuchsin (Ziehl); *c*: lipid droplets in lepra-cells stained with Sudan Black B.

d, *e*, *f* - Three different lysis stages of leprosy bacilli by macrophages of patients with the tuberculoid form of leprosy.

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M. leprae are added to the macrophages of lepromatous patients, lysis can be observed. This fact confirms that the demonstration of differences between lepromatous and tuberculoid patients with respect to the lysogenic power of their macrophages against *M. leprae* depends upon the integrity of the bacterial wall.

It is also interesting to stress that the absence of lysogenic ability of the macrophages of lepromatous patients seems to be specific to *M. leprae* since, in all observed cultures of macrophages from lepromatous subjects, they were able to lyse *M. lepraemurium* and *M. tuberculosis*.

The technique described herewith, will probably furnish the possibility to pursue problems of great practical and theoretical implications, provided that it is verified whether the observed differences between patients with the polar forms of leprosy do exist among healthy individuals, and whether the patterns of reactions of the other clinical variants of leprosy will be characterized.

Of course, those problems will be concerned to the investigation of the possible age groups and sex differences with respect to the lysogenic ability to *M. leprae*, the search for the supposed lysogenic thresholds of macrophages to *M. leprae*, the investigation of the enzyme systems involved in the destruction of the bacterial wall and the action of different factors that are able to modify these eventual thresholds. Another important research line will be the study of the macrophage enzyme-system which is involved in the destruction of the mycobacterial wall. Will the inability to lyse *M. leprae* be circumscribed within the " inborn errors of metabolism "? A hereditary error which would specifically unable the macrophages to lyse those bacilli? It seems that now a new tool exists to pursue research work trying to answer those and other important but open questions.

Summary

The mechanism and the familial pattern of the late lepromin reaction (Mitsuda reaction) have been discussed. The interpretation of the familial correlation as mainly depending on a pair of allelic genes has been analysed thoroughly. A new technique has been described for identifying constitutional resistance or susceptibility to leprosy at an *in vitro* tissular level. The possibilities of this technique have been stressed.

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RIASSUNTO

Vengono discussi il meccanismo e le caratteristiche familiari della reazione tardiva alla lepromina (reazione di Mitsuda). È stata attentamente analizzata l'interpretazione secondo cui la correlazione familiare sarebbe dovuta *prevalentemente ad una coppia di geni*. Viene descritta una nuova tecnica per identificare la resistenza o la suscettibilità costituzionale alla lebbra ad un livello tissutale *in vitro*. Vengono sottolineate le possibilità di questa tecnica.

RÉSUMÉ

L'on discute le mécanisme et les characteristiques familiales de la réaction tardive à la lépromine (réaction de Mitsuda). L'interprétation de la corrélation familiale comme dépendant d'un seul couple de gènes a *été attentivement analysée*. Une nouvelle technique a été décrite pour l'identification de la résistance ou de la susceptibilité constitutionnelle à la lèpre au niveau de tissus *in vitro*. Les possibilités de cette technique ont été soulignées.

ZUSAMMENFASSUNG

Erörterung über den Mechanismus und die Familieneigenschaften einer verspäteten Lepromin-Reaktion (Mitsuda Reaktion). Eingehende Analyse der Auslegung, dass die Familienkorrelation vorwiegend durch ein Genpaar bedingt sei. Beschreibung einer neuen Technik, um die konstitutionsbedingte Lepra-Resistenz oder -Empfänglichkeit eines Gewebes *in vitro* festzustellen. Die Möglichkeiten dieser Technik werden betont.

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