

# The Pathogenesis of Tuberculous Meningitis. A Criticism of Rich's Focus-theory.

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Received May 20, 1954

## Introduction

Since tuberculous meningitis has been treated with streptomycin, a large number of reports on the effect of the chemotherapy have been published in our country as well as overseas, and moreover with isonicotinic acid hydrazide the prognosis has become more favourable. It is certain that, definite results of the use of the new drug will be established in the near future.

On the contrary, there are still at present many different theories concerning the pathogenesis of tuberculous meningitis.

Our attempt to examine once more the pathogenesis of tuberculous meningitis will serve some useful purpose.

Since the summer of 1952, we have been trying to reveal the pathogenesis of tuberculous meningitis chiefly by the findings of spread specimens of the meninges which will be explained in the following part. First we will describe our results and next comment upon several theories about the pathogenesis, especially Rich's focus-theory.

## The Authors' Observation

The pathological findings of the meningeal blood-vessels, namely, the formation of tuberculous nodules and the perivascular cell infiltration on a microscopic

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specimen, whose section is vertical to the surface of the brain, will not be always easy for us to determine from which of the under mentioned they are caused:

A) Are they caused from the sitting and proliferation of bacilli in the blood stream to the vessel wall themselves?

B) Are they regarded as the inflammatory reaction of the meningeal blood-vessels caused by the invasion of bacilli discharged already in the subarachnoid space?

To reveal this question we have used a new method, that is to say the spread specimens of the meninges, which were made up by the imitation of the extension specimens of subcutaneous tissues. This method will be the best to observe the changes of the meningeal blood-vessels cubically as they are. But they are too thick to observe delicacies, so we have also applied the specimens by the usual method.

It is very simple to make the spread specimens of the meninges. Man may strip the meninges, the pia together with the arachnoid, from the fixed brain and stain them variously and then spread on an object glass. By this method 10 brains of infants, who died of tuberculous meningitis both treated with streptomycin and without, have been examined. After a while we found the literature, in which Schuermann applied the same method for the meninges of infants, died accidentally by B.C.G. inoculation in Luebeck.

Generally the vascular changes in the meninges detected in our materials may be classified in the under two types.

#### **1) The type of tuberculous nodules**

This tuberculous nodules have 200–800 millimicrons in diameter mostly around arterioles of about 100 millimicrons in diameter. The nodules are found comparatively abundant in the areas, where arterioles bend or branch off, and they are mainly composed of epitheloid cells, lymphocytes and plasma cells. But giant cells of Langhans type are scarcely found. A great number of them are caseated in the center. Recently we have found clearly these findings in an infant who died of miliary tuberculosis without clinical signs and no pathological findings of cerebrospinal fluid.

In all ten cases (which we have) examined, these multiple nodules have been found densely distributed.

#### **2) The type of the perivascular cell infiltration**

This infiltration exist around the small meningeal blood-vessels and these cells are composed of lymphocytes, plasma cells and macrophages, which are assumed to originate from monocytes. But leucocytes are scarcely found. Additionally, in the networks of connective tissues distant from these small blood-vessels there are a mass of fibrin and inflammatory cells mostly composed of macrophages.

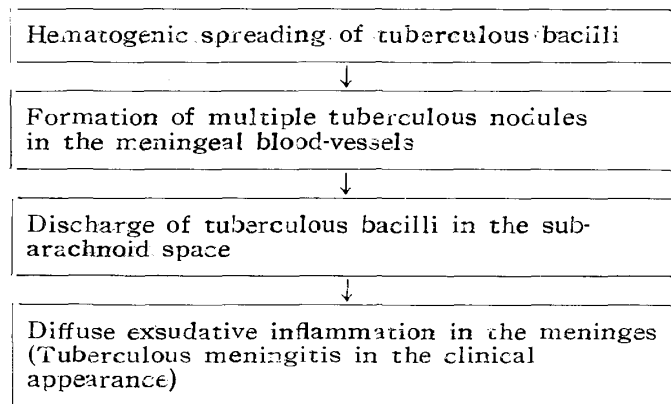
Although some specimens present either the type of tuberculous nodules or of the perivascular cell infiltration, a great number of them present both types.

Then how do both changes of the meningeal blood-vessels occur ?

We believe firmly that the small multiple nodules will grow and enlarge in the wall of the meningeal arterioles, where bacilli will have settled and also in other words, they may be regarded as meningeal miliary tuberculosis. As above mentioned, tuberculous nodules in the meninges are found multiple and fairly dense in all our cases, but the more chronic the cases become and fibrosis increases in the meninges, the more the nodules become complicated and undistinguished. These facts will support our judgment.

Secondly, the authors have the opinion that the perivascular cell infiltration originates quite differently from the former mechanisms. Namely, it will be the inflammatory reaction of the small blood-vessels in the meninges against the tuberculous bacilli, which have already been discharged in the subarachnoid space. This latter finding is the essential change of diffuse exudative tuberculous meningitis and the former is, as it were, a forerunner-like change. From the small nodules, tuberculous bacilli must be discharged suddenly and numerously.

We can show a sketch according to our theory as follows :



Then we have attempted to confirm our above-mentioned conclusion by the animal experiments.

Since former times there have been many experiments which attempted to cause tuberculous meningitis by the injection of bacilli in blood-vessels of animals. But they have almost always ended in failure and Rich and McCordock regarded their negative results in the same experiments as a powerful support to their own theory.

According to our results, when previously a small quantity of old tuberculin solution is injected into the subarachnoid space of tuberculous rabbits and then tuberculous bacilli are introduced into their auricular veins, there occur tuberculous nodules in the meningeal arterioles, but not the perivascular cell infiltration. On

the contrary, when the suspension of bacilli is injected directly into the subarachnoid space of infected rabbits, the latter only occur, and not the former. About these detailed results H. Saito, one of the authors, will soon publish an original report.

Recently T. Matsubara has succeeded in causing multiple nodules in the meninges together with caseous foci in the brain by the injection of bacilli suspended in 33% glucose solution into the internal carotid arteries of tuberculous rabbits.

### Discussion

Concerning the pathogenesis of tuberculous meningitis, as we mentioned in the beginning, nowadays there is no definite theory admitted by everybody. Next we will comment upon the several theories.

Rich and McCordock introduced the so-called Rich's foci theory from the findings in 82 autopsies of tuberculous meningitis cases and the results of animal experiments. They emphasized as the cause of meningitis the solitary tuberculous nodules of different size, which is usually in the brain, sometimes in the meninges discharging bacilli into the subarachnoid space.

Namely they persisted that tuberculous foci in the brain and meninges were much older than meningitis in age and they detected this foci in 56 cases in the brains, 2 cases in both brains and meninges, and 17 cases in the meninges.

As soon as this theory was published in 1933, one after another investigated it. For instance, McGregor and Green found caseous foci in 74 brains out of their 88 cases, which they recognized as the sources of tuberculous meningitis. Moreover Schwarz and Lincoln etc. agreed with this theory from the results of their own researches.

But there are not a few students, who stand against this theory. Ragins stated that there were 32 cases out of 39, in which the Rich's foci were not detected. Beres and Meltzer stated that they could not find foci in brains in 14 cases out of 28, and yet there were only 6 cases, in which the foci might be presumably connected with the origin of tuberculous meningitis.

In our country Aizawa could not confirm any foci in the brains except 3 cases out of 23 cases. And yet in these 3 case there was localized intense proliferation of connective tissues in the communicating areas of the foci into the subarachnoid space.

Now we paid special attention to the research on tuberculous foci in the brains, too. According to our results in the infant cases we found them only in 6 cases out of 19 and yet there was only one case, in which foci might be assumed as the source of meningitis. This case, 8 years old male, at first presented the clinical symptoms like encephalitis. In autopsy a caseous focus were revealed in the oblongata and in the wall of left ventricle, were surrounded with dense connective tissue and included many giant cells of Langhans type. The foci in the wall of ventricle broke into the subarachnoid space. Therefore we believe that the foci

in the brains will not be so important as insisted by Rich etc. so far as assumed to be the origin of tuberculous meningitis. At least in the infant, the meningitis are often used to occur at the same period with acute miliary tuberculosis resulted from the primary infection.

Next we should discuss the extension from the caseous foci in the meninges themselves, on which Rich and McCordock insisted too. According to their description, such foci are found in the form of flattened caseous plaques, partly or completely encapsulated and vary in size from a few millimeters to more than a centimeter in diameter and may discharge bacilli into the adjacent spaces, which are directly responsible for the development of diffuse meningitis in the period of lowered resistance. Therefore we should ascertain differences between Rich's foci in the meninges and multiple tuberculous nodules recognized in our spread specimens of the meninges. In some cases such foci were found in the depth of sulci when cutting the entire brain in slices not thicker than three millimeters. Rich's foci in the meninges are usually one or two and surrounded by connective fibre completely or partially. On the contrary, the nodules which we pointed out are, as above mentioned, found densely multiple in each case and much more fresh than those of Rich. Namely, our nodules are different from Rich's foci as to the number and age. Rich et al stated on the other hand that in infant the foci in the brains and meninges increased in size caseated before they would get the acquired resistance, and were not be surrounded by connective fibre at all. If such foci would be limited only to the meninges, not in the brain and grow up profusely, Rich's foci would be identical with our nodules.

Now we should refer to the study by Schuermann, who detailed the pathologic findings in the brains of infants died of tuberculosis, not meningitis in Luebeck. Those infants showed transient meningeal irritations and revealed in some cases no pathological findings of cerebrospinal fluid, but in a great number of cases slight pleocytosis without increase of globulin. He prepared the some spread specimens as ours. According to his study, there were very small focal infiltrates composed of lymphocytes and macrophages scattered on branches of small meningeal blood-vessels, which sometimes were found macroscopically and showed even the caseation. These findings could be detected in some cases without any signs of meningitis. This very small focal infiltrates may be regarded as the early or healing form of our multiple nodules in the meninges.

Recently, Lincoln introduced the term of serous tuberculous meningitis, which he found in 12 cases and these cases corresponded with the above-mentioned by Schuermann in both clinical and fluid findings. In the 2 cases out of 5, died of other causes after the healing of serous meningitis, there was the residue of non-specific meningitis and in 3 cases the caseous foci in the brain. As the cause he thought much of the collateral inflammation around the foci in the brains. But

it is not unprobable that it might be caused by such multiple cell infiltrates in the meninges as the cases by Schuermann. Rich and McCordock regarded them as caused by bacilli discharged in the arachnoid space. Nonne and Luce classified them into two groups; (1) the tuberculous inflammation in each stratum of meningeal blood-vessels and (2) tuberculous nodules on their walls. The former appears as the round cell infiltration in the adventitia, which next invades the media and sometimes even the intima and then develop to the panangitis. The latter like to grow up in the adventitia, too, but sometimes invade the media and present typical nodules, which caseate and have giant cells of Langhans type. In Japan Kimura observed in detail the changes in the meningeal blood-vessels and found epitheloid cell tubercles around arterioles, the perivascular cell infiltration of lymphocytes and panangitis as above mentioned. Recently Nakajima reached the same conclusion, namely, dividing them into the following two classes, the first shows scattered small nodules in the end branches of arterioles and junctions of capillaries and the second belongs to the successive changes of blood-vessels, which accompany the exsudative inflammation in the subarachnoid space.

Next we should refer to the theory, which was induced by Kment in 1924 and supported by Knaup, Huebschmann etc. According to it, the typical form of tuberculous meningitis is caused by the discharge of bacilli chiefly from the foci in the choroid plexus and sometimes in the pia mater. In the latter cases present localized meningitis and not diffuse one. They asserted that the meningitis is the result of the caseous foci in the choroid plexus. In our 19 cases examined we could not find such old caseous foci in the choroid plexus as the original foci of meningitis. Takahashi pointed out that the tuberculous changes in the choroid plexus were found in all cases except two out of 105 tuberculous meningitis, but these changes occurred at the same time with meningitis, or later.

### Summary

1) The pathogenesis of tuberculous meningitis was studied by the preparation of the spreading specimens of meninges.

2) The tuberculous meningitis in infant succeeded to primary tuberculosis will break out by the cerebrospinal fluid infection from multiple caseous foci in meninges, which were formed in the walls of meningeal arteriols in the early dissemination.

3) Sometimes caseous foci in brains and choroid plexuses were found, but these foci are not essential as the cause of meningitis.

4) There will be rarely some cases, in which bacilli will be discharged in the subarachnoid space from the caseous foci in brains. In such cases tuberculous meningitis apt to be chronic and to relapse in spite of the adequate therapy.

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Fig. 1 Tub. nodules in infant (spread specimen)



Fig. 2 Tub. nodules in infant (usual specimen)





Fig. 3 Tub. nodules in infant died of miliary tub. without meningitis (spread)



Fig. 4 Tub. nodules in rabbit (spread)



Fig. 5 Perivascular infiltration in infarct (usual specimen)

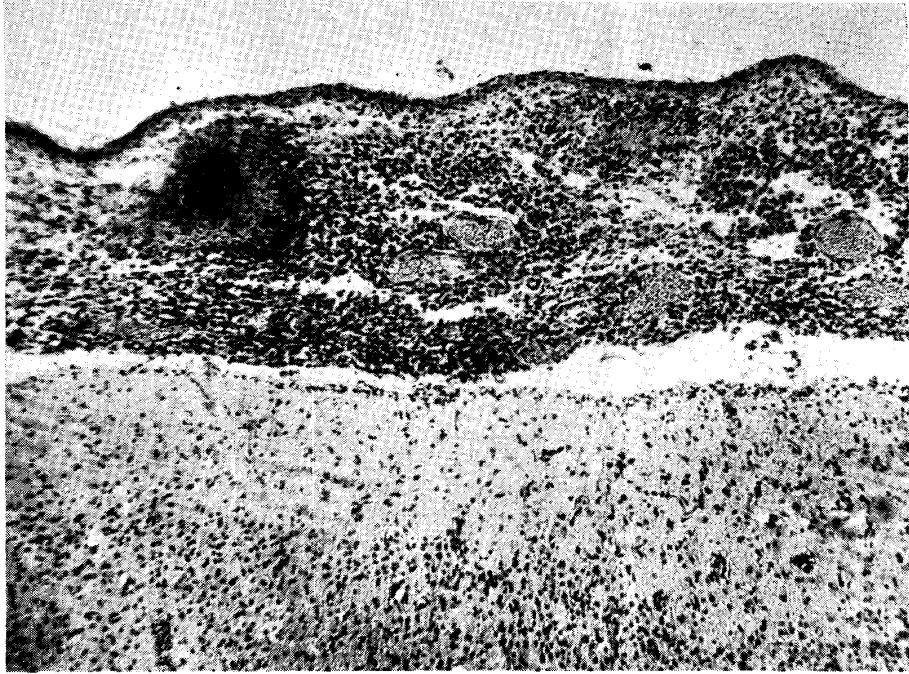


Fig. 6 Perivascular infiltration in rabbit (spread)

