

Mitsuda's Skin Reaction in Leprosy

FUMIO HAYASHI.

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KENSUKE MITSUDA reported, first in 1916 in the Japanese Journal of Dermatology and Urology, and again in 1932 before the Third International Leprosy Congress at Strasburg, that the intracutaneous injection of boiled emulsion of bacteria obtained from leprosy nodules usually gives a negative reaction in nodular leprosy, but gives a positive reaction in neuro-macular leprosy. I have recently continued this investigation, making similar tests on 192 cases. Only the conclusions of my work are given here; details were reported at the Nippon leprosy conference in 1929, 1930, and 1931.⁽¹⁾

Preparation of the Vaccine.—Fresh nodules are boiled in physiological salt solution for from thirty to sixty minutes, and ground in a mortar. To 1 gram of the ground nodular material are added 20 cubic centimeters of the salt solution used in the boiling, fresh salt solution being added, if necessary, to make up the required volume. The whole is filtered through gauze and the filtrate heated at 60 deg. C. for one hour. Carbolic acid is added to make 0.5 per cent. concentration. One-tenth cubic centimeter of the material prepared in this manner is used for an intracutaneous injection.

The reaction.—The reaction is looked for on the 8th, 16th, and 24th days after the injection, as late reactions may not appear before the second or third week. In the negative reaction in nodular leprosy there is slight reddening which lasts only from two to four days, and never over eight days.

In reading the positive reactions, those with infiltrated areas 0.3 to 0.5 centimeter in diameter are classed as one plus (+), those 0.5 to 1.0 centimeter as two plus (++), and those over 1.0 centimeter and those with pus formation as three plus (+++). Some reactions start eruptively, while other begin more diffusively, the latter type with large areas gradually becoming strongly positive.

Results obtained.—Of the 192 lepers tested, 64 were neuro-macular and 125 nodular cases. Of the former all but two (97 per cent.) showed positive reactions, while of the nodular cases all but eleven (91 per cent.) were negative

Significance of the reaction.—The intracutaneous injection of leprosy bacilli produces no reaction in patients who have reached the nodular state, with unlimited proliferation of the bacilli.

The positive reaction appears only in normal individuals resistant to leprosy and in lepers in the neuro-macular stage in which a certain degree of resistance is to be presumed. In no case does the negative reaction appear in the normal, tuberculous, or syphilitic.

In this phenomenon there is a striking change in the transition of a case from the neuro-macular type to the nodular type, a transition which is also accompanied by the disappearance of the well-known blood lymphocytosis and by the appearance of complement binding and precipitation reactions. A case of nerve leprosy in which the reaction is negative may be expected sooner or later to turn into the nodular type. On the other hand, a positive reaction in nodular leprosy may be looked upon as a sign of favourable prognosis. In fact, the majority of cases belonging to the latter category simulate the nerve type, owing to the disappearance of the nodular infiltration. More will be said on this point later.

Classification of leprosy.—Mitsuda classifies leprosy in three types namely :—nodular, neural, and macular. This classification has been recognized and used by the Department of Home Affairs in Japan. It is based, not only upon the clinical symptoms, but also upon the pathological and serological observations. There are plain differences between the nodular and the other types, as shown in the comparative table below. The difference between the neural and the macular types is only relative ; we call a case neural or macular according to whether neural or macular symptoms are the more prominent.

TABLE 1.—*The principal differences between types of leprosy.*

NEURO-MACULAR.	NODULAR.
1. No nodules or infiltration of the nodular type present.	1. Nodules or infiltration of the nodular type are or have been present.
2. Few bacilli in the tissues.	2. Ordinarily many bacilli in the tissues.
3. No vacuolated cells.	3. Virchow's vacuolated cells present ; that is, leprous lipid metamorphosis in the tissues.
4. Lymphocytosis in the blood.	4. No lymphocytosis.
5. Bacilli not in the blood.	5. Leprosy bacilli in the blood (with exceptions).
6. Serum reactions negative.	6. Complement binding reaction and other reactions of precipitation of the serum (with exceptions).
7. Mitsuda's reaction positive.	7. Mitsuda's reaction negative (with exceptions).

Nature of the reaction.—My studies on the biological nature of the reaction may be summarized as follows :

1. A nodule was divided into two portions. One portion was boiled and the other was not. Vaccine was prepared from each portion, and tests showed no differences in the reactions they produced.

2. The filtrate obtained by passing the leprosy vaccine through a bacterial filter gave only negative reactions. In some cases of the nerve type areas of rubefaction 4 or 5 centimeters in diameter appeared a day or two after the injection. This is the kind of incidental phenomenon that sometimes occurs in the reaction to the vaccine itself, in which the reddening disappears in one or two days but is followed by an extremely strong true reaction, with pus formation. It was, therefore, decided that the prodromic reddening is caused by the filtrate. This may be a protein reaction.

3. Intracutaneous tests were made, using the serum of both nodular and neural lepers, but no reactions were seen.

4. Since, as shown above, the filtrate was not the reacting substance of the vaccine, it remained to be decided which of the solids, the bacilli or the nodular tissue, is responsible for the reaction. I therefore tested the reaction to lymph nodes from a case in which the nodular infiltration had been absorbed. The inguinal node in such a case is swollen, and consists entirely of leprous tissue, but contains very few bacilli. The vaccine prepared from this kind of lymph node gave very much feebler reactions than did those given by our standard leprous vaccine. Thus it was decided that the reaction was dependent on the bacilli.

5. Vaccines prepared from various acid-fast bacilli other than leprosy bacilli all gave positive reactions when tested on lepers, without reference to the type of leprosy, showing that the other acid-fast bacilli are different from the leprosy bacilli in that respect. The bacilli tested were timothy hay and rat leprosy bacilli. The vaccines were prepared by suspending one platinum loopful of the culture in 1 cubic centimeter of physiological salt solution.

6. Cultures obtained by the methods of Clegg, Needham, McCoy, Duval, and Kedrowsky, methods previously reported as yielding pure cultures of leprosy bacilli, were next tested. All of these gave positive reactions in nodular leprosy, and none had the property of giving negative reactions in this type as the leprosy bacillus does. This fact should be of use in determining whether a cultivated

organism is the leprosy bacillus or not. Such a test is to be desired, especially as long as leprosy cannot be transmitted to experimental animals.

7. Injections of the vaccine were made inside and outside the affected areas in macular leprosy. Quicker and stronger reactions occurred inside the areas than outside, especially in the case of tuberculoid macules. In these the infiltrated, elevated borders react particularly strongly. Macules in the nodular leper give negative reactions.

8. The von Pirquet reaction appeared in similar intensity and with the same rapidity when applied within and outside the affected area in tuberculoid macules, as well as on the border line. The different parts of the affected area showed no differences in their reactions. The same held true with the intradermal reaction of Mantoux. (Results of the von Pirquet test in our lepers are given under Other Observations.)

9. Similar results occurred after similar tests with the so-called leprosy cultures (according to Kedrowsky and Needham). They showed no such specificity as does the leprosy vaccine. This fact is of additional help in evaluating the alleged pure cultures.

10. Similar experiments were made, using the moxa cautery.* Stronger reactions took place outside the macule than inside it (Fig. 1). The diameter of the reddened area outside the macule measured some 2 centimeters, whereas that within the macule was only a thin pinkish ring 0.1 centimeter in diameter.

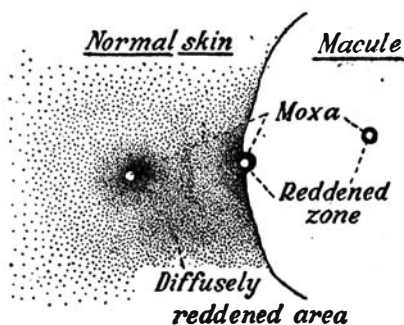


FIGURE 1.—Showing inhibition of erythematous reaction to Moxa cautery in a macule.

11. Removal of acid-fastness by treatment with acid does not change the leprosy vaccine as to its property to give positive reactions in maculo-neural leprosy, negative

* Moxa cautery is a method of treatment much used among the people in Nippon. Leaves of "moxa" are burned on the skin; the stimulation by the heat is believed to cure the sickness.

reactions in the nodular type of the disease, and the different reactions in and outside the maculæ.

OTHER OBSERVATIONS.

1. *Subconjunctival reaction*.—Dr. Shionuma, (²) one of my co-workers, carried out the injection of the vaccine under the conjunctival membrane of the eye of lepers, using 0.1 cubic centimeter for the test. He found that the reactions completely paralleled those obtained in the skin.

2. *Recrudescence after reaction*.—A patient apparently cured of macular leprosy was tested with both the leprosy vaccine and the suspension containing living bacilli. Ten months after the injection macules appeared all over the body with an explosive intensity (so-called “akuter Schub”). About one month before this sudden manifestation the site of the injection of living bacilli had become red, indicating that the explosive phenomenon was forthcoming. This fact is of great interest when considered in association with the appearance in the scar of the so-called rash as in small-pox (initial exanthem), if it occurs within one month after the vaccination.

3. *von Pirquet's reaction*.—Masa Igarashi, of our medical staff, tried out von Pirquet's reaction on 826 lepers in the Zensei Leper Hospital, 193 of the neuro-macular type and 633 of the nodular. Positive reactions occurred in 67.2 per cent. of the cases (or 73.6 per cent. if + reactions are counted as positive). Of the neuro-macular cases 66.9 per cent. were positive; of the nodular cases, 67.3 per cent. No marked difference was noted in the nature of the reactions in the two types of the disease.

4. *The sympathetic nervous system*.—I examined the functioning of the sympathetic nervous system in leprosy, chiefly observing the symptoms caused by injection of atropin, adrenalin, and pilocarpin. No difference from the healthy was found, irrespective of the type of leprosy. I also investigated the results of intracutaneous injection of adrenalin, pilocarpin and atropin. These also showed no difference from the normal. Mitsuda's reaction has no relation to the sympathetic nerve system.

5. *Anomalous reactions*.—As I have mentioned before, we call nodular those cases that have, or have had, nodules or infiltration of nodular character. There were some nodular cases which showed positive skin reactions. In these cases the infiltration and the nodules had already been absorbed, and it was very difficult to find bacilli in the skin.

Mitsuda described this anomalous reaction in 1917. Of the 400 patients whom he examined at that time about 199 yet remain. According to my examination of them, 15 nodular cases that gave negative reactions in 1917 gave positive reactions in 1930. These had been of the severe nodular type, but the lesions are now absorbed as a result of therapy, and some of them are very difficult to distinguish from the neural type.

Though of rare occurrence, I have seen negative reactions in some neural cases that became nodular not long after the injection. Such reaction anticipates the change of the type of the leprosy. In autopsies on neural lepers we have seen a few cases that had nodular infiltration in the testicles or in some other place. These two facts are consistent with each other.

MICROSCOPIC OBSERVATIONS.

A description of the microscopic changes in the reaction was published by Mitsuda in 1919. My observations have been consistent with his. Acute inflammatory changes can be seen not long after the injection, but later they are replaced by slight chronic changes. The papillary layer of the skin becomes thinner, and epithelioid and giant cells appear, in which many leprosy bacilli are phagocytized. Surrounding the area of giant and epithelioid cell infiltration is a layer of lymphoid cells, where bacilli are seldom seen.

Once I examined microscopically the scar of a reaction two months after the injection. There were still many bacilli which had been neither destroyed nor deprived of their acid-fast character.

REACTION AND TYPE CURVES.

As a result of my investigations over several years, I have determined the relationship between Mitsuda's reaction and the condition of leprosy. This can be seen in the curves in Fig. 2 (page 165).

Curve 1 represents a case that is maculo-neural throughout. The reactions are constantly positive.

Curve 2 represents a maculo-neural case which changed to the nodular type. The positive reaction became negative previous to the change.

Curve 3 is of a continuously nodular case, with a constantly negative reaction.

Curves 4*a* and 4*b* represent nodular cases (4*b* figuring one that commenced as maculo-neural), the nodular lesions in which were absorbed as the result of the treatment and remained so. In them the reaction, which was negative

during the actual nodular stage, became positive after the change in type. Such cases are not numerous.

Curve 5 shows a course of progress that is typical. H. Hayashi observed the progress of about 622 nodular cases and concluded that most of them follow such a course. That is, nodular cases have been apparently cured for a duration of six and one-half years on the average, and then have relapsed. Sometimes the patient gradually recovers, though not so completely as previously. According to Hayashi's observations the duration of the secondary improvement is about three and one-half years on the average, after which time the disease again becomes more severe.

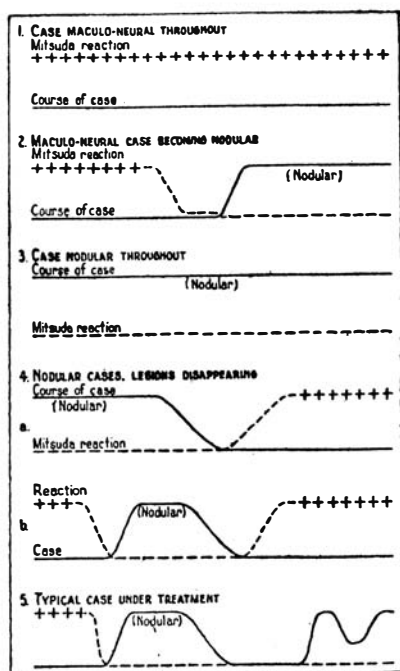


FIGURE 2.—Curves illustrating the relation of the Mitsuda reaction to the progress of cases.

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- (2) Shionuma, H., and Hayashi, F.—“ Skin and Ophthalmo-reactions in Leprosy.” *Acta Societatis Ophthalmologicae Japonicae*. Vol. 34, No. 6.