

# The Report on Inoculated Tuberculosis Accidentally Caused by Typhoid Vaccin Injection.

## The Clinical Observation

### Part I

**Masashi TAMURA, M.D.**

田村政司

(Received Oct., 15, 1954)

### Forward

To study tuberculosis on human materials from possibly multitudinous angles is still an important part of research in this region. Especially, it is most keenly believed by those who know the difficulty to expect the same results from animal experiments as in the study of human tuberculosis. Beside this and rare as it is, the inoculated tuberculosis reported here should be highly esteemed, as it offers very interesting and important facts to the field of tuberculosis investigation.

The case of subcutaneous infection of human tubercle bacilli is very rare, though there have been a few such cases as in the reports of Selter (this case occurred as the result of subcutaneous injections to produce immunity), Lindemann, Lehmann, Elsenberg, Deneke, Hiki, Mitani and Narabayashi, but those clinical or autopsy reports lacked enough data.

Typhoid preventive injection was held at Dojo Primary School in Hyogo Prefecture May 1946 to have resulted that tuberculosis was inoculated on many children at the injected locals. A survey as to the cause of the accident was made by Dr. Hamano, Chief of Bureau of Disease Prevention, Ministry of Welfare, April 1947 and reported at the 22nd meeting of the Japanese Association for Tuberculosis. Then we were able to take opportunities since October 1946 to observe the

\* From the Hyogo National Sanatorium (Chief: G. OGAWA, M.D.), Hyogo Prefecture, and the Division of Paediatrics (Chief: Prof. I. SAGAWA, M.D.), Tuberculosis Research Institute, Kyoto University, Japan.

physical condition of these children day after day, so that I would like to describe the main findings, referring to data of their local changes and X-ray photographs of their chests since then.

### I. Materials and Means of Observation

At the Dojo Primary School in Hyogo Prefecture, the typhoid and paratyphoid A. B. mixed vaccine, which had been produced at Kobe Sanitary Laboratory, was injected to all the school children, from the 1st year of primary course up to the 2nd year of senior course, and at the same time to the girls of the Girls' Youth School, all 631 in number. The injection was held twice, 1st time on May 6, 1946 and 2nd time on May 13, 1946. The injections, 1st time 0.3 cc-0.5 cc and 2nd time 0.5 cc-1 cc, were made to the upper arms of the boys and girls.

At the injection, tubercle bacilli seemed to have been injected simultaneously by some unknown reasons. Consequently, about one month after the 2nd injection, there some 102 patients were affected by tubercle bacilli on the injection locals (skin induration) and on the regional axillary lymph node swelling. On these symptoms, Prof. Dr. Z. Ishikawa of the Hyogo Prefectural Medical College proved that these changes were due to tuberculous infection.

The injection operators were a female doctor, a public health nurse and a nurse. Later the female doctor was found to be an open pulmonary tuberculosis patient, her Gaffky number having been five to six, but both of the nurses proved to be quite sound and healthy.

The description over the pathological and histological findings on skin induration and regional axillary lymph nodes will be given in the following report. The inoculated tubercle bacilli were determined to be of human type by the Sanitary Department of Hyogo Prefectural Government and by Dr. M. Shiraishi and Dr. S. Katayama of the Tuberculosis Research Institute, Kyoto University, both under supervision of Prof. Dr. S. Ueda.

According to Dr. M. Shiraishi and Dr. S. Katayama, the strains separated from the school children and the female doctor were human type, but the identification of them has not been possible yet. Judging from the results of the experiment by the two doctors, the strains separated from the children had much similarity and seem to be of the same origin. As compared with the Frankfurt strain from the female doctor had a greater likeness to the childrens strains than to the Frankfurt strain, though, the two doctors declined us to give a decisive answer to the matter.

In respect to the geographical relation, we first treated some of the infected children on local lesions together with a regular periodical of chest by X-ray photography, occasional culture of bacilli from sputum and tuberculin reaction. Later, over a pretty long period, close observation was made on one-half of the infected children who were transferred to the Hyogo National Sanatorium since November,

1947. For the purpose of comparison, mass examinations together with X-ray photography of chest were held on positive tuberculin reactors and negative reactors of the same school simultaneously.

In regard to the changes of the local lesions in the early stage, we referred to the description of Prof. Z. Ishikawa at the Hyogo Prefectural Medical College (Division of Surgery), of the Anti-tuberculosis Association, and in the Shunkaen National Sanatorium.

The views and findings of X-ray photographs of chest taken around October to November, 1946 were referred chiefly to the diagnosis of Dr. T. Iwasaki of the Research Institute of Tuberculosis in the Anti-Tuberculosis Association, and the others taken around January to February, 1947 to the diagnosis of Dr. M. Tomita who was working here at that time, now chief of the section of Medical Affairs of Kochi National Sanatorium.

For the tuberculin reaction, 2,000 times diluted tuberculin solution produced at Amako Laboratory was injected, intra-cutaneously, 0.1 cc to each person. Presence of skin erythema more than 10 mm in diameter 48 hours after the injection was regarded as positive reaction. In the description, “+” means erythema only, “+<sub>1</sub>” means erythema with induration, and “+<sub>2</sub>” means double erythema or erythema with blister.

For red cell sedimentation rate, we applied Westergren’s method and the values at one hour at the room temperature were measured.

The tubercle bacilli in sputum were examined by culture. The media for it was Oka-Katakura’s, but for the patients who did not present sputum, pharynx and larynx mucous was taken for use by purified cotton.

## II. Number of the children who indicated some local symptoms.

Changes of injection locals and lymph nodes were seen on 102 children, and this was 16.1% when compared with 631 children who received the injection. As it is shown in table 1, 44 children of the 3rd year of the primary course were

Table 1 Number of Patients Classified by School-year

School year	P. I	P. II	P. III	P. IV	P. V	P. VI	S. I	S. II	Youth School	total
Number of the Injection receivers	86	68	90	68	107	82	44	52	34	631
Number of affected cases	boy	6	3	24	4	5	1	6	0	49
	girl	0	5	20	9	9	7	0	0	53
	total	6	8	44	13	14	8	6	0	102
%	6.9	11.7	48.8	19.1	13.0	9.7	13.6	0	8.8	16.1

(P.…… Primary course, S.…… Senior course)

affected (nearly equal to the half of total patient's number, but no patient was found in the 2nd year of the senior course, while 3 were found in Girls Youth School. The girls and boys affected were almost same in number. That most cases were found in 3rd year of the primary course might have some connections with the fact the 1st time injection was started from 1st year (to the 2nd year and 3rd year) of the primary course, and the 2nd time injection was started from the 3rd year of primary course, while the 1st and 2nd year pupils of the primary course were injected together with the senior course pupils in case of the 2nd injection.

There were 83 children who remembered by whom the injections were given. The affected pupils were injected by any one of the following three; a female doctor, a public nurse and a nurse. There were 35 affected pupils who were twice injected by the female doctor, 37 once by the doctor, and 11 by the others (not by the doctor).

About that time in the other public school, the same doctor made the typhoid vaccine injection produced by the same laboratory, but no inoculated tuberculosis case was found there.

### III. The preventive injection and the affected sides.

Out of the 102 patients, 96 had lesions on their left upper arms and axilla, while 6 on their right upper arm, but none had lesion on both arms.

Table 2 List of Injected side and Affected side

Injected side Affected side	left at both times	right at both times	left at 1st time right at 2nd time	only left at 1st time	unknown	total
left	92	0	1	1	2	96
right	0	5	1	0	0	6

As the table 2 shows, the side where skin lesions appeared coincided with the side where the 1st and the 2nd injection were made (one patient, Case 74, received the injection only once). On the other hand, there were two children who got the 1st injection on their left arm and the 2nd injection on the right. One of them had local change on the left arm (Case 2) and the other on right arm (Case 65). Judging from the above-mentioned fact, it can be said that they might have had a chance of tubercle bacilli infection on either of two injections. By the way the one, who got only the 1st injection on the left arm (of whom I just mentioned), was given it by the doctor and the other one, who indicated the right arm local lesion, was injected on the left arm first by the nurse, and indicated on the right arm by the public health nurse secondly.

#### IV. Findings in the vicinity of the injection locals.

One hundred and one persons indicated induration and swelling on the upper arms where the injection was supposed to have been made. Nearly one half of them noticed their induration and swelling during June, 1946, about one month after injection. Though there were some who found the swelling later than the others; they noticed it before October or November 1946, at the latest. Only one person (Case 93) found it during May 1947, a year after the injection (See table No. 3).

Table 3 The time when the local changes were perceived

Date	June 1946	Jul. 1946	Aug. 1946	Sep. 1946	Oct. 1946	Nov. 1946	May 1947	unknown
Number of cases	45	18	5	5	4	1	1	23

Some children narrated that they noticed local swelling within a week after the injection or that they became feverish to a little extent then, but it is not clear whether or not it was due to the local reaction of the injection itself or it had any continuous connection with the local induration incised later. None had an acute skin ulcer that corresponded to the Koch's phenomenon.

The symptom, at the beginning, was a slowly growing skin induration and reddening accompanied by no pain, then the induration gradually softened and reached to the size of the tip of a small finger or some times to the size of a pigeon's egg and was accompanied by a mild pain and then appeared the swelling of axillary lymph nodes. There was only one case (Case 33) that obviously had the glandular swelling antecedent to local lesion on the upper arm.

Eight children had spontaneous rupture of induration after the softening. The quickest rupture happened on June 25, 1946 (Case 62). Almost all of the rest were given incision operations before their spontaneous rupture, starting with patient Case 32 on June 25, 1946. Most of incised wounds reached to the subcutaneous tissue, but a few reached to the muscular layer, and the granulation covered by pus or pus moss was anemic placid and was shallow-undermined beneath the marginal sound skin. The biggest incised wound was 55×30 mm. in diameter. It took at least one month and at the latest several months to heal. Not a few cases were reincised for induration abscess which appeared after the ordinary cicatricial healing. But the primary foci recovered in each of our patients by September, 1947.

Subcutaneous induration was extirpated from 9 children who did not received incision beforehand. They adhered to muscles at the base, but were movable from skin and each of them was a size of a pea or a bean without infiltration in its surrounding. Only one pupil (Case 101) had two palpable indurations at the time of the primary examination. They adhered to fascia in the subcutaneous

adipose tissue, and were surrounded by membranous substance, the size being equal to a pea or bean, and caseous substances were recognized in their central parts. There were some subcutaneous indurations that had already softened at the time of operation.

There were 40 patients who indicated subcutaneous metastatic indurations beside the induration of primary focus which appeared first. Generally most subcutaneous indurations were centripetal for primary foci of upper arm. Only 6 cases showed the retrograde indurations in the lymph pathway (Case 15, 19, 26, 62, 83 & 88). In 18 patients, pea-sized or thumb-tip-sized subcutaneous indurations were found in the middle-way, on the inner surface of the upper arm, between primary foci and regional axillary lymphatics. Two cases (Case 25, 56) out of these 18 patients had subcutaneous induration before the extirpation, while the rest of them showed the induration after the extirpation of regional lymphatics and the healing of primary foci, and in an extreme case the induration appeared 2 years and 2 months after the injection, namely in July 1948 (case 29). In a certain case (case 86), spontaneous rupture of subcutaneous metastatic induration appeared near the primary focus in Sept. 1948. On the other hand, there were 8 cases in which subcutaneous metastatic indurations had once appeared but disappeared later. Two subcutaneous metastatic indurations were found in one case. And tuberculosis of muscle of left upper arm was found in the other (case 15). In this case, pathologico-histological examination of the regional axillary lymph node led us to an inference of reinfection, and this will be discussed later.

#### V. Tuberculin Reaction

Tuberculin reaction was held in Oct. 1944 for all pupils of Dojo primary School, but it was not held in 1945. In 1944, the positive percentage of every school year ranged from 13.7% to 18.5%, and the mean value was 15.9%. Soon after the occurrence of this tragedy, namely from the end of 1946 up to the beginning of 1947, the average positive percentage was 38.3%. The highest was 70.7% of the 3rd year of primary course (as is shown in Table 4). Five pupils out of 195 negative tuberculin reactors of 1946 (Dec.) turned positive at the end of 1947. The average percentage of natural infection (turning newly positive) was 2.8%.

One hundred and two pupils who indicated local lesions were all positive reactors. The short diameter of reactive erythema or induration was measured in Table 5.

In Dec. 1946, there were all patients who showed distinctly colored, sharp outline erythema and induration, while 10 pupils marked double erythema and other two pupils indicated blister formation. As the time passed by, the induration tended to become smaller and size of erythema did not always become small. In one case, blister formation was noticed on the double erythema in Dec. 1948. Within two and half a year after the typhoid vaccine injection no one became

Table 4 Tuberculin Reaction at the End of 1946

School year	P. I	P. II	P. III	P. IV	P. V	P. VI	S. I	S. II	total	
Number of persons	87	70	92	51	118	89	44	51	602	
Positive	Positive reactors in 1944			12 (1)	9 (1)	6 (1)	9	5	7	48 (3)
	Positive reactors before the injection	0	0	0	0	6	3	1	0	10
	Persons with no connection with the injection	0	3	2	1	4	2	2	1	15
	Persons with local lesion	6	7	43	12	13	8	6	0	95
	Negative reactors in 1944			5	1	0	2	3	3	14
	Persons received no test in 1944	11	9	3	8	8	2	4	0	45
	total	17	19	65	31	37	26	21	11	227
	Positive tuberculin rate	19.8	27.1	70.7	16.1	32.1	29.5	47.8	22.9	38.3
Negative	Positive reactors in 1944			0	1	0	2	0	0	3
		69	51	27	18	78	60	23	37	363
Persons received no test	1	0	0	1	3	1	0	3	9	

( ) persones with local lesion.

Out of the pupils with local lesions, one removed to the other school in Nov. 1946.

Table 5 Tuberculin Reaction on Persons with Local Lesions

Reaction m.m.	0-4	5-9	10-19	20-29	30-39	40-49	50-	Remarks	
Dec. 1946	Erythema	0	0	32	39	11	1	2	double erythema 10, blisters 2, other 17 cases turned positive after wards.
	Induration	10	6	59	10	1	0	0	
Dec. 1947	Erythema	0	0	30	45	7	2	2	double erythema 3, blister 1, 16 persons with no test.
	Induration	34	7	42	2	1	0	0	
Dec. 1948	Erythema	0	0	22	26	26	10	8	double erythema and blisters 1, blisters 7, 10 persons with no test.
	Induration	36	1	43	12	0	0	0	

anergic. It was difficult to find out any relation between the intensity of tuberculin reaction and that of the local lesions, or the degree of pathological changes in X-ray pictures.

The local lesion appeared in 3 pupils out of 51 positive tuberculin reactors of 1944, too. So the majority of new positive reactors were of primary infection, but it is easily supposed that certain case of re-infection may have been among them in addition to the above-mentioned three.

Out of 269 negative tuberculin reactors of 1944, 14 pupils turned tuberculin reaction positive without local lesion. The percentage of new positive reactors during these 2 years was 5.2%, and as the percentage of them during 1947 was 2.8%, so that the former percentage seemed to be of due course. Among the positive tuberculin reactor of 1946, 45 did not received tuberculin reaction in 1944. Among these 45, only 12 had dwelled in this village from their infancy, while other 33 removed there from Osaka, Kobe, Nagoya, Kyoto, etc. Out of 14 positive tuberculin reactors without local lesion and 12 living there from their infancy, (namely out of 26), 6 were of same families. An investigation was made on the connection with family. Out of 7 sets of pupils, each consisting of two pupils and attending to the same school, 6 sets were all positive reactors. In two cases of one-pupil-per-one-family, apparent source of infection was found in their parents. One positive reactor had already (2 months before the typhoid vaccine injection) affected by pleurisy. On the other hand, out of 51 positive tuberculin reactors of 1944, 3 became anergic reactors in 1946.

(To be continued)