use may be recommenced in 12 to 24 hours. It is well recognized that digitalis poisoning readily occurs in elderly people with badly damaged hearts, and therefore careful supervision is all the more necessary.

Treatment of Congestive Heart Failure

The development of congestive heart failure within the first few weeks of a coronary thrombosis is regarded as a sign of ill omen. Its occurrence can often be anticipated and measures taken accordingly, for the more severe and the more protracted the initial shock the more probable is the early development of congestive failure.

Treatment should be directed to forestall the development of this serious complication. If digitalis has been used in the correction of the shock phase it should be continued in gentle doses for at least a week or two thereafter in the hope that the efficiency of the uninjured muscle may be maintained and enhanced. Bedford (1939) has noted the value of mercurial diuretics in acute left ventricular failure when oedema is confined to the pulmonary circuit.

After a coronary thrombosis, if moisture in the lungs persists for more than a few days or threatens to increase, digitalis and mercurials can be used cautiously, and even energetically should there be any hint of dyspnoea at rest. By so doing the formidable difficulties of advanced congestive failure, which is apt to develop rapidly in the week or two following recovery from the shock phase, can be eased or prevented and the patient guided through a treacherous stage of the recovery process in greater comfort. The importance of adequate rest and sound sleep during the early days of the illness cannot be over-emphasized, and there is no doubt of the value of a low-calorie diet, small meals, and simple salt restrictions.

It therefore seems that if a further advance is to be made in the treatment of the acute myocardial infarct the prompt correction of shock and the early adoption of measures to prevent the development of congestive heart failure are aspects worthy of more attention. The more adequate treatment is in the early days of the illness the greater the prospects of recovery.

Summary

Active measures in the treatment of acute coronary thrombosis are now yielding better results than ever before, even in the most gravely ill patients.

The employment of anticoagulants is an outstanding contribution to the treatment of this disease. By their efficient use the death rate over the first six weeks can be halved.

The dangers of thrombo-embolic complications can be reduced to negligible proportions.

Moreover, it appears that the prompt use of anticoagulants exerts a favourable influence on the outcome of the shock syndrome. Deaths from shock are less frequent when anticoagulants are in use.

The conquest of the thrombo-embolic aspects of the disease leads to a consideration of the other major causes of death—shock and congestive heart failure—in the hope that therapeutic measures as effective for their prevention and treatment may be forthcoming.

There is reason to believe that the occurrence of the severer grades of shock exerts a profound influence on the subsequent course of the illness. Severe and persistent shock, if survived, predisposes to death from congestive heart failure.

Prompt reversal of the shock mechanism should protect the healthy myocardium, reduce the death rate from this cause, and lessen the likelihood of congestive heart failure. The place of pressor drugs, intravenous and intra-arterial transfusions, and rapid digitalization in the treatment of shock is discussed. The early adoption of

routine measures to prevent the development of congestive heart failure is also considered.

Anticoagulants have revealed our therapeutic shortcomings so far as these complications are concerned, but further advances in treatment can be anticipated as our understanding of the mechanism of cardiogenic shock improves.

In the conduct of these investigations I am most grateful for the co-operation of my colleagues, Dr. W. A. Alexander, Professor Stanley Davidson, Professor D. M. Dunlop, and Dr. W. D. D. Small. Dr. John A. Tulloch has been my constant collaborator.

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TUBERCULOUS MENINGITIS

SOME ASPECTS OF ITS TREATMENT*

BY

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Large numbers of cases of tuberculous meningitis have now been treated in many countries and the results reported in full in the literature. This paper deals only with some aspects which have seemed important during treatment at this centre. During the period October, 1948, to May, 1951, 26 cases of tuberculous meningitis, admitted without selection, were started on treatment at Southfield Sanatorium. The youngest patient was aged 1 year and the oldest 27 years. Miliary tuberculosis was present in addition in 10 of the cases. In January, 1952, 14 (54%) of the patients were alive, with a minimum observation period of nine months and a maximum of 35 months since the beginning of treatment. Twelve of the 14 survivors have completed treatment and made a good recovery. The period of observation since finishing treatment is over twelve months in 10 of these 12 cases. The two cases remaining under treatment have been observed for twenty-eight and nine months respectively. In both a successful outcome is now confidently expected.

*Based on part of a thesis accepted by the University of Edinburgh for the degree of M.D.

Treatment

When streptomycin was first used in this centre for treating meningitis a large percentage of cases relapsed a few weeks after receiving an initial course of two to four months' continuous systemic streptomycin. In spite of the resumption of treatment most of these patients died. The results were better when treatment was resumed within two to three weeks of the initial period of two to four months' therapy, so long as the patient had shown no evidence of deterioration in the interval. In view of the frequency of relapse with brief courses of treatment, it was planned to give a continuous intramuscular course for six months, and this plan affected the cases in the second half of this series (see Chart). The daily dose for an adult was 1 g. and for children 0.5 to 1 g. according to age. Of eight patients receiving an initial six months' period of treatment (combined with intrathecal injections on approximately 75% of the days), none has relapsed or died. Of the 12 who have

given on 75% of the days on which intramuscular streptomycin was given. This percentage corresponds exactly to that recommended by the Ministry of Health (1950) in a survey of the treatment of over 350 cases of tuberculous meningitis. There were no subsequent deaths of patients who received 144 intrathecal injections.

Deafness

Deafness has been the most serious toxic manifestation of streptomycin encountered. Eight of the surviving cases received dihydrostreptomycin sulphate, both intramuscularly and intrathecally, during treatment, and all but one have shown impairment of hearing. Three cases were treated entirely with dihydrostreptomycin, and all have become totally deaf. The other four cases were treated partly with dihydrostreptomycin and partly with the streptomycin calcium chloride complex; one patient is totally deaf and three show varying degrees of deafness. In a previous com-

An analysis of the duration of intramuscular and intrathecal streptomycin treatment in 26 cases of tuberculous meningitis.

completed treatment, the average total duration of intramuscular streptomycin was 10 days over the six months. The Chart shows that the minimum duration was 14 weeks (Case 10) and the maximum 49 weeks (Case 24). Relapse occurred in 5 out of 10 patients whose treatment was stopped before the end of six months, and only one responded when it was resumed. In only one of the dead did the total duration of treatment—that is, initial period plus subsequent courses of treatment—exceed that of the average of all the survivors. For these reasons all cases now receive a minimum of six months' streptomycin treatment.

Streptomycin was given intrathecally in all cases. The dose was 50 to 100 mg. The plan was to give an interrupted course of 42 injections every nine weeks. The injections were given continuously for four weeks, followed by seven days' rest, and during alternate weeks for the next four weeks. As each case was assessed independently it was not always possible to adhere to this plan. If it was followed throughout the average six months' course the number of injections would be about 120 in each case. The average number of intrathecal injections the survivors received was 144. This means that intrathecal therapy was

munication (Somner, 1951) I reported that of the six surviving patients who had received either streptomycin sulphate or calcium chloride complex none showed any auditory impairment. Since then, however, one of these patients has complained of slight deafness in one ear (October, 1951); but this has not increased, as in the other cases, in spite of continuing treatment for a further four months. Sometimes dihydrostreptomycin deafness appeared slowly during the course of treatment and was progressive even after the cessation of treatment; at other times the onset of deafness was delayed for a few weeks after all treatment had been discontinued. In no case has any improvement occurred. Though it is perhaps difficult completely to exclude the possibility that the deafness was due to the disease, the difference in incidence with the two forms of streptomycin, and the onset of deafness at a time when other symptoms were absent or improving, strongly suggest that dihydrostreptomycin was responsible.

Biagi (1951) also stresses the danger to hearing from the use of dihydrostreptomycin in tuberculous meningitis. That the deafness is not dependent upon the intrathecal use of the drug was shown by Allison, Volk, and Vitagliano (1949),

Shane and Laurie (1950), and O'Connor, Christie, and Howlett (1951), who carried out controlled investigations on cases suffering from pulmonary tuberculosis alone. The incidence of deafness with dihydrostreptomycin was in striking contrast to that produced by streptomycin. In view of this risk, and in particular because of the possibility of a delayed onset of deafness even after the drug is stopped, its use in the prolonged treatment of meningitis is no longer justifiable. At present streptomycin itself seems the drug of choice.

Sugar Content of Cerebrospinal Fluid

A normal sugar is regarded as 50 mg. per 100 ml. or over in this paper. Other workers have regarded 45 mg. as a normal figure, but experience with the cases under discussion has shown this figure to be too low, as recrudescence of the disease is still apt to occur if treatment is discontinued at this stage.

The sugar estimation has been found to be the most valuable single factor in the early diagnosis of cases of tuberculous meningitis not complicated by miliary tuberculosis. With cases of miliary tuberculosis it may be possible to recognize a subsequent development of meningitis by the slight pleocytosis of the cerebrospinal fluid (C.S.F.) found on routine lumbar puncture before an appreciable fall in the sugar level occurs. The assessment of progress of the meningitis is also accurately portrayed by the sugar estimation. All the cases which presented with features of tuberculous meningitis, uncomplicated by miliary tuberculosis, gave a sugar value below 50 mg. per 100 ml. The cases that presented with miliary tuberculosis and subsequently developed meningitis were naturally diagnosed at an earlier stage and generally presented slightly higher sugar levels. In two instances of the latter, levels of 50 mg. per 100 ml. were obtained at the time of diagnosis.

The sugar level falls with progressive disease and rises as the disease process undergoes resolution. It is a most reliable guide and not subject to the fluctuations shown by the other constituents of the C.S.F. It has been found that the morbid state of the disease is quite accurately portrayed by the sugar levels; which is fortunate, for it cannot be accurately assessed from the patient's clinical condition. The sugar estimation at the time of diagnosis is usually in accord with the clinical severity of the disease, but once streptomycin therapy is started the clinical improvement which occurs often bears little relation to the C.S.F. findings. A striking fact seen in many of these cases is the remarkable clinical improvement which occurs under treatment, yet the persistent failure of the sugar to rise is a sober reminder that all is far from well. The lesson has been forcibly learned that a patient without symptoms and without clinical evidence of meningitis but with a C.S.F. sugar below 50 mg. per 100 ml. is in danger of recrudescence of the disease in the near future if streptomycin treatment is interrupted or discontinued.

It is now the practice to continue streptomycin treatment in all patients until the sugar level is 50 mg. per 100 ml. or over, no matter how favourable all other aspects of their condition appear. In the patient making a normal response to treatment the clinical improvement moves ahead of the improvement in the sugar values of the C.S.F. The Table shows that, with the minor exceptions mentioned in the three cases treated in 1949-50, the sugar level had risen above 50 mg. per 100 ml. before treatment was discontinued, and it further shows the prolonged period necessary before this occurs. Relapse has so far occurred in only one patient (Case 15) who had attained a sugar level about 50 mg. per 100 ml. The initial period of treatment in this patient, on retrospect, appears inadequate. If the sugar remains stationary at a low level month after month the outlook is unfavourable, but persistent treatment may lead to eventual success. Any interruption of treatment usually leads to failure. A falling sugar level after the institution of energetic treatment is always a bad prognostic sign.

An Analysis of the Time Required for the C.S.F. Sugar Level to Rise Above 50 mg. per 100 ml. in Cases of Tuberculous Meningitis Successfully Treated

Case No.	Months of Streptomycin Treatment	Month After Admission at which C.S.F. Sugar Level of 50 mg./100 ml. Reached	Remarks
6	14	16th	Treatment stopped at 49 mg./100ml. 2 months before C.S.F. sugar over 50 mg./100 ml.
8	8	5th	Treatment stopped at 46 mg./100 ml., 2 months before C.S.F. sugar over 50 mg./100 ml.
10	5	7th	
12	6	7th	Treatment stopped at 48 mg./100 ml. 1 month before C.S.F. sugar over 50 mg./100 ml.
15	23	27th	Still under treatment Treatment completed Still under treatment. Sugar 48 mg./100 ml.
16	10	10th	
17	10	10th	
18	6	6th	
19	8	7th	
20	6	5th	
21	5	4th	
23	7	7th	
24	12	10th	
25	9	—	

Chloride Content of C.S.F.

The constancy and reliability of the sugar estimation now being realized, less significance is attached to the chloride content of the C.S.F. A normal chloride is regarded as 720 mg. per 100 ml. or over in this paper. From the diagnostic standpoint, all cases presenting features of meningitis on admission, with one exception, had a chloride value below 700 mg. per 100 ml. In 5 of the 26 cases meningitis was diagnosed when the level was above this, and these developed meningitis while under treatment for miliary tuberculosis. Though less reliable than the sugar value and tending to fluctuate for little apparent reason, the chloride content of the C.S.F. has nevertheless reflected the changes in the clinical state of the patient and in general has followed the same course as the sugar. The chloride value usually reaches normality before the sugar content does, but thereafter the former shows slight fluctuations between normality and abnormality for a short time, not seen with the sugar value. In all 26 cases in this series the sugar values were closely paralleled by the rising and falling chloride content, and in all the survivors the chloride content was above 720 mg. per 100 ml. at the time treatment was stopped.

White-cell and Protein Content of C.S.F.

These two constituents of the C.S.F. are considered together because each appears to vary in the same direction during the course of treatment of meningitis. Smith and Vollum (1950) have published several interesting observations on the relationship of streptomycin to the C.S.F. changes in tuberculous meningitis. They point out that the total cell count in the treated case was usually above the range seen in the untreated case. During the first week or two of intrathecal streptomycin the cell count would rise and show frequent fluctuations, and at the peaks about 80% of the cells were polymorphonuclear leucocytes. This phenomenon continued during the acute stage, but as improvement occurred, and while intrathecal streptomycin continued to be given, the cell fluctuations and their total numbers fell steadily, while the polymorph was gradually replaced by the lymphocyte. Elevation and fluctuation of the protein level frequently occurred during treatment, corresponding approximately to the fluctuations of the cellular element, and as the patient improved the protein level became reduced in spite of the continuation of treatment. The C.S.F. picture of the present cases conformed closely to this general pattern.

In support of the view that the high and fluctuating cell and protein contents are an indication of the activity of the

meningitis, Smith and Vollum (1950) further point out that it is not possible to reproduce these phenomena when subsequent intrathecal streptomycin is given if active meningitis has subsided. The phenomena are thus regarded as a specific reaction of tuberculous meningitis influenced by streptomycin, and may be due to the liberation of bacterial breakdown products—for example, tuberculin—into the subarachnoid space of the sensitized patient.

In the assessment of progress under treatment the protein and cell contents, though an additional aid, have not been found comparable to the sugar value in accuracy and constancy. As the disease process comes under control a gradual fall occurs with the former, but in all the cases apparently cured it has been noted that a normal cell count (5 cells per c.mm.) and protein content (40 mg. per 100 ml.) are never obtained so long as intrathecal streptomycin continues to be given. They are the last of the C.S.F. constituents to return to normal, usually long after the sugar and chloride have done so. The time taken for the cells, and particularly the protein content, to return to normal after the cessation of treatment has been found to vary between 2 and 20 months in the survivors in this series.

Spinal Block and Cisternal Streptomycin Injections

Spinal block occurred, sometimes more than once in the same patient, in 11 of the 26 cases under discussion. Partial block was much commoner than complete block.

The common cause of spinal obstruction is the presence of gelatinous exudate within the narrow spinal subarachnoid space. The duration of this complication is variable and unpredictable. In fact, it is surprising how quickly evidence of partial block subsides, and it does not always seem reasonable to suppose that canalization through the exudate could have taken place in so short a time. The answer to this may lie, as Choremis *et al.* (1951) have pointed out, in the ability of streptomycin itself to precipitate an already incipient block. Streptomycin injected into the normal theca causes an immediate pleocytosis and outpouring of protein into the C.S.F. (Choremis *et al.*, 1948; Cathie, 1948). As a result of this congestion of the meninges and of the tuberculous exudate already there from a downward extension of the disease, it is reasonable to suppose that spinal obstruction can be readily produced. Several cases in this series have shown interesting examples of this. Partial spinal obstruction was diagnosed and intrathecal streptomycin was administered by the cisternal route. In some cases, when a lumbar puncture was repeated after a matter of only a few days, it was surprising to find that all evidence of spinal block had disappeared. This has occurred on so many occasions that there can be little doubt that the administration of intrathecal streptomycin can precipitate the development of spinal block and that a few days' rest will often lead to its resolution. When resumed again the intrathecal dose is reduced from 100 to 50 mg. for adults and from 50 to 25 mg. for children.

In other cases the partial spinal obstruction persisted and resort was made to the cisternal injection of streptomycin. The cisternal route was never used as an alternative to the lumbar route simply to rest this area or where lumbar puncture was difficult, for it has been found that reactions by the cisternal route are not only annoying to the patient but are also potentially dangerous if repeated too often.

The cisternal punctures were carried out, apart from the initial one, without the use of a local analgesic, and it was surprising how little was the discomfort caused to the patient. While the streptomycin was being injected patients complained of various symptoms. The commonest were a sensation of "burning pain" in the region of the head, face, and neck or a bursting sensation in the ears; in some, vomiting occurred immediately the injection was completed, and this tendency was reduced by withdrawal of 5 ml. of C.S.F. before the injection was given. The patient often felt drowsy for most of the remainder of the day. The most consistent feature following cisternal streptomycin has

been the acute vestibular disturbance which occurred about half an hour after nearly every injection: a coarse nystagmus developed—often so coarse that lateral movement of the eyes was not required to elicit it; sometimes it caused jerking movements of the upper eyelids. The patient very commonly complained of double vision, which prevented reading. Both these features persisted for the greater part of the day, though gradually diminishing, and were either minimal or absent at the time of the injection next day, which again led to their exacerbation.

One important drawback to repeated cisternal streptomycin injections has been the occurrence of haemorrhage into the subarachnoid space. The largest number of cisternal injections given to any patient in this series was 46 within a period of 12 weeks. Haemorrhage occurred on four different occasions and caused her so much distress that this route had to be finally abandoned in favour of the lumbar route, which had not yet opened up completely. The symptoms of these episodes were severe headache and backache and root pains radiating around the trunk. A cisternal puncture on the day following the symptoms of haemorrhage confirmed that the C.S.F. was heavily blood-stained. The symptoms cleared up in about five days, and during this period intrathecal streptomycin was omitted. It seems very undesirable that such haemorrhages should occur, as the blood must aggravate the partial obstruction caused by the tuberculous exudate in the narrow spinal subarachnoid space.

Choroidal Tubercles

Cases of miliary tuberculosis and tuberculous meningitis may show tubercles of the choroid. The prolongation of life which has resulted from the use of streptomycin has provided the opportunity of studying the natural history of these choroidal lesions.

Emery and Lorber (1950) drew attention to the fact that in a series of 52 children who died of miliary tuberculosis, histologically proved, in only one-third was the diagnosis made by x-ray examination during life. On the other hand, choroidal tubercles were seen in half the cases during life, and in general led to a diagnosis of miliary tuberculosis more often than did radiological examination. Illingworth and Wright (1948) fully reviewed the subject, and found choroidal tubercles in 25 (60%) of their 42 cases of miliary tuberculosis. In the present series of 26 cases of tuberculous meningitis 10 suffered from miliary tuberculosis and choroidal tubercles were found in 7 of these (70%). None were found in the 16 cases of meningitis in which there was no miliary disease. (Since this series was investigated a single choroidal tubercle has been found in the fundus of a case of meningitis without radiological evidence of miliary disease.) Though the choroidal tubercles were usually found at the time of the first or second examination, this was not always the case.

In a girl aged 7 years two tubercles were present in the left fundus at the time miliary tuberculosis was diagnosed. Meningitis subsequently developed, but it was not until nine months later that a third tubercle was found. Fourteen months after the beginning of her illness a further three tubercles were found, quite unexpectedly, and one month later again a seventh one, all in the original fundus. It seems probable that these lesions had been previously missed. Each succeeding tubercle found was further and further away from the disk, and thus was more easily overlooked on routine examination, which had been carried out at least once a fortnight throughout the course of her illness. In fact, the seventh tubercle to be discovered was only just visible with the pupil fully dilated by homatropine. The tubercles that were found last were obviously not the result of fresh dissemination, because all contained some degree of pigmentation.

In the earliest stages the choroidal tubercles appeared as circular pale-yellow areas with an indefinite edge merging into the red background of the choroid. The larger ones

appeared raised above the surface. The largest number found in one fundus was 13. In three cases tubercles were present in one eye only, and in the other four cases in both fundi. They were found to be most numerous close to the disk, and were about one-fifth the diameter of the optic disk. During the treatment of these seven cases only slight changes have been observed in the choroidal tubercles over a period of many months—the longest period has been 27 months. No tubercles have been seen to disappear completely. Most remain unchanged for about three months. The first change noticed was that the tubercle became a deeper yellow and the outline became more distinct as the retinal oedema subsided. Fine dots of black pigmentation then appeared in and around the tubercle. Later still this pigmentation increased in, and particularly around, the lesion.

Illingworth and Wright (1948) regard the healed tubercle as one which shows a parchment-white scar, with a well-defined sharp edge and heavy black pigmentation. None of the cases in this series, including that observed for 27 months, showed such a picture,* but instead one in which the individual lesions became a deeper yellow, sometimes even orange-yellow, so that the contrast between the colour of the tubercle and that of the normal choroid became less and less distinctive. The edge of each lesion became sharp in outline, though sometimes it was of an irregular shape, and dots of pigmentation occurred within and around the tubercle. This final phase of development has seldom been seen to occur in less than six months. Of the seven patients with tubercles in the fundi, five have survived, and the minimum observation period has been 16 months. In none have the choroidal tubercles developed beyond the "intermediate stage" described by Illingworth and Wright, who state that the final stage of healing may be reached in 12 to 14 weeks. It is of course not possible to say that the choroidal lesions in the present series are definitely healed, but when assessed in conjunction with the state of the miliary and meningeal disease it may be surmised that the phase of arrest or healing has been reached. Lastly, Illingworth and Wright noted that the survival rate was more encouraging in those who showed the tubercles to be in the "final or healed stage" than when in the "intermediate stage" which they describe. As all the cases observed by me fall into this "intermediate stage," a survival rate of five out of seven cases cannot be regarded as unsatisfactory.

Summary

The streptomycin treatment of 26 cases of tuberculous meningitis is described. There are 14 survivors, 10 of whom have been followed up for over twelve months since stopping treatment. The average duration of the systemic administration of the drug to the survivors was a little over six months, and intrathecal injections were given to each on an average of 75% of the days on which intramuscular streptomycin was given. None of those who died received treatment of greater duration. The serious incidence of deafness occurring with the use of dihydrostreptomycin is reported.

The sugar content of the cerebrospinal fluid was found to be the most valuable index of assessment of progress, and it is suggested that treatment should never be discontinued so long as this level is below 50 mg. per 100 ml. The significance of the protein and cell contents is discussed. It is pointed out that neither of them may return to normal for many months after treatment has ceased.

*A case of miliary tuberculosis with meningitis, admitted too late to be included in the series and still under treatment, does show this picture very clearly. Two tubercles are pure white with a dense central and peripheral zone of pigmentation. It is interesting to find in addition in this patient three tubercles in the early stage of development entirely devoid of pigmentation.

Intrathecal streptomycin was found to be an additional factor in the development of spinal block in some cases. Symptoms and signs resulting from the alternative use of the cisternal route are described.

A description is given of choroidal tubercles, with special reference to the appearance of the healed lesion as seen in 7 out of 10 cases of miliary tuberculosis.

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OBSERVATIONS ON THE LABORATORY DIAGNOSIS OF TUBERCULOUS MENINGITIS

BY

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Rapid laboratory diagnosis of tuberculous meningitis is sometimes thought to be a matter of difficulty, and since the introduction of streptomycin therapy emphasis has shifted from late confirmatory to rapid presumptive methods. The former include cultural and animal inoculation tests, the latter simple biochemical tests, cell counts, and microscopical examination of clot or centrifuged deposit of tubercle bacilli.

This report summarizes the experience gained from the examination of cerebrospinal fluids from 150 cases of tuberculous meningitis admitted to hospital for treatment with streptomycin. The report relates exclusively (except where otherwise stated) to the examination of the first specimen received from each patient—that is, to the specimen submitted to establish the diagnosis. The tests were carried out in a routine laboratory and not in a special department. The tests were often made on as little as 3 ml. of fluid, and in the early stages of the investigations the available fluid was divided into two equal parts so that accurate chemical tests could be made in another laboratory. With comparatively few exceptions, however, it was possible to make a rapid presumptive diagnosis of tuberculous meningitis which was confirmed by cultural and animal inoculation tests.

Technical Methods

The following tests were used: (1) Test for glucose (using Benedict's solution); (2) Pandy's test for globulin; (3) cell count; (4) microscopical examination for *Mycobacterium tuberculosis*; (5) culture; (6) animal inoculation.