Streptomycin Concentration in Tuberculous Focus of Bone and Joint.

especially, on the effect of the drug combined with the cleansing of the focus.

by

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Introduction and Review of Literature.

Much is unknown about the mechanism of antibiotic function of streptomycin (in the following, shorten into SM.), even after the many studies from biochemical, biological, bacteriological and pathological fields by Umbreit(1), Jensen(2), P. Garrod(3), I. Rhymer(4), I. Smith(5), Y. Sugihara(33) and Silverthone(35) etc. But it is true that excellent results have been obtained on the operative or conservative treatment for tuberculosis of bone and joint, since the clinical application of the drug-

For instance, the results in Prof. E. Kondo's(6) cleansing of the tuberculous focus are that, in 76 cases. treated pre-SM. days, 41.4% were died and fistulae formed in 9.1%, but on the contrary to these results, since the application of SM., in 126 cases, only one case was died and the cases in which fistulae formed were only 4% of all cases. A. D. Smith(7) and A. A. Michele(8) reported that in the arthrodesis of tuberculous joint using SM. at the same time, the joint became fused in shorter period than of pre-SM. days. D. M. Bosworth(9), B. L. Brock(10), E. Winterhoff(11). D. E. Harken(12) and M. S. DeRoy(13) reported that cold abscess did not reponse to SM., when treated without surgery, and they reported that healing of tuberculus lesion with fistulae is better than that without fistulae. By the reason of this, they did incision of cold abscess to form fistulae,

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which had been the absolute contra iudication, and got excellent results. W. H. Bickel(14) and F. Jansey(15) reported that SM. arrests the process of tuberculosis of bone and joint, but the drug can not be a substitution of surgery.

D. M. Bosworth(16), E. T. Evans(17) and R. Harris(18) support this opinion too. A public health service cooperative investigations report(19) recognizes the efficiency of this drug in the treatment for bone and joint tuberculosis. R. K. Ghomley(20), A. D. Smith(21), J. A. Key(22) state that the chronic lesion does not response to SM. and must be treated with surgery, and the operation itself becomes safer and easier with the application of SM.

In short, since the application of SM., incision of the cold abscess is the first step of healing, and the fistulae, which had threatened the patient's life because of mixed infection, act as the useful excretory organs.

This time, the author has found a fact to explain above results by the data of SM. concentration in blood, exudate, bone marrow, pus etc., the author wishes to publish it here

Cases and Materials.

All cases of the author's experiment were patients, with tuberculosis of bone and joint, who were admitted to the Orthopaedic Clinic of the Kyoto University Hospital and treated with SM. in conjunction with or without surgical procedures in the period from July 1950. to March 1951. Studying the passage of SM., intramuscular administered, into pus of cold abscesses and fistulae, exudate in the joint and bone marrow material, punctured by M. Nojima M. B. (23), the author compared the SM. concentration in these materials with that in the blood.

Cases the author experimented were selected from the patients above mentioned by at random method, and the author excluded the cases in which other autibiotics, for instance, penicillin, para-aminosalicylic acid, thiosemicarbazone, solfonamide etc. were administered. The number of cases were 14 in all, 8 cases were male and 6 were female, 3 cases were children younger than 15 years old, 4 cases were young men from 15 to 25 years old and 7 cases were middle-aged persons from 25 to 57 years old. And number of lesions were that: 4 cases were tuberculoris of the lumbar vertebra, 2 cases were tuberculosis of the knee, 2 cases were hip, 2 cases were ankle joint, and tuberculosis of the trochanter major, sacroiliac joint, humerus and pericostal tuberculosis was each one case.

The author has examined in 11 cases, 13 times the SM. concentration in blood for 12 hours after the intramuscular administration of the drug. In

these 11 cases, 4 had fistulae. The author examined SM. concentration in pus discharged from these fistulae 6 times and by one case with an abscess, the author examined the pus aspirated by puncture. In other 3 cases, the author examined SM. concentration in aspirated bone marrow material. And the author examined other 3 cases with cold abscess and one case with exudate in joint. In these cases the assay of SM. concentration in blood was performed for 4 to 6 hours before and after the time when the material of examination was obtained.

Method and Data

To measure SM. concentration in the material, the author utilized the "Superposition Method" described by Torii(24) and Morikubo(25), but in the case of pus discharged from fistula, the author utilized the "Paper Disc Method for assay of penicillin" discribed by Yoshitomo(7), because of a small quantity of the material and the posibility of intermixture of banal germs. In every case of the author's experiments, the author used blood plasma and pus plasma for assay of SM. concentration in blood and pus respectively. In addition, when Yoshitomo's method was employed, the au- heated the series of standard SM. tubes, 100 degrees C. for one minutes, to correct the errors caused by vaporization. The author has found that Yoshitomo's method can be in conformity with SM., and a linear relation can be substantiated on the constant difference diagram from 50 to 0.1γ in the series of standard SM. tubes.

The SM. concentration in blood was measured after the intramuscular administration of the drug 250 mg (we inject the drug 250 or 500 mg. at the interval of 12 hours), 15, 30 minutes, 1, 2, 3, 4, 6, 8, 12 hours, and at the same time, pus discharged from fistulae was absorbed in a small paper disc to assay SM. concentration.

The SM. concentration in blood ascends to the maximum between thirty minutes and an hour, after the administration of the drug, descends remarkably in two or three hours and afterwards, in a relative gentle slope, returns gradually to the level before the administration (vide Fig. 1. to 10. and 13.). And in general, these data are much the same as described by C. S. Keefer (27).

Then the concentration in pus, discharged from fistulae, ascends to its maximum, which is lower than that of blood concentration in every case and is one or two hours later than the maximum in blood. And later, it returns gradualy to the level before the administration (vide Fig 1. to 6.).

The author had no chance to assay the concentration of SM., by the hour in the closed abscess, because it was technically difficult to puncture several

times in a period of twelve hours to obtain pus in the abscess, but the author examined the SM. concentration in the pus punctured after the administration certain hours, in two cases of Pott's disease with gravitation abscesses and in one case of tuberculosis of the knee joint with a periarticular abscess, to get the following data.

As shown in Fig. 11., in a case of Pott's disease with an abscess at the iliac fossa, which was filled up with so creamy caseous material that it was impossible to aspirate the pus even with a trocar, the author could not prove SM. in the abscess in spite of the high concentration of SM. in blood, seven hours and forty minutes after the administration of the drug 500 mg. And as in Fig. 12. a case of Pott's disease also, with a gravitation abscess at the thigh, SM. concentration in the abscess was lower than 0.1γ, six hours after the administration of the drug 250 mg.

These two cases mentioned above had been treated without surgical operation, and if the operation was attempted, they were examined before the operation.

But, on tne contrary to these cases, in a case of tuberculosis of the knee with a periarticular abscess, of which the main focus, pyogenous membrane, anemic granule etc. namely the tuberculous productive tissue had been cleansed, in the secound week (Fig. 13.) and in the fourth week (Fig. 14.) after the operation, the author proved 10γ. of SM. an hour after the intramuscular administration of the drug 250 mg. and o.14γ. three hours after the administration of 500 mg., in the periarticular abscess respectively. In this case too, the author had been not able to prove SM. in the pus obtained before the operation.

To assay the SM. concentration in bone marrow (Fig. 8. 9. 10.), aspiration was performed at the lower ends of the both tibiae, at the same region and at the upper ends of the both tibiae respectively, then the concentration in the aspirated marrow material of the both limbs were compared. In every case, 250 mg, of SM. was injected. In the case of Fig. 8., after the injection 40 minutes, at the right 1.45 and at the left 1.24γ. was proved. In the case of Fig. 9., after 2 hours, r. 1.64 1. 1.7γ., and in the case of Fig 10., after an hour both 1.12γ. was proved respectively. In addition to these data, the author hereby certified, by means of microscopy of the smear of marrow material that the material was not mixed up with the peripheral circulating blood. It appeared that SM. concentration at the diseased limb was a little lower than that of the healthy limb, but large difference could not be found between them.

The fourth material of this experiment was the exudate in the hydrops, which took place in the knee joint of a patient suffering from Pott's disease,

The author has found 7.3 γ. of SM. in the exudate three hours after the administration of 250 mg. (Fig. 15.).

All cases, except those of Fig. 13. and 14., were treated without surgical procedures. Some cases, in which the surgical operation was necessary, had been examined before the operation was performed.

Discussion.

In consideration of the data above mentioned, the author believes that the following articles are able to be conjectured. And these articles are the answer to the problem which always happens, as a matter of course, in the SM. therapy combined with surgery in the treatment of bone and joint tuberculosis.

1) As C. S. Keefer(28) has published that the minimal bacteriostatic SM. concentration in blood for the mycobacterium tuberculosis var hominis is between 0.6 and 1.2 microgram, so the author considers that the hematogenous spreading of tuberculosis, above all, tuberculous meningitis and miliary tuberculosis which had been apt to attack the patient, because blood-vessels of bone marrow can't contract after the direct surgical infringement, namely cleansing of the focus or arthrectomy, heretofore, will be prevented considerably, by this SM. concentration in blood.

And this concentration in blood proves the fact that the rults of the culture of tubercle bacillus, by S. Hattori M. B. (29) of this Clinic, from the patient's blood before and after the cleansing to whom SM. was administered uninterruptedly, has been negative in all cases.

E. H. Winterhoff(11) says that the intoxication of the eighth cerebral nerve happens in relation to the average SM. concentration rather than the maximum concentration in blood. As you see in my cases, when 500 mg of the drng is administered every 12 hours, the blood concentration is not so high. The reason why the symptoms of intoxication, for instance vertigo, headache, buzzing etc. have not appeared in our cases is that on the one hand, the period of the administration of SM. was short, and on the other hand the concentration is not so high.

2) It was reported by B. L. Brock (10), D. M. Bosworth (9) (16), R. Harris (18) that, when they treated tuberculosis of bone and joint conservatively with SM. only, the results in patients with fistulae is better fhan those without fistulae. E. H. Winterhoff(11), D. E. Harken(12) and M. S. DeRoy(13) insisted on the incision and drainage of the tuberculous abscess, which had been a contra-indication. Now it seems that a revolution has happened in the treatment of tuberculosis of bone and joint.

We(19) have an idea, even in pre-SM. days, that fistulae and sinus tracts

of tuberculosis of bone and joint act as excretory organs to discharge detrimental substance in the focus or abscess, namely sequester, necrotic debris and caseous substance which can not be absorbed spontaneously, and by the existence of fistulae, self-purification of the focus is promoted, accordingly, existence of fistulae is a good condition for healing of the focus. Much more, it is a matter of course that the self-purification of the focus is promoted by SM. which accelerate pacification and demarcation of the focus.

And there is another idea to explain this phenamenon, that tubercle bacillus does not obtain SM. fastness, because of mixed infection which repeats over and over again in the focus, attacking from the outside through the fistula (A theory that SM. resistant substance in the tubercle bacillus removes to other germs of various kinds, namely streptococci, staphylococci etc., on this way the tubercle bacillus loses its resistance to SM., and for this reason, the drug becomes effective on the tubercle bacillus.). But the author wishes to insist on a theory about the significance of fistulae as following.

H. W. Mahon(30) has reported that SM. intramuscular administered can't reach the caseous focus penetrating through the fibrous, rather avascular wall of the focus, and the report by the Public Health Service Cooperative Investigation (19) has the same opinion.

This phenomenon was proved in the author's cases too (see Fig. 11. 12. and the Chapter of METHOD and DATA.). But in my case, as shown in comparison of Fig. 1. to 6. with 11. and 12., SM. intramuscular administered is found in the pus drained from fistulae, in much higher concentration than the pus in closed abscesses.

About this phenomenon, there is one idea that when the focus has a draining fistula and constant discharge of pus, passage of plasma from blood to pus becomes greater than the focus without fistula, consequently, passage of SM. from blood to pus becomes greater, but the author has another idea in addition to this, that by the existence of mixed infection, acute inflammation is arised in the focus repeatedly so that the passage of SM. into the focus is increased very much, and for this reason, healing is much improved.

However it may be, as K. Akasaki (31) has mentioned that the region where high concentration of SM. can reach shows remarkable healing, and A. C. Charkar (32) and R. Harris (18) has reported that direct injection of SM. into fistulae is very effective to dry up it, the author is convinced that large quantity of SM. which appears in pus dischargsd from fistulae is a good condition for healing of the disease.

3) In addition, even in the case with fistula, you will notice that SM.

concentration in the pus drained from fistula shown in Fig. 1., is much different from that in Fig. 2. and 4., though these three experiments were performed in the same case.

Y. Sugihara (33) has reported that, in microscopic findings of tuberculous tissue, SM. improves the fibrotic healing of tubercle and the growth of granulation around the focus. T. Yonezawa (34) too, has reported that engorged granulation tissue appears around the focus. And M. C. Silverthone (35) has found the increase of collagen fibre in the focus and considered that surplus of tissue response was obtained, because SM. inhibites the bacilli. H. W. Mahon(30) has reported that on the internal wall of cavities in lung, capillary of granulations layer is much dilatated and in stroma, extravasation of blood is seen. According to this finding, he has described that SM. improves the demarcation by healthy granulation. And M. G. Netsky(36) and J. Winter(37) has reported that fibrosis of the focus is proceeded by SM. And these findings are the same as seen in experimental guinea pig tuberculous reported by R. G. Bloch (38).

Now, in the author's experiment, Fig. 1. consists of the data, which had been obtained one week after the beginning of the administration and Fig 2. and 4. consist of the data after the administration of five and six weeks respectively. The author thinks that in this period SM. has acted upon the tuberculous productive focus to change it into granulation with good circulation, the same phenomenon as this, is described by O. Shimada (39) who has investigated histological findings of granulation treated with penicillin. And consquently, the passage of SM. into the focus is much increased. (Namely, the selfpurification in the focus is improved by SM. therapy.)

According to the investigation by T. Kodama M.B (40) and Y. Fujita M.B. (41) of this Clinic, tuberculous pus plasma has tuberculostatic function, which becomes stronger when the focus becomes quiet and is strongest when the patient is treated with SM.

Besides, the drained pus obtained in the experiment of Fig. 1. was thick and often contained caseous material, and in the experiment of Fig. 2. and 4., the pus changed into serous one. This phenomenon too, proves the self-purification by SM. therapy.

4) The principles of our cleansing of tuberculous focus is only to remove sequestra, pyogenous membrane, caseous substance, anemic granule etc., but not to remove extensive focus with its sarrowinding healthy tissue. When the focus is thus treated, very high concentration of SM. penetrates into it, though little or no SM. reaches the chronic focus as the author has described at the article 2. (compare Fig. 11. 12 with Fig 13. 14.) The author surmises that this phenomenon depends upon the surgical procedure by which

the main focus and its surrounding chronic tuberculous tissue with a bad condition of circulation is removed and upon the fact that the tissue of focus is engorged by the mechanical stimulus of curettage and the circulation becomes better, then the penetration of SM. into the focus is much increased. That is to say that artificial self-purification takes place in the tuberculous focus. And it is unquestionable that this improvement of circulation is a good condition for the healing of the focus. And the permiation of SM. into the cleansed focus of the author's cases is the same that reported by Otani (42), who has investigated the passage of SM. into the cleansed experimental tuberculous focus of guinea pig.

The indication of our cleansing is the case with localized chronic focus, which is so encapsulated and isolated from circulation of the whole body, that it seems to be parasitic on the body. P. Pitzen (43) has reported that some cases of Pott's disease with abscesses are emveloped by the abscess-wall and fibrous tissue so fast that the focus has no influence upon the sedimentation rate. The passage of SM. into the focus, above described by the author or reported by P. Pitzen (43), may be impossible, without any surgical procedures.

Moreover, Kodama M. B. (40) of this Clinic has reported that innumerable active tubercle bacilli exist in such a focus as mentioned above. Accordingly we cann't conclude that such focus can be cured with SM. only, and wish to advocacy the necessity of surgical procedures.

5) Tuberculosis of bone and joint often relapses, even after cleansing or removal of the focus. As one of the reasons for relapse, a fact is reported that tuberculous changes can be found by the histological findings in a part at a distance from the focus so far, that it is thought, by the roentgenographic examination, that the part can not be under the influence of the focus. Then the fact, the author discovered and indicated in Fig. 8., 9. and 10. that SM. intramusculor administered is found in bone marrow, is of significance to prevent the relapse, especially in our cleansing, the principle of which is the minimal attack. In many reports by K. Akazaki (31), Y. Sugihara (33), T. Yonezawa (34), M. C. Silverthone (35), M. G. Netsky(36) and J. Winter (37), they have mentioned the same conclusion that the best response to SM. in the all froms of tuberculous foci is seen in tubercle of miliary tuberculosis. These reports support the significance of SM. in such a case, whose focus has been cleansed.

I. Horowitz (44) has repoted that, aspirating the bone marrow material of 20 cases with pulmonary tuberculosis, he proved, in 14 cases, acid-fast bacilli by direct examination of the smear and in 5 cases, tuberculous bacilli by culture of the bone marrow material. Accordingly we can assume that

many tubercle bacilli lie hiddin in the heathy bone marrow of the patient, then the significance of SM. must be considered here again, namely SM. may be of significance to prevent an attack of this disease at bone and joint.

The reason why SM. concentration in the marrow of diseased limb is lower than that of healthy limb, may depend on bad condition of blood circulation in the tissue neighbouring the focus. K. Yamada M. D. (45) and M. Nojima M. B. (23) of this Clinic has reported this condition of blood circulation.

6) It has been said that antibiotics, for instance penicillin, intramuscular administered can't arrive in the joint, unless it is administered by a direct puncture of the joint, but when the joint has been attacked by an inflammation, as indicated in Fig. 15., in which the experiment was performed with SM., the author has found the considerable concentration of the drug intramuscular administered in the joint. The signification of this datum is that SM. even intramuscular administered can arrive in a joint of which the puncture is difficult on account of its anatomical position, or which is fixed with plaster bandage for a complete rest and alleviation of the charge. But this is the case whose exudate of joint is serous, then the principle of treatment is much different from those we consider as the indications of our cleansing.

Summary.

Today's best treatment of chronic localized tuberculous focus of bone and joint is surgical cleansing combined with SM.

Treatment with cleansing only or SM. only is not so effective as the combined therapy. The author has proved it by the data of assay of SM. in the focus.

Surgical procedure becomes safer and more reliable, when combined with SM. therapy. And effective bacteriostatic concentration of the drug can reach the focus, only when the surgical operation has been performed. The auther considers that this relation is the same as we experience in the potentiating action arised by two medicines of different sites of action.

From this reason, we insist that, cleansing of the focus is the answer by modern science to the difficult problem of medicine, tuberculosis of bone and joint.

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Explanation of the Figures.

A full line in Fig. 1. to 15. means the SM. concentration in blood; a broken line in Fig. 1. to 6. means the concentration in pus drained fron fistulae; a small cross which is pointed by an arrow in Fig. 8. to 10. means the time of puncture and the SM. concentration in bone marrow at that time. And a small cross pointed by an arrow in Fig. 11. and 12. means the SM. concentration in an abscess, when surgical infingement reached its cavity.

The same mark in Fig. 13. and 14. means the SM. concentration in an abscess and the time of puncture to obtain its contents.

The same mark in Fig. 15. means the S.M. concentration in exudat of hydrops and the time of puncture to obtain the material.

Cases and nature of the disease of each figure are as followings.

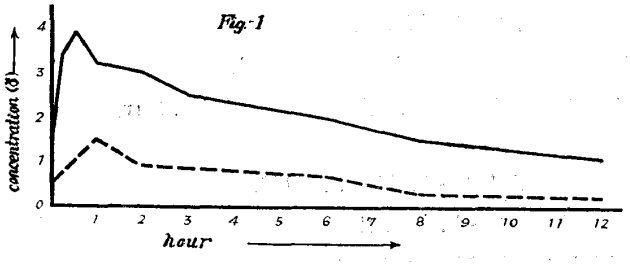


Fig. 1. A male. 51 years of age, with Pott's disease and a fistula at the iliac fossa. One week after the commencement of SM. therapy, 250 mg. of the drug was intramuscular administered at intervals of every twelve hours.

Fig. 2. The same case with Fig. 1., five weeks after the commencement of SM. therapy, the same dose and the same intervals.

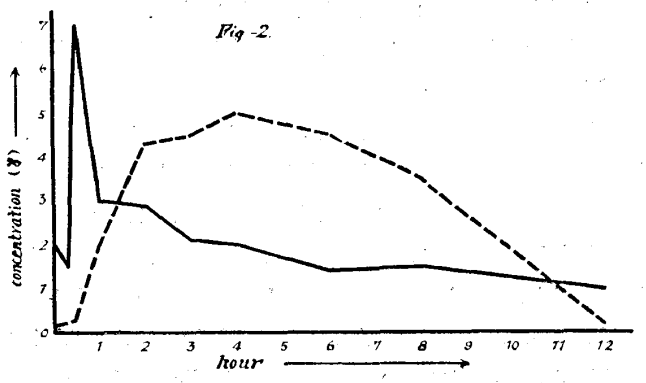
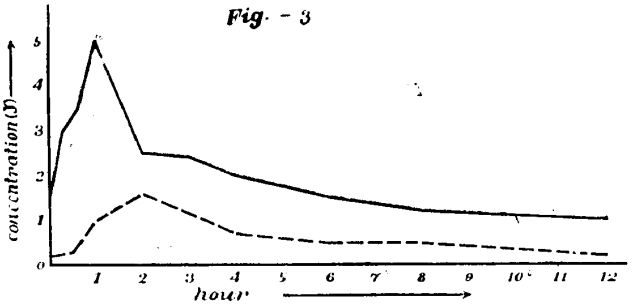


Fig. 3. A female, 21 years of age, with tuberculosis of the right trochanter major and femoral fistula, just after the commencement of SM. therapy. At the intervals of every twelve hours, 250 mg. of the drug was intramuscular administered.



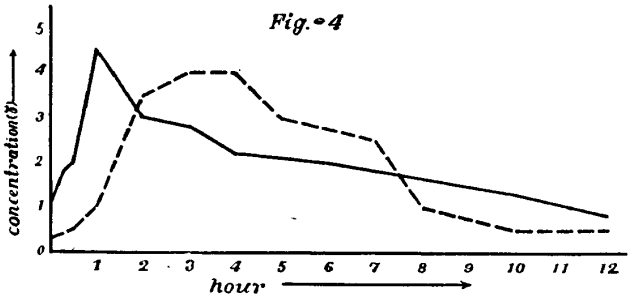
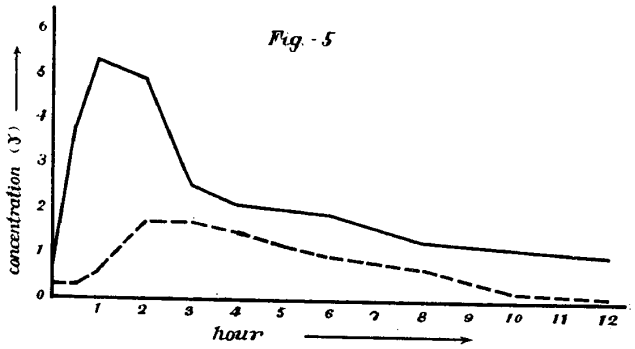


Fig. 4. The same case with Fig. 1. too, six weeks after the commencement of the therapy. Dose and interval is the same with that in Fig. 1.

Fig. 5. A male, 26 years of age, with tuberculosis of the right sacro-iliac joint and a fistula in the gluteal region. Five days after the commencement of SM. therapy. Dose and interval is 250mg. and twelve hours respectively.



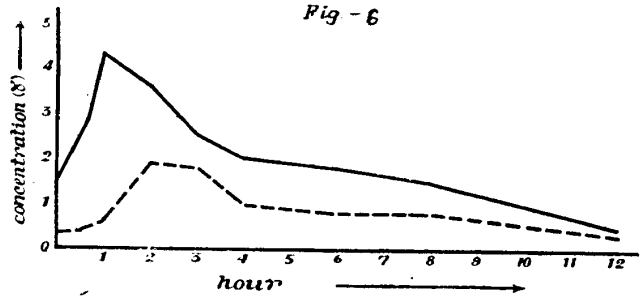
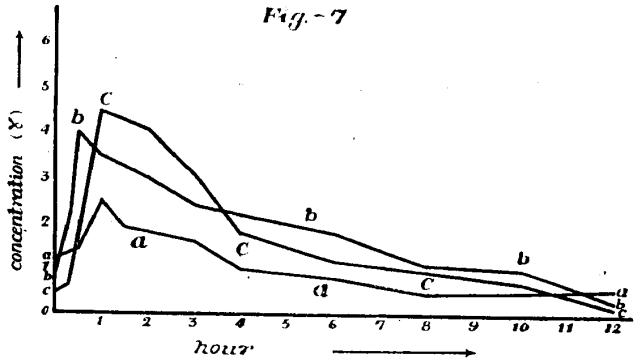


Fig. 6. A male, 13 years of age, with tuberculosis of the right hip and a fistula in the gluteal region, 3 days after the commencement of SM. therapy.

Fig. 7. a) A female, 28 years of age, with pericostal tuberculosis.
b) A female, 12 years of age, with tuberculosis of the left humerus
c) A female, 11 years of age, with tuberculosis of the left hip.



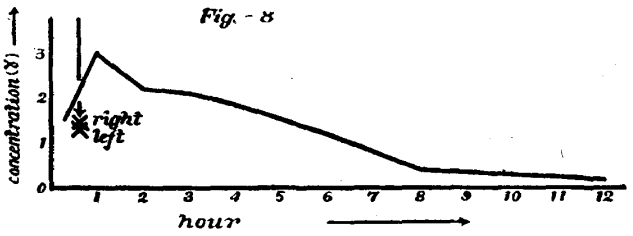


Fig. 8. A female, 16 years of age, with tuberculosis of the left ankle. Dose and interval is 250mg. and twelve hours respectively.

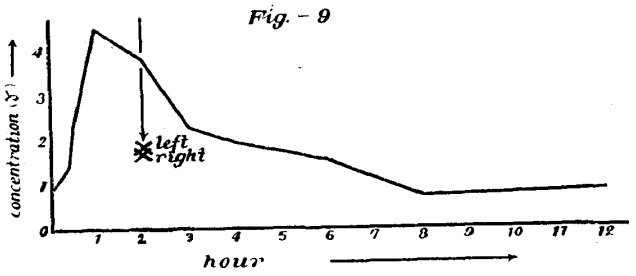


Fig. 9. A female, 20 years of age, with tuberculosis of the left ankle. Dose and interval is 250mg. and twelve hours respectively.

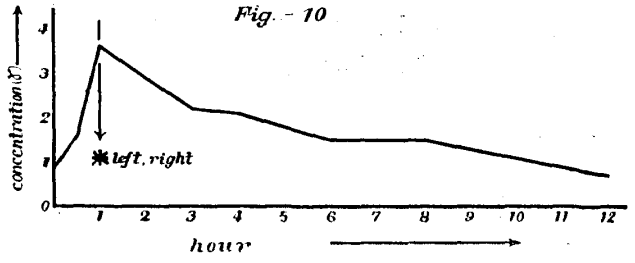


Fig. 10. A male, 31 years of age, with tuberculosis of the left knee. Dose and interval is the same with that in Fig. 8.

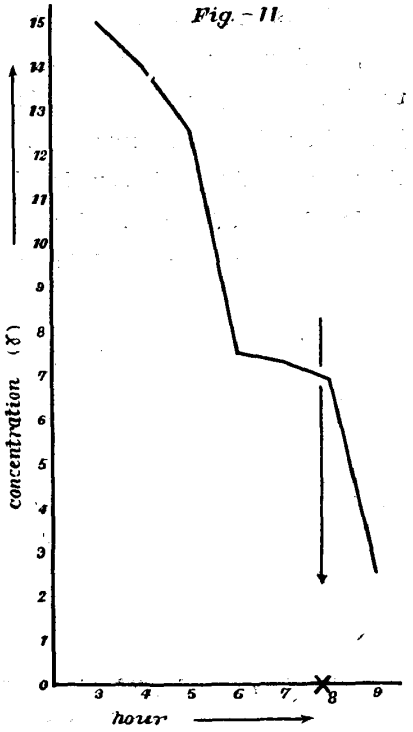


Fig. 11. A male, 26 years of age, with tuberculosis of the lumbar vertebra and an abscess at the iliac fossa. Seven hours and forty minutes before the experiment, 500mg. of the drug was intramuscular administered.

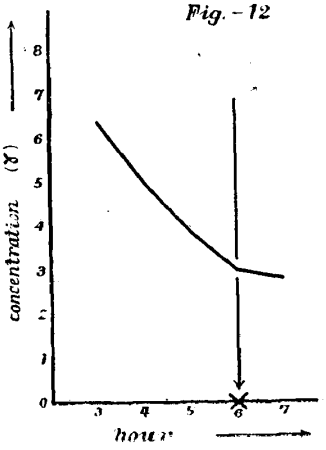


Fig. 12. A male, 36 years of age, with tuberculosis of the lumbar vertebra and a gravitation abscess at the thigh. Six hours before the experiment, 500mg. of SM. was administered.

Fig. - 13

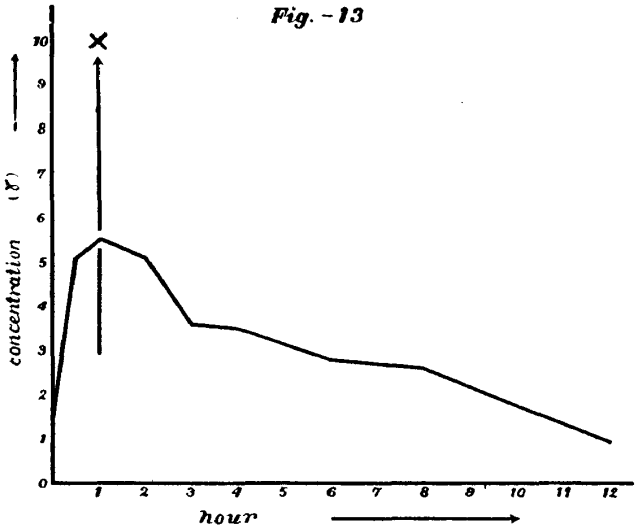


Fig. 13. A male, 19 years of age, with tuberculosis of the left knee surrounded by a periarticular abscess. This patient was treated by the cleansing two weeks ago, 250 mg of SM. was administered every twelve hours.

Fig. - 14

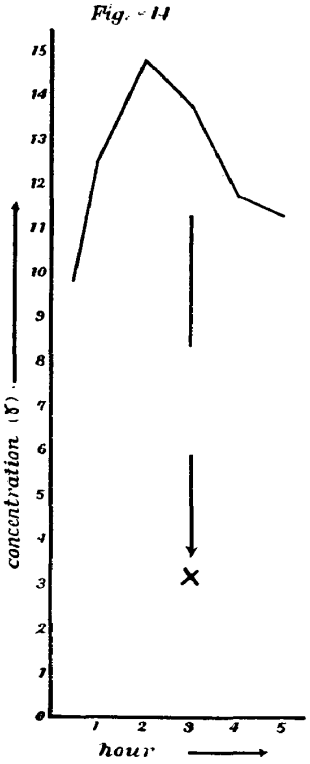


Fig. 14. The same case with Fig. 13. 500 mg of SM. was administered before the experiment three hours. This experiment was performed four weeks after the surgical procedure.

Fig. - 15

Fig. 15. A male 36 years of age, with tuberculosis of the lumbar vertebra and of the knee (hydropical form). 250 mg of SM. was administered every twelve hours.