

# Mitsuda's Reactions. Induced by BCG in the normal Rhesus ("Macacca mulatta")

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Baccillar structural complexes are common both to *Mycobacterium tuberculosis* and *M. leprae*, with a decurrent intimate relationship in their antigenic capacity. The existence of crossed immunity phenomena between tuberculosis and leprosy is confirmed by the verification that tuberculosis-infection and tuberculosis-disease are capable of provoking positive Mitsuda reactions. The BCG vaccine also causes the reversal of the lepromin reaction, there already existing a considerable amount of literature on the subject (1-6). The prognostic advantages of positive lepromine-reactions are well-known in leprology. Individuals with the benign, tuberculoid form of leprosy display them. So, one soon began to think about the possibility of obtaining a certain anti-leprotic protection, by mass application of BCG into the endemic areas. However, besides the objection that we do not know in view of the leprotic infection if the Mitsuda's reaction induced by BCG has the same value as the one naturally acquired, some facts have been claimed as possible interferences in the induction experiments of that reaction. In fact, even in communities not struck by leprosy, there can spontaneously occur positive Mitsuda's reactions (due to tuberculosis infections and other causes), and in the endemic leprosy areas it is difficult to securely separate the communicants, part of which react positively to lepromin. Walls and his colleagues (7) are supposed to have obtained reversals of the Mitsuda reaction with various other vaccines besides BCG, such as the anti-diphtheric, anti-tetanic, etc. BLANC and others (8) are also said to have obtained reversals after the injection of a *Mycobacterium sp.* suspension. On the other side, PAULA SOUZA and collaborators (9) using living and died BCG and a control group, are said to have obtained reversals in 70.6% of the controls, during 11 months of observation, a rate which is superior to the percentage found among the persons that received BCG.

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\* Paper of the Instituto Oswaldo Cruz and of the Campanha Nacional Contra a Tuberculose. A note on this paper was presented at the National Tuberculosis Congress, which was held in Nov. 1953, in Curitiba. (State of Paraná).

The present paper deals with the induction of Mitsuda's reaction by BCG Vaccines.

In the here reported experiments, Rhesus monkeys reared in isolation in an attempt to avoid environmental interferences, were used.

Positive Mitsuda's reactions induced by BCG in guinea-pigs were previously reported (10).

#### MATERIAL AND METHODS

In the tuberculin tests (Tbn), tuberculin prepared in the Instituto Oswaldo Cruz (IOC) was used, in 1/10 dilution, 0.1 ml. being injected; for the infra-tuberculin (Itbn) tests the "extract of total BCG" of Professor PEDRO DOMINGOS (Havana-Cuba) was used, with injection of the same dosis. Lepromin was furnished by Dr. J. B. Risi, Chief of the Instituto de Leprologia, 0.1 ml. being used in the same manner. BCG vaccine from 1 to 3 days old, was obtained from the Instituto Viscondessa de Morais. The acid alcohol fast bacilli cultures were provenient from the collection of mycobacteria of the IOC (257-*Mycobacterium avium*, 258- *M. smegmatis*, and 279-*Mycobacterium sp*). The monkeys came from the IOC stock, at Pinheiro Island, situated in Manguinhos. The Rhesus were all previously tested and found negative to radiograph, tuberculin and lepromin tests. In the course of the experiments, the monkeys were weighed and X-rayed several times. The results of cutaneous tests were recorded according to the following criteria: *Mitsuda's Reaction (M.R.): Negative* — Absence of any lasting reaction up to 45 days. *Weakly positive (+)* = Nodule measuring up to 0.5 cm. without erythema. *Positive (++)* = Nodule measuring more than 0.5 cm. with or without erythema. *Strongly positive (+++)* = Nodule with definite erythema and necrosis. *Tbn and Itbn Reactions: Negative* = Absence of reaction between 48 and 96 hours. *Weakly positive (+)* = Slight erythema. *Positive (++)* = Erythema and local infiltration of 1 cm. *Strongly positive (+++)* = Papule or nodule with definite erythema, measuring more than 1 cm.

#### EXPERIMENTS

We have tried to observe the lepromin and tuberculin answers, after application of BCG vaccine by different via. Tests were effected *a long time after BCG* (from 7 to up and above 12 months), and also *shortly after the application of BCG* (from after a few days to above 2 months). Experiments extended over a period which went from July 1952 until August 1954.

##### I — *Mitsuda's Reactions effected a long time after the application of BCG*

A — On Sept. 25, 1952 two Rhesus were injected using 1 ml. (= 0,02 g) of BCG, into peritoneon (no. 1) and left testicle (No. 2), respectively. The second animal presented inflammatory reaction in the injected organ, remaining over a period of 3 weeks. On June 4, 1953 (more than 8 months after BCG application), first M.R. (left arm) and a "Itb" reaction (right arm) were effected. The following are the results of these test as well as of others carried out later on.

##### *Rhesus No. 1*

*1st M.R.* — On the 19th day a nodule measuring 0,5 cm could be felt, under an erythematous area, which was found to become larger during the following days, with slight ulceration. Reaction (+++). On July, 7, 1953, a biopsy was made; Histologically, a giant-histocytary nodular proliferation, characteristic of Mitsuda's reaction, was found.



Figure 1. Rhesus. Positive Mitsuda's reaction (left arm) after BCG vaccination.

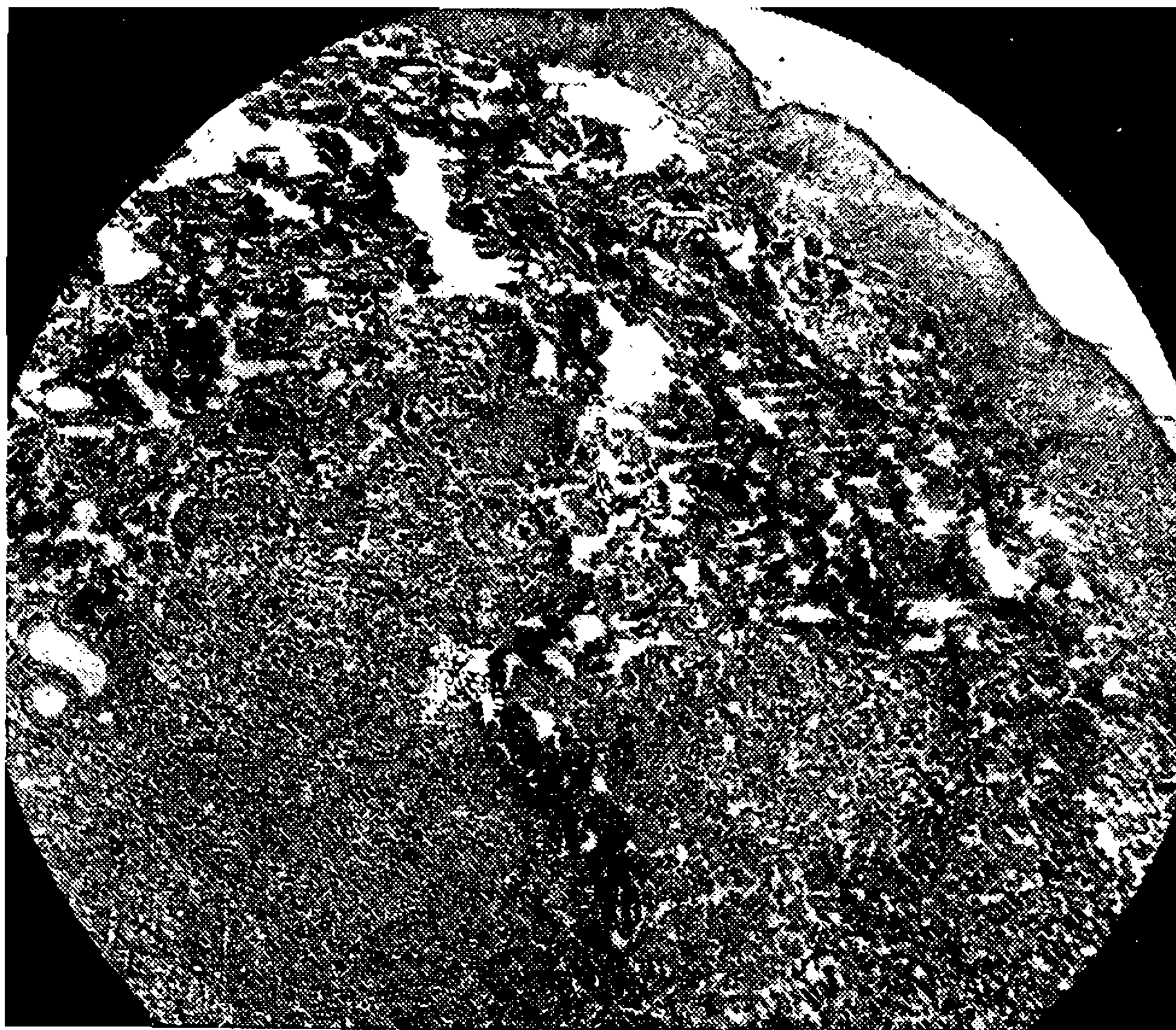


Figure 2. Section of the BCG induced Mitsuda's reaction on Rhesus. Nodular infiltration with histocytes and giant cells.

*2nd M.R.* — (More than 10 months after BCG) On August 18, 1953. After 48 hours' observation, one could observe a nodule at the point of injection (left thigh), which, with its evolution, became slightly ulcerated. Reaction (+++). On Oct. 8, 1953, the reaction entered a regression phase.

*3rd M.R.* — (More than 12 months after the BCG). On Oct. 22nd, 1953. After 48 hours, an erythematous nodule measuring 0,9 cm, could be seen at the point where the test had been effected (right side of abdomen); this one, equally, in due course, became ulcerated. Reaction (+++).

*"Itbn" Reaction.* After 96 hours, (++). This reaction disappeared after a few days. But, on the 20th day of observation, there appeared another non-erythematous nodule, which lasted for 11 days.

*Other "Tbn" and "Itbn" Reactions* (Oct. 23, 1953), were also found (++).

#### *Rhesus No. 2*

*1st R.M.* On the 16th day, an erythematous nodule could be observed, which, after measuring 0.8 cm started its necrosis. Reaction (+++). On July 7, 1953, a biopsy was made. Histopathology was found to be similar to that of the biopsy of Rhesus No. 1.

*2nd R.M.* (Aug. 18th, 1953), after 48 hours, an erythematous nodule, which in due course became ulcerated, could be seen at the place where the test was made (left thigh). Reaction (+++). On Oct. 22nd, 1953 this reaction began to recede.

*3rd R.M.* (Oct. 22, 1953) After 96 hours, a nodule could be felt at the point of injection (left side of abdomen), reaching a size of 0,9 cm. finally ulcerating. Reaction (+++).

*"Itbn" Reaction* — After 96 hours, (+++). This reaction disappeared after a few days of the test, another nodule could be felt, remaining so for 14 days.

*Other "Tbn" and Itbn Reactions* (Oct. 23, 1953), were also positive (+).

*B* — On Oct. 13, 1952. four Rhesus were given BCG orally, with the following single dosis: 0.2 g (No. 3 and No. 4), 0.6 g (No. 5) and 1.2 g (No. 6).

On June 4, 1953 (*more than 7 months after BCG*) the 1st M.R., left arm) and a "Itbn" reaction (right arm) were effected. The following are the results of these tests, as well as of others subsequently effected.

#### *Rhesus No. 3*

*1st M.R.* — Negative.

*2nd M.R.* — (More than 9 months after BCG), effected on Aug. 18, 1953. On the 28th day a non-erythematous nodule, measuring 0.3 cm, could be felt at the point of the test. Reaction (+). By Oct. 14, 1953, this nodule began to disappear.

*3rd M.R.* — (More than 11 months after BCG) effected on Oct. 22, 1953. On the 17th day, there could be felt at the local of injection (right side of abdomen) a small nodule, similar to the preceding one, which remained for 20 days, Reaction (+).

*"Itbn" Reaction* — Negative.

*Other "Tbn" and "Itbn" Reactions* (Oct. 23, 1953). Negative.

#### *Rhesus No. 4*

*1st M.R.* — Negative.

*2nd M.R.* — Effected on Aug. 18, 1953 (right thigh). Negative. The monkey died of intercurrent disease before the 3rd M.R. could be effected.

*"Itbn" Reaction.* After 48 hours: positive (++)

*Rhesus No. 5*

*1st M.R.* — On the 43rd day, a deep sub-cutaneous nodule was felt, measuring 0.3 cm. Reaction (+), which lasted for 26 days.

*2nd M.R.* — Effected on Aug. 18, 1953 (right thigh). On the 28th day, a small nodule could be felt, similar to that of the preceding test. Reaction (+). On the 45th day of observation, this nodule stood out and was visible.

*3rd M.R.* — Effected on Oct. 22, 1953 (right side of abdomen). On the 12th day, there could be felt a deep nodule, measuring 0.5 cm, without erythema, which lasted for more than 20 days. Reaction (+).

*"Itbn" Reaction.* After 48 hours: (+).

*Other "Tbn" and "Itbn" Reactions* (Oct. 23, 1953). The first was negative, the second weakly positive (+).

*Rhesus No. 6*

*1st M.R.* — On the 28th day, a deep, non-erythematous nodule could be felt, measuring around 0.3 cm. Reaction (+). This nodule remained without alterations for more than a month.

*2nd M.R.* — Effected on Aug. 18, 1953 (left thigh). On the 28th day, a small nodule was felt, similar to the preceding one. Reaction (+). On September 30, 1953, a biopsy was made. Histologically, the giant-histocytary reaction, characteristic of the Mitsuda reaction, was found.

*3rd M.R.* — Effected on Oct. 22, 1953 (abdomen, right side). On the 17th day, a small nodule was felt, similar to the preceding one, and which lasted for more than 20 days. Reaction (+).

*"Itbn" Reaction.* Negative.

*Other "Tbn" and "Itbn" Reactions.* (Oct. 23rd, 1953) Negative.

II — *Mitsuda's reactions effected short terms after the application of BCG.*

On Aug. 12, 1953, six Rhesus received a single BCG dosis, according to the following techniques:

Rhesus No. 7: Intradermically (right arm), 0,1 cm = 0.002 g.

Rhesus No. 8: Orally, 30 cc = 0.6 g.

Rhesus No. 9: Scarifications (right arm), on one drop of the vaccine.

Rhesus No. 10: Intradermically (right arm), 0.2 cc = 0.004 g.

Rhesus No. 11: Intradermically (right arm), 0.3 cc = 0.006 g.

Rhesus No. 12: Multipunctures (right arm), on one drop of the vaccine.

*Appearance and Evolution of local BCG Reactions.*

All monkeys that received the vaccine by parenteral via, presented more or less intensive reaction, the following being a summary of their appearance and evolution.

*Rhesus No. 7.* After 48 hours, a nodule appeared which, on the 6th day, was erythematous and necrotic, measuring 0.4 cm. No noticeable changes appeared until Sept. 30, 1953, when the lesion started going back. After 2 months' observation, it still had not disappeared entirely.

*Rhesus No. 9.* On the 10th day a local infiltration was initiated, increasing during the following days and transforming itself into an erythematous papule measuring 0.6 cm, which lasted for a month.

*Rhesus No. 10.* Similar reaction to that described for Rhesus No. 7. On Aug. 20, 1953, a partial biopsy of the lesion was made. Histologically, mono-histocytary infiltration, with globia of innumerable acid alcohol fast bacilli was observed.

*Rhesus No. 11.* Similar reaction, though quicker and more intensive, as the one observed in the preceding Rhesus. A total biopsy was effected on the 6th day, the same above described histologic aspect being found. *Obs.:* On that same date, Aug. 18th, 1953, a new BCG injection was effected, with the same technique and dosis (left thigh). On the 10th day, another necrotic nodule had formed, similar to the one cut off by the biopsy. This lesion lasted 2 months.

*Rhesus No. 12.* On the 4 day, a deep nodule could be felt, which increased rapidly and became definitely erythematous. On Aug. 21, 1953, necrosis and fistulization started in, eliminating caseous material. The tumour came to measure 2x2 cm. It had almost 3 months' duration.

#### *Mitsuda, Tbn and Itb Reactions.*

On August 18, 1953, (6 days after the application of BCG), the 1st M.R. was made (left arm). The following are the results of this test, as well as of others subsequently effected.

#### *Rhesus No. 7*

*1st M.R.* On the 41st day, a small, deep nodule, measuring 0.3 cm. and without erythema was felt. Reaction (+). This nodule remained unaltered until the animal's death (on Oct. 14th, 1953), due to intercurrentence.

*Itbn Reaction* (on Sept. 30th, 1953), Positive (+) in 48 hours.

#### *Rhesus No. 8*

*1st M.R.* — On the 27th day, a nodule similar to the one described for Rhesus No. 7 could be felt. Reaction (+). In Sept. 30th, the biopsy was made. Histologically, it presented the structure typical for Mitsuda's reaction.

*2nd M.R.* — Effected on Oct. 19th, 1953 (abdomen, right side). After 48 hours, a small, protuberating nodule, measuring 0.5 cm, could be felt. Reaction (+). This reaction lasted for more than 20 days. This test was effected more than 2 months after the BCG application.

*Itbn Reaction* — (Sept. 30th, 1953). Negative.

*Itb and Tbn Reactions* — (Oct. 23rd., 1953). Negative.

#### *Rhesus No. 9*

*1st M.R.* On the 15th day, a deep, non-erythematous nodule, measuring 0.3 cm, could be felt. Reaction (+). This reaction continued for more than 30 days.

*2nd M.R.* — Effected on Oct. 19, 1953 (abdomen, right side). After 48 hours, a nodule measuring 0.4 cm and similar to the preceding one could be felt. Reaction (+). This reaction lasted for more than 20 days.

*Itbn Reaction* — (Sept. 30th, 1953). Positive (+), after 48 hours.

*Tbn and Itbn Reactions.* — October 23, 1953. The first was negative and the second, positive. (+).

*Rhesus No. 10*

*1st M. R.* — On the 9th day, a small nodule could be felt at the place of injection, on the whole similar to the ones described in this series. Reaction (+). This nodule persisted up to the animal's death, due to intercurrent (on Sept. 4th, 1953). Histologically, a structure similar to the one described for Rhesus No. 8 was found.

*Rhesus No. 11*

*1st M. R.* — On the 10th day, a nodule could be felt, which became protuberant and erythematous, attaining a diameter of 0.6 cm. Reaction (++). On Sept. 30th, 1953, the biopsy was effected, the giant-histocytary reaction characteristic of the Mitsuda reaction was found.

*2nd M. R.* — Effected on Oct. 19th, 1953 (abdomen, right side). After 48 hours, it was possible to observe an erythematous nodule, measuring 0.6 cm on the 15th day of the test [Reaction (++)] which extended over a period of more than 20 days.

Eight Mitsuda's reactions observed in 8 different Rhesus monkeys were biopsied and studied histopathologically. Two were found strongly positive (+++), and 6 weakly positive (+). Among all of them, macroscopically, reactional gradations were observed. But, from the microscopic point of view, the differences were of a quantitative nature only, with a regular repetition of the giant-histocytary structure. In the two cases with necrosis, of course, the inflammatory infiltration covered the typical histologic lesions, more or less extensively. But at a distance from the ulcerated zone, however, epithelioid and giant cells were organised in nodules, in a very characteristic manner.

### SUMMARY AND CONCLUSIONS

The reversals of Mitsuda's reactions induced by BCG have been objected to based on the possible interference of other determination causes of the phenomenon: tuberculous primo-infections, communicants of unsuspected leprosy, reversals due to other causes, such as anti-diphtheric and anti-tetanic vaccination, etc.

In order to study the problem, we have used Rhesus monkeys (*Macaca mulatta*), which were reared in isolation, in an attempt to avoid the referred to interferences. Prior to the experiments, all animals were tested and found negative to radiograph, tuberculin and lepromin tests and were then submitted to the application of BCG vaccine (from 1 to 3 days old), in different doses and by different via.

At different times, after the application of BCG, they were again submitted to the radiographic, tuberculin and lepromin tests. In the tables I to IV the experiences were summarised.

**TABLE I**  
*Mitsuda's reactions on Rhesus long time after BCG vaccine.*

RHESUS NUMBERS	Via and dosis of BCG vaccine	MITSUDA'S REACTIONS					
		1st		2nd		3rd	
		Time elapsed after BCG	Results (days)	Time elapsed after BCG	Results (days)	Time elapsed after BCG	Results (days)
1	Peritoneal 0.02 g	More than 8 months	+++ (19)	More than 10 months	+++ (2)	More than 12 months	+++ (2)
2	Testicular 0.02 g		+++ (16)		+++ (2)		+++ (4)
3	Oral 0.2 g	More than 7 months	Negative	More than 9 months	+ (28)	More than 11 months	+ (17)
4	Oral 0.2 g		Negative		Negative		+
5	Oral 0.6 g		+ (13)		+ (28)		+ (12)
6	Oral 1.2 g		+ (28)		+ (28)		+ (17)

† = Dead of the Rhesus  
 + = weakly positive reaction.  
 ++ = positive reaction.  
 +++ = strongly positive reaction.

**TABLE II**  
*Mitsuda's reactions on Rhesus short time after BCG vaccine.*

RHESUS NUMBERS	Via and dosis of BCG vaccine	MITSUDA'S REACTIONS			
		1st		2nd	
		Time elapsed after BCG	Results (days)	Time elapsed after BCG	Results (days)
7	Intradermic 0.002 g	6 days	+ (41)	+	
8	Oral 0.6 g		+ (27)	2 months	+ (2)
9	Scarifications (drop)		+ (15)		+ (2)
10	Intradermic 0.004 g		+ (9)	+	
11	Intradermic 0.006 g		++ (10)		++ (2)
12	Multipunctures (drop)		+ (21)		+ (2)

† = Dead of the Rhesus  
 + = weakly positive reaction.  
 ++ = positive reaction.



**TABLE III**  
*Mitsuda's reactions on Rhesus after died BCG vaccines and other living mycobacteria. (Control group).*

RHESUS NUMBERS	Via and dosis of died BCG and of other mycobacteria	MITSUDA'S REACTIONS					
		1st		2nd		3rd	
		Time elapsed after ...	Results (days)	Time elapsed after ...	Results (days)	Time elapsed after ...	Results (days)
13	Died BCG Intradermic 0.006 g	10 days	+ (39)	1.5 month	+ (2)	4 Months	(2) (2)
14	<i>Mycobacterium</i> sp. Intradermic 0.3 ml		Negative		Negative		+
15	<i>M. avium</i> Intradermic 0.3 ml		Negative		+		
16	<i>M. smegmatis</i> Intradermic 0.3 ml		Negative	2.5 months	Negative		+
17	Died BCG Oral 1.2 g		+ (39)	2 months	+ (2)		+

† = Dead of the Rhesus

+ = weakly positive reaction.

**TABLE IV**  
*Comparisons of lepromin and tuberculin, reactions on Rhesus after the application of BCG.*

RHESUS Numbers	BCG via	REACTIONS				
		Lepromin			Tuberculin	
		1st	2nd	3rd	1st	2nd
1	P	+++	+++	+++	++	++ (++)
2	T	+++	+++	+++	+++	++ (+)
3	O		+	+		( )
4	O				++	
5	O	+	+	+	+	(+)
6	O	+	+	+		( )
7	I	+			+	
8	O	+	+			( )
9	E	+	+		+	(+)
10	I	+				+
11	I	+++	++			(+)
12	M	+	+		+	(+)
13	I	+	+	+		( )
17	O	+	+			( )

Legend: P = Peritoneal  
 T = testicular  
 O = oral  
 I = intradermal  
 E = escharifications  
 M = multipunctures

† = Dead of the Rhesus  
 — = negative  
 + = weakly positive  
 ++ = positive  
 +++ = strongly positive  
 ( ) = Itbn

From the experiments, the following conclusions were reached:

1 — From 12 Rhesus that received BCG 11 showed reversals of the Mitsuda reaction (91.7%).

2 — These reverseals took place both in tests effected *shortly after BCG* (from 6 days to 2 months), and tests effected *much later* (from 7 to 12 months after BCG)

3 — Some differences were found in the results, according to the dosis and the application via of the BCG.

a) — The *testicular* and *peritoneal* via (0,02g) were the only that determined strong positive Mitsuda's reactions(+++).

b) — By *oral via*, animals that received high dosis (0.6g and 1.2 g), there resulted uniform and regular reversals, even though of low intensity (+); but from those who got small doses (0.2 g.) one showed no reversals in all tests, and the other presented reversals in the 2nd and 3rd tests only, also with low positivity (+).

c) — By *intradermic via*, in Rhesus which received higher doses, (0.004 g and 0.006 g), reversals was more rapid (9 and 10 days), and the more intensive positivity (++) corresponded to the higher doses.

d) — The Rhesus that received BCG by means of *scarifications* and *multipunctures* also presents reversals with low positivity (+).

4) In the 2nd and 3rd Mitsuda's reactions in the same animals, positivity was always precocious (generally within 48 hours), one getting the impression that there occurs a sensibilization of the animal body by the antigen with the repetition of the tests, even though the intensity of the reaction always remains the same. This precocious reaction (Fernandez type) occurs both shortly and long time after the application of the BCG.

Its precocity depends not of the antigen only because the first Mitsuda's reaction after the BCG application occurs after some time and seems not influenced by the control lepromin test effected on the Rhesus before the BCG.

5) On the *control group*, the animals which received a.a.f. bacilli suspensions (*Mycobacterium* sp.; *M. avium*, and *M. smegmatis*), *did not show reverseals of the Mitsuda's reaction*. Two Rhesus, however, which received dead BCG (120°C autoclave 1 hour), one intradermically (0.006 g) and the other orally (1.2 g), did both present reversals of the Mitsuda's reaction, with weak positivity (+). In all animals of the control-group, the allergic reactions were found negative.

6) Strong local inflammatory reactions were observed in the Rhesus that had received living BCG by *intradermal via*, and in the one submitted to *multipunctures*, there occurred the formation of a large caseous abcess.

7) The allergic tuberculinic and infratuberculinic reactions appeared dissociated from the Mitsuda's reactions: sometimes they are

more precocious, occurring before of the lepromin test; on other occasions they disappear, when the Mitsuda's reactions still persist; and finally, they may be absent, when the latter occur, especially after the oral application of the BCG.

8) In Rhesus which received BCG by *testicular and peritoneal via*, in the infratuberculinic test (0.1 ml of total BCG extract), besides the classic answer, which occurs between 48 and 96 hours, one could observe a delayed answer (15 to 20 days), represented by a non-erythematous nodule, which persists for 11-14 days.

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