

ORIGIN OF THE LEPRONIN TEST

It has been suggested that the record should be put straight as to when the test which is universally known by Mitsuda's name was first introduced, and to whom credit should be given for its inception. An attempt to this is made here, with certain correlative historical facts.

It appears¹ that, in 1928, as a result of a movement by the 12th Health Congress of the League of Nations to convene an international leprosy congress, Nagayo undertook the difficult task of compiling the scientific studies on leprosy which had been made in Japan since 1890. Subsequently Tamiya² prepared a supplement covering the years 1929 and 1930, and these two documents, each with an author index, were published in the following year. This valuable reference material seems not to be generally known.

The first—and only—reference to the skin reaction to be found in Nagayo's compilation is a report by Mitsuda which

¹ NAGAYO, M. *Recherches sur la lèpre au Japon (1890-1928)*. Japanese J. Exper. Med. **9**(1931) 403-482.

² TAMIYA, T. *Researches in leprosy published in Japan during 1929-1930*. [Supplement to the above item.] *Ibid.* pp. 483-507.

appeared in 1919.³ (It is of interest that Nagayo was so little impressed by this report that he merely listed the title, without an abstract.) The idea that Mitsuda's first report was made in 1916 is wrong; Fumio Hayashi⁴ gave that date; but he also gave, in the next line of the same article, the date of the Strasbourg conference as 1932, whereas it was of course held in 1923.⁵ He gave no dates in a pamphlet, evidently printed privately, which he had distributed somewhat earlier,⁶ nor did Mitsuda give any date or reference in his brief Strasbourg report.⁷

The term "lepromin" was coined in 1926 by Bargehr⁸ for the leproma paste which he used by the von Pirquet method in work which, like that of Mariani in 1924 and 1925,^{9, 10} was apparently—there being no indication to the contrary—undertaken quite independently. Mitsuda had called his preparation an "emulsion," and Hayashi spoke of it as a "vaccine." Bargehr's term was for a time substituted by others with "leprolin," and since several other workers employed his procedure this latter designation caused some confusion.¹¹

Mitsuda did no more work in this field, and it was not until a decade after the publication of his original report, apparently

³ MITSUDA, K. [Valeur diagnostique de la réaction cutanée de la lèpre au moyen de l'émulsion du nodule lépreux.] *Hifuka Hinyōka Zasshi* (Japanese J. Dermatol. & Urol.) **19** (1919) No. 8 [p. 69?].

⁴ HAYASHI, F. Mitsuda's skin reaction in leprosy. *Internat. J. Lep.* **1** (1933) 31-38.

⁵ The latter error is perhaps a typographical one, but in any case it should have been caught by the editor, then engaged in his maiden effort in that field.

⁶ HAYASHI, F. Mitsuda's skin reaction and leprosy classification (abstract). Privately printed; undated, but probably 1931 or early 1932.

⁷ MITSUDA, K. Les lépreux maculo-nerveux, d'une part, les tubéreux, d'autre part, se comportent différemment à la suite d'une inoculation d'émulsion de tubercle lépreux. 3^{me} Conf. internat. de la Lèpre, 1923, *Comm. et Debats.* Paris, 1924, Beillière et Fils, pp. 219-220.

⁸ BARGEHR, P. Künstliche lepraspezifische Allergie und aktive Immunisierung gegen Lepra *Ztschr. f. Immun. u. Exper. Therap.* **49** (1926) 346-353.

⁹ MARIANI, G. Osservazioni sopra una forma speciale di allergia cutanea nella lebbra (lepra tuberculoide sperimentale nell'uomo). *Pathologica* **16** (1924) 471-477.

¹⁰ MARIANI, G. Nuove osservazioni sulle reazioni provocate sperimentalmente con materiale lebbroso nell'uomo. *Gior. italiano Dermat. e Sifil.* **66** (1923) 402-426.

¹¹ H. W. W. "Leprolin" vs "lepromin." *Internat. J. Leprosy* **7** (1939) 272-273 (editorial).

in 1929,¹² that it was taken up by Fumio Hayashi, then a junior assistant of Mitsuda's. For reviving the matter and bringing it actively to the attention of foreign workers, as well as for establishing a technique of preparing the antigen which in its essentials is still widely used, his place in the picture is well established.

Also connected with the matter is one Yoshinobu Hayashi, who had been Mitsuda's senior assistant and succeeded him in charge of the Tokyo leprosarium when he moved to Nagashima, and still holds that position. Ota and Nitto¹³ have stated, "The value of the so-called 'Mitsuda reaction' was first investigated by Yoshinobu Hayashi (1918) . . ." Elsewhere,¹⁴ speaking of the "Hayashi-Mitsuda-Hayashi" reaction, they said that in 1917 Y. Hayashi¹⁵ had made a *Presssaft* of leproma material which had been kept in Ringer's solution, and found that on intracutaneous injection most neural cases showed a marked local inflammation (positive reaction), whereas nodular cases, especially severe ones, gave only slight, transient erythema. Mitsuda had taken up the matter in 1918. Textually:

Yoshinobu Hayashi hat 1917 zuerst beobachtet, dass menschliches Leprom, zum Zweck der Anreicherung von Leprabacillen in *Ringerscher* Lösung aufbewahrt, einen *Presssaft* liefert, welcher, intracutan eingespritzt, bei der Mehrzahl von Nervenleprakranken eine starke, lokale Entzündung (positive Reaktion) hervorruft, während er bei Knotenleprakranken, besonders in schweren Fällen, nur ein leichtes, vorübergehendes Erythema erzeugt (negative Reaktion). *Kensuke Mitsuda* hat 1918 diesen Versuch nachgeprüft und gesehen, dass diese Reaktion bei Knotenlepra in 15 bis 65% der Fälle und bei Nervenlepra in 8 bis 21% der Fälle negativ ausfällt.

What Mitsuda himself said of the matter has been learned from Dr. Harry L. Arnold, Jr., of Honolulu, who has had a volunteer translator render some of Mitsuda's reports into

¹² Hayashi wrote in 1933 (reference 4) that he had reported on the subject at the Japan leprosy conferences in 1929, 1930 and 1931, and referred to the Tokyo Iji Shinsi (1930) 2661, 2677 and 2737. Tamiya gives an abstract of a report with the first of these page references, and also one of "Skin reaction in leprosy (II)" in the Japanese J. Urol. & Dermatol. 30 (1930) No. 5.

¹³ OTA, M. and NITTO, S. The serial transmission of human leprosy in fowls, continued for seven generations. Internat. J. Leprosy 9 (1941) 299-304.

¹⁴ OTA, M. and NITTO, S. Ueber *Mitsudasche* Reaktion, aufgestellt mit einem Antigen aus leprösem Gewebe von mit menschlicher Lepra infizierten Hühnern. Japanese J. Exper. Med. 18 (1940) 345-351.

¹⁵ HAYASHI, Y. [Kulturversuche des Leprabacillus sowie Kutireaktion bei Leprösen.] Saikingaku Zasshi (1918) No. 272 (in Japanese).

English. The pertinent passage has it that Yoshinobu Hayashi "...manufactured inoculation material from nutritive fluid (culture medium?) inoculated with material from leprosy patients..." and that with this material he got a luetin-like reaction, especially strong in "lepra nervorum." Mitsuda then went on to say that it is hard to get enough of this sort of material, so he just ground up 1 gm. of leproma in 10 cc. of saline and used it, after phenolizing and boiling, for the test material.

Whether or not there is any connection with Y. Hayashi's work, R. O. Stein in 1916¹⁶ had made skin tests with a sterile bacillus suspension from leprosy lymph nodes; five cases were practically nonresponsive, but two reactional cases (with strong *Lepraerysipeloidattacken*) gave strong skin reactions. Much earlier Babes¹⁷ had made skin tests with a substance extracted from skin nodules, lymph nodes and spleen, which induced in patients a reaction analogous to that to tuberculin. This result he regarded as indicating that the lepra bacillus produces a toxin—which was, at the time, the supposed nature of tuberculin itself—but it is probably to be regarded as an early demonstration of what is now called the early or Fernandez reaction to lepromin.

From the statements of Ota and Nitto and of Mitsuda which have been cited, it appears that Yoshinobu Hayashi is entitled to recognition as initiating a test which was made practical by Mitsuda, and further developed by Fumio Hayashi, and that he undoubtedly has a definite place in the history of the lepromin test. It seems highly unlikely, however, that the compound designation applied by Ota and Nitto will often be employed except when it is specifically intended to indicate the course of its development.

—H. W. WADE

¹⁶ STEIN, R. O. Die Cutireaktion bei Lepra und ihre Beziehungen zum Lepra-Erysipeloid. Arch. f. Dermat. **123** (1916) 908.

¹⁷ BABES, V. Sur des réactions réputées comme spécifiques dans la lèpre. Lepra **11** (1910) 321-333. Also, Ueber spezifische Reaktionen bei Lepra. Ztschr. f. Immun. u. Exper. Therap. **7** (1910) 578-623.