University of Wisconsin Library
Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the University of Wisconsin Library are open for inspection, but are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages may be copied only with the permission of the authors, and proper credit must be given in subsequent written or published work. Extensive copying or publication of the thesis in whole or in part requires also the consent of the Dean of the Graduate School of the University of Wisconsin.

This thesis by Isabelle Jeanne Anderson has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

A Library which borrows this thesis for use by its patrons is expected to secure the signature of each user.

NAME AND ADDRESS DATE

STREPTOMYCIN THERAPY

IN

TUBERCULOUS MENINGITIS

BY

ISABELLE JEANNE ANDERSON

A Thesis Submitted in Partial Fulfillment

of the Requirements for the Degree of

DOCTOR OF MEDICINE

at the

UNIVERSITY OF WISCONSIN

1950

TABLE OF CONTENTS

I. INTRODUCTION

From the time Robert Whytt described the syndrome of symptoms in his classical, Observations on Dropsy of Brain in 1768 to 1944, children who contracted meningitis of tuberculous origin were considered to have a fatal disease. Few isolated cases of spontaneous cure had been reported in the literature, but the disease meant almost certain death.

In January, 1944, Schatz, Bugie and Waksman isolated streptomycin from Actinomyces griseus, and in April, 1944, workers at the Mayo Foundation tried the drug on guinea pigs inoculated with the tubercle bacillus. Since that time hope for survival in tuberculous meningitis has risen greatly. First and isolated reports were very favorable though long range view of the use of the drug reveals it is not the whole answer for cure.

II. NATURAL HISTORY

Tuberculous meningitis is primarily a disease of children. It is rare under six months of age and occurs most often in the two to three year age group[12]. In cases where no previous diagnosis of tuberculosis exists, the greatest age incidence is one to two years, but if previous tuberculosis is known to exist, incidence increases to five years[23]. The reason for the great incidence in childhood has been attributed to increased susceptibility of brain and meninges of children and to the frequency of primary tuberculosis infection in childhood.[32]

Definite relationship to primary tuberculosis infection has been established. Lincoln states meningitis most frequently occurs when the primary lesion is fresh[23]. In the majority of cases six months or less had elapsed since the primary infection was contracted--40 per cent less than three months since discovery of the primary lesion[27].

Both sexes are equally susceptible to meningeal tuberculosis. Negro and Mexican races are particularly susceptible to the disease[21]. Incidence of disease is highest in spring, with winter and early summer ranking next highest. Contributory factors include lack of vitamins and frequency of colds in these seasons of the year[32].

Severe pertussis, measles, severe trauma, physical

reaction to shock, overexposure to sun and surgical operations[27] also may cause precipitation of meningitis. Craig states that 20 to 30 per cent of cases under three years of age have history of recent ear discharges[12]. Any conditions which may activate an otherwise latent foci may lead to onset of meningeal symptoms.

History of exposure to tuberculosis is elicited in varying number of cases. Lincoln states about 57 per cent of her cases give a history of contact[23], while others place the contact history around 30 per cent[27,31].

III. PATHOGENESIS

A great deal of controversy over the source of meningeal infection has occurred. The old idea derived from frequent association of meningitis with miliary disease was that the meninges were infected from direct hematogenous spread. Rich[30] in 1933 reviewed the "old idea" and claimed that the sequence of events was not first, primary lesion; then, meningitis with miliary spread. He claimed primary lesion was followed by dissemination of bacilli to form foci. From these central foci bacilli were discharged to cause meningitis.

Reasons for his argument stemmed from the following facts: "(1) widespread miliary disease could be found in every organ without meningitis being present; (2) age and character of miliary tubercles found in autopsy did not correspond with age or character of meningitis; (3) meningitis is found in complete absence of miliary tuberculosis; (4) the chief organs in hematogenous spread are spleen, lung, bone and liver." Great variance is found in spread to meninges.

In Rich's original series of 82 cases, 78 were found to have tuberculous foci. In order of frequency they are found in (1) brain substance itself either as single or conglomerate tuberculoma, (2) in the meninges, and (3) in bone enclosing the central nervous system. Only one tuber-

culoma was found in choroid plexus in opposition to Kment's idea that the tuberculomata were primarily in choroid plexus; when these tuberculous foci become superficial enough or break into the longitudinal sinus via Pacchionian bodies and the subarachnoid space, bacilli enter meninges.

Controversy still exists over this idea. Schwartz agrees[32] with both Rich and Kment but states foci in choroid plexus rare as the plexus are infected by cerebrospinal fluid. Yet Levinson[22] in a very recent paper claims belief in the hematogenous spread.

Tuberculous meningitis is characterized by an exudative inflammatory process with widespread necrosis in the areas of the inflammatory exudate and in surrounding contiguous meningeal tissues. The exudate covers the base of the brain from the optic chiasma to the cerebellum, and tuberculomata may be seen grossly throughout the exudate. However, in some cases exudate and tuberculomata are discovered only by the microscopic examination[5]. Organization of exudate in leptomeninges with marked amount of tuberculosis in brain substance is the usual post mortem picture[7]. The brain substance, convolutions, choroid plexuses, meninges and spinal cord are markedly edematous[21].

IV. SIGNS AND SYMPTOMS

The triad of vomiting, headache and constipation so frequently called the "triad of meningitis" does not hold rigidly true in tuberculosis meningitis. Signs and symptoms are more vague and Levinson[22] emphasizes that the picture is more frequently one of encephalitic envolvement (irritability, somnolence, convulsions) than of meningeal signs.

In general Jamieson lists listlessness, pyrexia and sickness as the order of events[20].

Most workers divide signs and symptoms into three phases--each phase averaging one week in duration.

Stage I or "prodromal period":[12,23,31]

This phase averages one week but may last up to three months. Gastrointestinal symptoms with anoxeria and vomiting, apathy, fretfulness, lassitude, headache, fatigue, failure to gain, restlessness occur. Lincoln states that headache appears in only 20 per cent of cases, and never under three years of age. This phase is characterized by its "vagueness, insidiousness, slow progression, and ominous persistence."[12]

Stage II or "period of irritation or invasion stage":

In this phase lassitude increases to drowsiness; breathing tends to be irregular--a long deep sigh. The child is resentful to examination and may push away the examiner. He may want just to sit undisturbed with legs in a

flexed position[12].

Mothers frequently describe the child as "just not himself"[31], "being different," "moody[12]. These periods may alternate with periods of apparent well-being and interest in his surroundings.

Physical examination shows slow pulse, neck rigidity (Craig[12] describes it as an "objection" more than rigidity), increased deep reflexes, decreased abdominal reflexes, boggy fontanelles. (Fever may or may not be present.) Kernig's and Brudzinski's signs may be present, as may ankle and patella clonus. Involvement of cranial nerves with strabimus, ptois, nystagmus, and irregular pupils may occur [12,23].

Rubie and Mohun[31] say that diarrhea, abdominal pain, convulsions, and loss of speech are the less common findings at this time.

Diagnosis is most common eight to fifteen days after onset of this stage.

Stage III:

This stage is characterized by increase in stupor which may alternate with periods of wakefulness. Coma, delirium, and convulsions are common. The pulse becomes rapid; temperature becomes steadily higher; flushing is pronounced; breathing becomes Biot or Cheynes-Stokes in character; and wasting is rapid. Death occurs in approximately one week[12,21,23].

One phase of physical examination which is generally overlooked has been stressed as most helpful by the French group of investigators[14] and by ophthalmologists[15]. That is the fundoscopic examination. Eye lesions are classified by chorio-retinal or optic nerve involvement. Chorio-retinal lesion include small miliary tubercles, single or multiple about one-half disc size; small white blurred spots not elevated; and single isolated tubercles, one to two times the disc diameter. Optic nerve lesions include congestion of nerve head, choked discs and a few cases of atrophy. A new series of investigations[15] has revealed eye lesions in 68.9 per cent of tuberculous meningitis with miliary involvement and in 19.3 per cent of meningitis without miliary involvement.

V. LABORATORY WORK

Following the history and physical examination, laboratory work usually requested for diagnosis includes Mantoux test, chest X-ray and spinal fluid analysis.

Mantoux skin test is positive in 85 to 100 per cent of cases[22,23] but should be done on all cases. It may be used as a progress indication. If a case is far advanced on admission, skin testing may be negative and later become positive on improvement. If meningitis is not so severe on admission, a positive skin test may become less marked with improvement, followed by a definite response with further regression of meningitis[10].

Blood work on tuberculous meningitis shows a white blood count range average of 7500 to 25,000 cells, predominantly polymorphonuclear leucocytes. Eosinophilia of 5 to 11 per cent may occur, especially during the third month of streptomycin therapy. Sedimentation rate usually is nonspecific but may be elevated to a twenty-thirty range [21,22].

Lumbar puncture findings may be equivocal early in the disease, but in general they are:[11,12,22,23,25,31]

1. Xanthochromia, from minute hemorrhages of cord and stasis of spinal fluid.
2. Cell count elevation. Counts vary from 30-1,000, average 250 per cu. mm.

Lymphocytes are predominant. If the reaction is acute, many polymorphonuclear cells may be present.

3. Protein increase: 75-275 mg. per 100 ml.
4. Chlorides lowered. If chlorides are under 650 mgs. per 100 ml., it is suggestive, but chlorides are not a valid criteria for diagnosis.
5. Sugar lowered, under 45 mg. per 100 ml.
6. Pellicle formation if present.
7. Direct smear for tubercle bacilli--as many as 58 per cent[31] may have bacilli present in direct smear.
8. Guinea pig inoculation or culture for bacilli.

However, diagnosis cannot await return of the more prolonged procedures, such as guinea pig inoculation or culture. If tuberculous meningitis is suspected, and there is abnormal spinal fluid with increasing symptoms, treatment should be started immediately.

VI. DIFFERENTIAL DIAGNOSIS

Differential diagnosis of tuberculous meningitis includes other meningeal and encephalitic infections such as polio encephalitis, benign lymphocytic choriomengitis, glandular fever, and mump encephalitis[31]. However, the hardest differentiation to establish is that between true tuberculous meningitis and what Lincoln[23] classifies as serous tuberculous meningitis.

Serous meningitis is a condition found when there are meningeal symptoms in a generalized hematogenous or miliary tuberculous, but where no tubercle bacilli are demonstrable in the spinal fluid. Prognosis differs greatly from tuberculous meningitis. Spontaneous recovery is the rule for serous meningitis.

Pathology as explained by Greek workers[9] consists of serous meningitis arising from a simple inflammatory process or development of tubercles which do not spread. Bacilli may be present but disappear spontaneously because they either are circulating free in spinal fluid without a focal lesion or arise from focal lesions too small to give clinical manifestations.

Both tuberculous and serous meningitis have the same general symptoms of vomiting, drowsiness, apathy, sudden increase in temperature, irritability, headaches. Both are found in hematogenous spread. However, a marked gener-

alized response with few demonstrable neurologic changes suggests serous type of infection. Meningeal symptoms synchronous with a recent pulmonic extension is suggestive of serous type. If cranial nerves are involved, caseous tuberculous meningitis is suspected[23].

Spinal fluid findings of slight to moderate cellular increase and slight pressure increase may be found in either, but if sugar, chlorides and protein are normal and no bacilli demonstrable, likelihood of serous infection comes to the foreground. Jamieson[20] suggests in the case of abnormal spinal fluid to watch the situation for one to two days. If there is an increase in drowsiness or decrease in spinal fluid sugar, it should be treated as caseous tuberculous meningitis.

VII. METHODS OF TREATMENT WITH STREPTOMYCIN

Routes:

In a study of routes of[17] administration of streptomycin it was decided intermittent intramuscular administration is the method of choice. Blood concentrations remain up in effective amounts three to six hours following administration.

Subcutaneous route maintains high potency but the drug must be highly refined. Crude drugs cause pain and local reaction.

Oral administration causes no rise in blood stream concentration even when administered up to 500,000 units per day.

Intrathecal method of administration may be used with concentration maintained at least twenty-four hours.

Dosages:

Throughout the literature except for a few scattered reports[2,22] the method of treatment includes use of both intramuscular and intrathecal routes.

In a recent roung table discussion of chemotherapy in tuberculosis of children[16] the procedure of choice included:

> 0.05-3.0 gm. per day, single or divided doses, IM for 2-6 mos.

0.025-0.100 gm. per day intrathecally
for 4-8 weeks.

An over-all picture of the literature shows the dosages usually consist of 2 gm. IM and .05-.2 gm. daily intrathecally [18,19,25,27]. However, the group from Athens[10] emphasizes that the more severe the signs, the smaller the intrathecal dosage should be. This concept arises from the idea that the amount of reaction in meninges governs the amount of diffusion across the blood into the spinal fluid. They recommend doses of 0.01-0.05 gms. intrathecally.

The intramuscular dosage is frequently calculated by body weight, 0.02 gm. per pound of body weight the average dose. If intramuscular dose is used alone without the use of intrathecal as reported from Alperin and Toomey[2], 0.25-4 gms. of streptomycin are used daily in divided doses every six hours depending on size of patient.

Duration:

Length of time of administration varies more than does the dosage. Early writers[19,25,27] and some of the more recent reports prefer the continuous administration for three to six months by intramuscular route and four to seven weeks by intrathecal route. Other groups[10,31] prefer the method of administration where rest periods are used. Athens group suggests four to six weeks combined therapy, "period of clinical improvement." Then the therapy is discontinued for five to ten days. Therapy, combined intramuscu-

lar and intrathecal is resumed for ten to fifteen days, then another rest period. The intermittent treatment, "stage of laboratory restitution," is continued as long as three months.

Rubie and Mohun[31] lay out a plan of treatment as follows:

IM and intrathecal - 28 days
IM alone - 28 days

IM and intrathecal - 28 days
Rest period - 28 days
IM - 28 days

However, it has been well established that too short a period of treatment results in relapses. One report[4] states that under four to five month course of therapy, the majority of patients relapse. But if a protracted course, six to seven months, is carried out, relapse incidence is cut to 50 per cent.

VIII. STREPTOMYCIN CONCENTRATIONS

Stress is laid on the fact that there is no diffusion of streptomycin from the blood into normal spinal fluid, even in doses up to 200,000 units[17]. However, if meningitis is present, levels in spinal fluid up to one-fifth the blood level can be found. With increasing infection of the meninges there is increasing facility for the drug to enter the meningeal spaces from the blood[27].

Estimates of concentration found by Levinson[22] when testing was done three hours after last injection intramuscularly and just before next injection are as follows:

Blood level = 0-160 units (usually 10-40 units) per cc.

Spinal fluid = 0-320 units (usually 5-20 units) per cc.

Other estimates[3] place the spinal fluid level at about one-half the blood level. Spinal fluid levels are usually lower than blood level but are sufficient to be bacteriostatic--if meningeal irritation is present so diffusion may occur.

Waksman[36] states that an intrathecal dose of 0.1 gm. will maintain a high peak of concentration--750 to 2000 ug. per ml.--for several hours.

IX. COURSE OF DISEASE UNDER TREATMENT

Lincoln[23] states that the course of disease untreated is steady progression to death in one to sixty-three days (average of nineteen and one-half days). The response to treatment, however, rests on many factors. British Medical Council fatality report lists[16] factors influencing response (where listed) as follows:

1. Age of patient. Under age three fatality is 82 per cent and between 6-8 years it is 44 per cent.
2. Stage of disease when treatment is started. In early disease fatality is 46 per cent and in advanced it is 86 per cent.
3. Development of resistant strains.
4. Presence of other active tuberculous foci unreached by the drug.

Response to treatment has been classified under good and fatal[16,27]. Good response may follow:

1. Uninterrupted improvement.
2. Combined improvement following an initial period of stationary or downhill course
3. Improvement following a relapse.

Fatal course under treatment may take one of four courses:

1. No response to treatment at all.
2. Slow progress downhill with no improvement.

3. Initial period of improvement followed by downhill course.

4. Relapse after long period of improvement.

If improvement is to result from treatment, symptomatic improvement should appear one to three weeks after therapy is started[18,19]. In the second month of treatment weight should increase; temperature should go down; and there should be a feeling of well-being with the decrease of toxic manifestations[25]. By eight weeks the temperature should be normal[18].

Laboratory results show irregular return to normal in three to twelve weeks with gradual return of cell count to normal by the fourth month[25]. However, it has been pointed out that streptomycin itself is a reducing agent and its action is most marked when the drug is in dilute solution[1]. Therefore, sugar content of spinal fluid is not considered a reliable index of improvement. Bacilli are absent from spinal fluid by either culture or guinea pig inoculation by six to eight weeks.

In generalized hematogenous tuberculosis, treatment frequently results in roentgen clearing by the second month.

Fundoscopic examination with regression of choroid tubercles is also used as index of response to treatment[14].

X. DIFFICULTIES AND FAILURES

Many difficulties arise in chemotherapy of tuberculous meningitis. Tuberculous lesions are relatively avascular. The tubercle bacilli are well encapsulated and are therefore resistant. The disease has an insidious onset and may have progressed far before it is recognized. Streptomycin in its action is bacteriostatic, not bacteriocidal. Time must be allowed for a healing process to become established.

For these reasons the more recent reports list the "cure" rate at 5-10 per cent, many of these with permanent neurological damage[13,35]. This is much below the expected rate when streptomycin was first found to be effective against the tubercle bacilli.

To the Athens group of workers[9] this problem raised several questions.

1. "Why do some cases respond to streptomycin immediately and others more slowly?" The question of differential diagnosis with serous meningitis is brought into play.

2. "Why is clinical improvement sometimes not accompanied by a parallel change in spinal fluid?"

3. "What is the criterion of 'cure'--clinical, laboratory or culture?" Waksman[36] states the criterion is "contrast between life and death."

Cure involves a long-range view of the problem

which is only now in the process of analysis.

Regardless of the black picture painted for permanent "cures," streptomycin has shown without a doubt its power to prolong life in tuberculous meningitis. Whereas death prior to treatment occurred in about two to three weeks, now the majority who will die eventually have life prolonged to over seven weeks average[22]. However, with this increase in life span there has been a new disease introduced--chronic tuberculous meningitis[36].

The chief death cause has shifted from paralytic nature to acute hydrocephalus[10]. Hydrocephalus results usually from blockage of exudate in anterior one-third to two-thirds of the basal cistern[27]. Though it is a rare diagnosis ante mortem, signs and symptoms of increased intracranial pressure such as increased drowsiness, voracious appetite, facial flush, glycosuria, hyperthermia, emotional instability[31], opisthotonus, uncontrolled vomiting, sudden increase in pulse, Cheynes-Stokes respiration should make the physician suspicious of hydrocephalus. Streptomycin therapy is stopped at once and started again in very small doses only if improvement of above signs and symptoms appears.

Relapses as noted before seem to correspond to length of therapy. They may be due to breakdown of inaccessible foci. Any change in condition of patient for the worse indicates a probable relapse. Dollfus and Albough[15] stress

the advantage fundoscopic examination has in prediction of ensuing relapse. Chorio-retinal tubercles precede systemic manifestations by days or weeks. Levinson[22] says relapses are mainly those of encephaletic nature with irritability, vomiting and lethargy. Meningitic signs are mild to absent.

XI. QUESTION OF INTRATHECAL THERAPY

Controversy has arisen over the necessity of intrathecal therapy with streptomycin. Much of the discussion arises from the known fact that streptomycin is irritating to the meninges and in itself will cause a pleocytosis in spinal fluid. A chemical meningitis results from intrathecal injection of the drug.

Early reports stressed the necessity of intrathecal route. In 1946 Hinshaw and his group boldly stated that "none of the patients who died had received intrathecal therapy and none who had received intrathecal therapy had died."[18] Larger range observations have not completely substantiated this, but in 1948 the Medical Research Council in England placed the comparative results as one-third of patients receiving combined intramuscular and intrathecal therapy were doing well--fatality rate of 58 per cent--and one-ninth of patients receiving intramuscular therapy alone were doing well with a fatality rate of 78 per cent.

Comments such as "intrathecal therapy is insufficient to halt the process alone but surpresses the disease a significant period without producing resistant strains"[28], "possible to cure with intramuscular alone but combined therapy is better"[31] have been the supportive quotations for intrathecal use. The Athens group[10] readily recognized the

irritant effect and stressed the need for precaution--small doses and intermittent courses intrathecally--but claimed the intrathecal route is indispensable. Medical Research Council in England makes the claim that initial response to intramuscular therapy alone is good but it is followed by progressive deterioration.[27]

However, in 1948 Alperin and Toomey[2] came out with a report of the use of intramuscular use alone. Their courage evoked many praises from associates in comments at the end of the article. They reported on nine cases; two of the group showed good clinical response and one had visual disturbances ahd hydrocephalus. However, they followed the pressure of the literature by stating, "In some cases intrathecal administration has been used to supplement the intramuscular route." They too stress the fact that over 50 mg. of the drug produces signs of meningeal irritation in itself.

The first report where a definite statement that intrathecal therapy is unnecessary is made by Levinson[22] in his work at Cook County Hospital, Chicago, reported in June, 1949. In his series of nineteen cases, all except one were treated by intramuscular route alone, and the survival at present is eight alive from the nineteen.

Would the intramuscular route of therapy be as satisfactory as the combined method if physicians could ig-

nore their fear to treat without the intrathecal route?

XII. LIMITATIONS

Despite the hope streptomycin has given in tuberculous meningitis, it fails to meet the criteria for an "ideal" drug in most respects. Its primary action is only bacteriostatic, not bacteriocidal. Because of this, the mustering of natural defenses for healing by the slow process of resorption, fibrosis and calcification is required.[18,19] Even the bacteriostatic action is short lived. Drug fastness of the bacilli develops rapidly so that drug is limited to six to eight weeks of action.

The drug may not be used with impunity. High degree of toxicity has been shown by use. Toxic reactions may be classified as follows:

1. Generalized reactions. This includes slight increase in temperature, chills, headache, weight loss, somnolence, slow respiration, bradycardia, dyspnea, severe joint pains, nausea, stomatitis, glossitis.[14,17,34,36]

2. Local reactions. Slight erythema and discomfort at site of injection may result.[17,33]

3. Eighth nerve involvement. The drug seems to have a specific affinity for the eighth nerve. Disturbance of equilibrium is the most common complaint. Dizziness, light headedness and giddiness result, but these are not part of the true vertigo which also may occur. A constant low-pitched tinnitus should be considered a danger signal preceding onset of loss of hearing--one of the most feared and most permanent effects

of prolonged intensive streptomycin use[6,7,33].

4. Dermatitis. Exfoliative, urticarial and erythematous (transient type) reactions have been attributed to the drug use[7,14,17].

5. Meningeal irritation. The known irritant effect on the meninges has been stressed previously. Pleocytosis results from chemical irritation. A frequent complaint following continued use of intrathecal therapy is a sharp stabbing pain down the legs with sciatic radiation, worse on dependent side, starting at the time of injection and lasting up to three hours after injection.
Irritation resulting in paraplegia and transverse myelitis has also been reported. These changes recede when intrathecal therapy is stopped[7,14,31,36].

6. Renal irritation. No actual renal impairment has been reported, but irritation resulting in proteinurea, cylinduria, hematuria and occasional azotemia do occur. These conditions disappear with stoppage of drug. However, previous renal damage may interfere with excretion of drug and invite concentrations high enough for toxic reactions[7,17,33].

7. Hematologic picture. Eosinophilia, agranulocytosis and leukopenia have been reported in a few isolated cases, with recession after drug is stopped[7,28].

8. Other toxic effects include reports of hepatic disturbance, loss of scalp hair and paresthesias about the face.[31,33,34]

XIII. ADJUNCTS

Because the limitations of streptomycin are readily recognized, workers in the field are on a constant watch for further aids in therapy.

One such report comes from Cathie[8]. The fact that exudate exists in tuberculous meningitis--exudate containing fibrin plus bacilli--leads to the conclusion that streptomycin may not be able to penetrate this barrier to the bacilli. Therefore, the use of streptokinase has been advocated. Streptokinase is a product of some strains of streptococci which activates natural occurring profibrinolysin to produce fibrinolysis. This should allow penetration of the streptomycin to the bacilli. The series reported by Cathie shows that streptomycin alone (14 cases) gives recovery of 21 per cent and mortality of 79 per cent. In streptomycin combined with streptokinase (19 cases) recovery of 58 per cent with mortality of 42 per cent is given.

Work in using streptomycin in combination with other drugs is being carried out. First reports on use of promizole alone[26,29] showed it had no effect on tuberculous meningitis. But in a recent report by Lincoln it is shown that a combination of promizole with streptomycin gives a prolongation of bacteriostatic effect and lessens the toxicity of promizole.

The suggested course includes:

Streptomycin. Intramuscularly 1 gm. daily. Intrathecally--0.1 gm. daily until toxic or mechanical difficulties occur. Then every two days for 40 treatments.

Promizole. Orally every six hours. 1.0 gm. daily. If there are no toxic effects, raise to 2.0 gms. daily until therapeutic blood levels reach 1.0-3.0 mg. per 100 cc. Use for three years.

The Shanghai group[34] also report improvement of combined therapy over either drug separately. Toxic effects of promizole include cyanosis, thymus enlargement and early development of secondary sex characteristics.

Recommendations of addition of para-aminosalicylic acid[16] to the regimé has also been suggested. Waksman[36] speculates on the value of potassium iodide to "facilitate solution and absorption of caseous matter about the cells, exposing the bacilli." He also reports inconclusive studies of synergistic actions of streptomycin with chaulmoogra oil and "British antilewisite."

XIV. CASE HISTORIES--WISCONSIN GENERAL HOSPITAL

Case No. 1: S. R., Wisconsin General Hospital (253993)

This three-year-old white female entered Wisconsin General Hospital on June 9, 1947. Family history of a maternal uncle who had lived with the family when the child was an infant and later died of tuberculosis was obtained.

Birth and development were normal, but at the age of two months she developed "pneumonia." She was treated with X-ray therapy for enlarged thymus. At six months of age she was seen for wheezing and stridor of five months' duration. X-ray revealed atelectasis of mid and lower lobes on the right and enlarged hilar nodes. Diagnosis was childhood tuberculosis. At age of eleven months an abscess of left elbow was drained and healed.

Two weeks prior to entry anoxeria and low-grade fever were noted. One week later the local doctor placed her on sulfadiazene because many white blood cells had been found in her urine. She had been on penicillin therapy since June 6.

Physical examination revealed a disoriented, drowsy, hyperirritable child. Positive neurological findings included nonreaction to light by either pupil, the left pupil larger than right, questionable facial palsy on left, nuchal rigidity, exaggeration of deep reflexes on left, questionable bilateral Babinski, bilateral ankle clonus and

refusal to bear weight on left leg.

Laboratory findings included Hb 11.4 gm., RBC 5.54 million, WBC 26,500 with 79 per cent neutrophile, 18 per cent lymphocytes and 3 per cent monocytes. Urine showed many cells, trace of albumin, but no acid fast bacilli. Roentgen studies showed a widening of skull suture lines, clearing of atelectasis, and calcified Ghon focus at periphery right lung base. Spinal fluid findings done elsewhere the same day before admission showed an increased protein and cell count, decreased sugar and acid fast bacilli.

She was started on 250,000 units streptomycin intramuscularly every three hours for fifteen days. (Dilution 1,000,000 units or 1 gm. in every 20 cc. saline.) Then she was placed on 400,000 units every three hours until December 1. Toxic effect of the drug was shown by an initial slough and fibrosis at injection site. Progress was divided into three phases:

Phase 1 lasted from June 9 to July 20. During this period her temperature dropped by lysis from 103° F. at admission to normal on the fiftieth day. She was gravely ill and failed to respond to stimuli except loud noises. Oral feedings were maintained throughout this period though neurological symptoms were pronounced, such as opisthotonus and drowsiness.

Phase 2 occurred from July 20 to September 4.

During this time she showed symptomatic improvement, but a temperature rise. On July 30 she recognized her father for the first time. Her appetite increased and she responded and began to talk.

Because the literature so stressed intrathecal dosage, eight doses of streptomycin (50,000 units in 20 cc. saline) were given between August 7 and August 19. During this period she showed a marked increase in irritability, one episode of a chill with fever rise to 104° F., and a rise in spinal fluid cell count and protein.

During this period of treatment she lost her hearing.

Phase 3 occurred between September 4 and November 20. Her temperature was normal, and she was free of signs and symptoms. On October 20 her spinal fluid sugar was normal, and bacilli growth had ceased.

She was discharged on December 1. Progress examination on January 26, 1948, revealed a normal-appearing child, weight thirty-one pounds, normal eye grounds, and no abnormal reflexes. She was totally deaf and her gait unsteady.

Other studies in February, 1948, showed her I.Q. rating to be 93 per cent and her electro-encephalogram to be within normal limits.

Concentration studies carried out during this case

are as follows:

	Time after IM injection	CSF level	Blood level
7-9	2 1/2 hrs.	-	66? µg./ml.
7-17	1 1/2 hrs.	10 µg./ml.	33 µg.
7-30	2 1/2 hrs.	3.3 µg.	6.6 µg.
8-2	1	4.5 µg.	15. µg.
8-4	1/2 hr.	14 µg.	38.8 µg.
10-13	3	3 µg.	10 µg.
10-20	3	3.5 µg.	-
11-20		3.5 µg.	+20 µg.
11-28	3	1 µg.	8 µg.

Time after injection	CSF level	Blood level
30 min.	14 µg./ml.	38.8 µg./ml.
60 min.	4.5 µg.	15 µg.
90 min.	10 µg.	33 µg.
150 min.	3.3 µg.	6.6 µg.
180 min.	3.0 µg.	10 µg.
180 min.	1 µg.	8 µg.

Case No. 2: D. W., Wisconsin General Hospital (259971)

On July 17, 1948, this two-year-old white female infant entered another hospital in the state with the history of irritability, loss of appetite, and drowsiness for two weeks. She was semicomatose and had nuchal rigidity and positive Kernig's-sign. Spinal fluid had 264 cells, 74 per cent polymosphonuclear, 26 per cent lymphocytes. Protein was 30 mgm. and sugar 26 mgm. Pellicle formation with acid-fast bacilli was found. X-ray revealed miliary tuberculosis with bone involvement of left elbow. She was placed on one gm. streptomycin intramuscularly daily.

On July 31 she entered Wisconsin General Hospital. Additional history given showed she had become restless and drowsy without a fever on July 15. Three weeks earlier pain in left elbow with swelling had developed, followed in two weeks by drainage of the right ear of purulent material. Family history indicated the child's mother had died the previous year of miliary tuberculosis.

Physical examination revealed a poorly-nourished, lethargic, chronically ill child. Pupils reacted to light sluggishly. Perforation of the right ear drum was seen. Liver was palpable two centimeters below the right costal margin. Adenopathy of posterior cervical, inquinal, and right epitrochlear nodes was found. No nuchal rigidity was present, but reflexes were exaggerated, and Kernig's sign was questionably positive.

Entrance laboratory data included Hb 11.6 gms, RBC 7.07 million, WBC 10.1 thousand with a differential of 55 per cent neutrophiles and 45 per cent lymphocytes. X-ray report showed changes compatible with miliary tuberculosis in lung fields and infectious arthritis with abscess formation in left elbow. Spinal fluid specimen revealed cell count of 80, 95 per cent lymphocytes and 5 per cent polymorphonuclear. Protein 100 mgm, sugar 36 mgm., chlorides 623 mgm., and a gold sol curve of 3333210000.

She was placed on 125 mgm. streptomycin intramus-

cularly every six hours for a six-month period.

By August 6 her temperature was normal. However, on August 10 acid-fast bacilli were recovered from her left elbow. The arm was placed in flexion, and a cast applied.

Progress during August was poor. Spinal fluid cell count rose to 208 cells on August 20 with 400 mgm. protein. On August 21 X-ray showed clearing of chest lesions though cough persisted. On August 29 she had a clonic convulsion of entire body with a rise in temperature to 103° F. per rectum. The following day she responded poorly; nuchal rigidity was now present. By September 4 she took fluids better, but the Kernig's sign was slightly positive.

In October the spinal fluid cell count had shifted to 100 per cent lymphocytes and had dropped to 108. Sugar rose to 74 mgm., and protein also rose to 700 mgm. By October 15 she was very alert.

November 22 the spinal fluid cell count had dropped to 55 with 100 per cent lymphocytes, and protein had dropped to 240 mgm.

By March of 1949 she was well enough to be transferred to a children's sanatorium.

Interestingly, throughout her entire course at Wisconsin General there were no acid fast bacilli in the spinal fluid.

Subsequent orthopedic follow-up studies on this

child show that she was treated for a traumatic fracture of the right clavicle on April 1, 1949. At this time she had shown personality change from a pleasant child to one very difficult to manage. Roentgen studies of her left elbow show destruction of the condyles of humerus, coronoid, olecronon processes.

On June 20 the cast was removed from the left arm. A sinus tract was still present, and X-rays showed destruction of humeral condyles and excavation and cavitation of olecronon. Long arm cast was reapplied.

Examination September 23 revealed the clavicle had healed. She was able to walk and had good co-ordination. Reflexes were equal and brisk. Left pupil was larger than the right, but both reacted to light.

Concentration studies during this series of streptomycin therapy were:

	Time following IM injection 125 mgm.	CSF levels
8-12	2 hrs.	7.5 µg./ml.
8-20	5 1/2 hrs.	6 µg.
11-22	2 1/2 hrs.	9.9 µg.

Cases Nos. 3-6: Wisconsin General Hospital (257921, 257418, 254711, 259817)

Four other known cases of tuberculous meningitis treated at Wisconsin General Hospital since the introduction of streptomycin have ended fatally. Two of the cases were

comatose their entire stay in the hospital. One, a twelve-year-old girl, entered in coma with diagnosis of poliomyelitis and died five days later despite intensive therapy. The other, a boy age one, remained in coma for the sixteen days in Wisconsin General before his death.

Two other cases, a girl of 13 months and an Indian girl of two months, entered with wide-spread miliary tuberculosis and all the signs of meningeal involvement. They were started on streptomycin doses--150-250 mgm. every six hours intramuscularly. Despite the streptomycin and all supportive measures necessary, they followed a progressive downhill course and died in two to three months.

Post mortem examination of all of these cases revealed miliary tuberculous foci in the meninges plus miliary involvement of lungs.

Examination of the result of streptomycin therapy at Wisconsin General Hospital shows two "cures," two rapidly fatal outcomes, and two prolonged courses of the disease over two to three months. Streptomycin has been administered via the intramuscular route solely, except for very small intrathecal doses over eight days in one case. Studies show concentration levels are maintained in both the blood and spinal fluid though no drug is introduced directly into the intrathecal passages.

Case 1 also clearly indicates the irritant effect

of streptomycin when introduced into spinal fluid. Irritability, increase in temperature, increase in spinal fluid cell count resulted immediately and disappeared when intrathecal route on treatment was stopped.

These results would tend to substantiate Levinson's [7] statement that intrathecal route is unnecessary--that intramuscular route alone will maintain levels sufficient to halt the process and to allow regression of the disease.

Results of Case 2 also give rise to speculation of action of streptomycin on the tubercle bacilli. Why should a six-month course of therapy stop progression of meningeal inflammation but allow the progression and gradual destruction of the bones of the elbow? Is the difference in the tubercle bacillus, in the accessibility of the foci to the drug, or in the action of the drug on the bacilli?

These questions raised in this paper and many others still remain to be answered. Tuberculous meningitis remains a threat to childhood. A method of "cure" remains to be found. Streptomycin has offered hope, has given the first tangible evidence that a drug may be found which will control the evasive tubercle bacilli. That specific drug is a question of the future.

BIBLIOGRAPHY

1. M. Alando and M. Nicola, "Sugar Content Cerebro: Spinal Fluid in Tuberculosis Meningitis and Its Relationship to the Reducing Properties of Streptomycin," Riv. Clin. Pediat. 46:372-380 (1948). Abstract from Abstract of World Med., 6:249 (1949).

2. L. Alperin and J. A. Toomey, "Treatment of Tuberculous Meningitis," J. of Peds., 33:74-84 (1948).

3. E. Applebaum and C. Halkin, "Tuberculous Meningitis and Miliary Tuberculosis Arrested with Streptomycin," J.A.M.A., 135:153-155 (1947).

4. E. Benard, B. Kreis, Lottie, P. Chicke, and P. Y. Paley, "First One-Hundred Cases of Tuberculous Meningitis Treated with Streptomycin in Tuberculosis Clinic," Bull. Acad. Nat. Med., 133:34-51 (Paris, 1949). Abstract from Abstract of World Med., 6:501 (1949).

5. W. Boyd, Textbook of Pathology, Fifth Edition, 894 (Lea and Frebiger, Philadelphia, 1947).

6. H. A. Brown and H. C. Hinshaw, "Toxic Reaction of Streptomycin on Eighth Nerve Apparatus," Proc. Staff Mayo Clinic, 21:347-352 (1946).

7. P. A. Bunn, "One-Hundred Cases of Miliary and Meningeal Tuberculosis Treated with Streptomycin," Am. J. Med. Sc., 216:286-315 (1948).

8. I. A. B. Cathie, "Streptomycin-Streptokinase Treatment of Tuberculous Meningitis," Lancet, 1:441-442 (1949).

9. K. Choremis and G. Vrachnos, "Primary Tuberculosis with Meningism and Bacilli in Spinal Fluid," Lancet, 408-409 (1948).

10. K. Choremis, N. Zernos, V. Constantinides, and S. Pantazis, "Streptomycin Therapy in Tuberculous Meningitis in Children," Lancet, 2:595-599 (1948).

11. Clinical Pathological Conference, Barnes Hospital, Washington University Medical School, "Acute Meningitis," Am. J. of Med., 2:215-222 (1947).

12. W. S. Craig, "Observations of Tuberculous Meningitis in Children," Brit. Med. J., 2:374-378 (1948).

13. N. F. Dawling, H. K. Sweet, H. L. Hirsh, and M. H. Lepper, "Specific Therapy of Bacterial Infections of Central Nervous System," J.A.M.A., 139:755-758 (1949).

14. R. Debré, Thieffry, Brissaud, and Noufflard, "Streptomycin and Tuberculous Meningitis in Children," Brit. Med. J., 2:897-901 (1947).

15. M. A. Dollfus and C. M. Albough, "Fundus Lesions in Tuberculous Meningitis and Miliary Pulmonary Tuberculosis Treated with Streptomycin," Am. J. of Ophthmal., 32:821-824 (1949).

16. R. C. Eley, Round Table Discussion, "Therapeutics of Tuberculosis in Infancy and Childhood with Special References to Chemotherapy," Peds., 3:549-554 (1949).

17. D. H. Heilman, F. R. Heilman, H. C. Hinshaw, D. R. Nichols, and W. F. Herrell, "Streptomycin: Absorption, Diffusion, Excretion, and Toxicity," Am. J. Med. Sc., 210:576-588 (1945).

18. H. C. Hinshaw, W. N. Feldman, and K. N. Pfuetze, "Treatment of Tuberculosis with Streptomycin," J.A.M.A., 132:778-782 (1946).

19. H. C. Hinshaw, M. M. Pyle, and W. H. Feldman, "Streptomycin in Tuberculosis," Am. J. of Med., 2:429-435 (1947).

20. W. M. Jamieson, "Some Problems in Diagnosis of Meningeal Tuberculosis," Edinburgh Med. J., 56:221-229 (1949).

21. A. Levinson, "Meningitis," from Brenneman, ed., Practice of Pediatrics, Vol. 4, Ch. 8, 30-42 (W. F. Prior Company, Inc., Hagerstown, Md., 1948).

22. A. Levinson, "Streptomycin Therapy in Tuberculous Meningitis," Am. J. Dis. of Child, 77:709-728 (1949).

23. E. M. Lincoln, "Tuberculous Meningitis in Children," Am. Rev. Tuberc., 56:75-108 (1947).

24. E. M. Lincoln and T. Kirmse, "Chemotherapy of Tuberculosis in Children," Peds., 5:280-294 (1950).

25. E. M. Lincoln, T. Kirmse, and E. DeVito, "Tuberculous Meningitis in Children," J.A.M.A., 136:593-597 (1949).

26. E. M. Lincoln, S. Stone, and O. R. Hoffman, "Treatment of Miliary Tuberculosis with Promizole," Bull. Johns

Hopkins Hosp., 82:56-75 (1948).

27. Med. Research Council, "Streptomycin Therapy of Tuberculous Meningitis," Lancet, 1:582-596 (1948).

28. C. P. Mehas and W. E. Truax, "Streptomycin in Tuberculous Meningitis," J.A.M.A., 135:155-157 (1947).

29. L. Milgram, I. Levitt, and Maya Unna, "Promizole Treatment of Miliary Tuberculosis," Am. Rev. Tuberc., 55:144-159 (1947).

30. A. R. Rich and M. A. Cordock, "The Pathogenesis of Tuberculous Meningitis," Bull. Johns Hopkins Hosp., 52: 15-38 (1933).

31. J. Rubie and A. F. Mohun, "Tuberculous Meningitis," Brit. Med. J., 1:338-345 (1949).

32. J. Schwartz, "Tuberculous Meningitis," Am. Rev. Tuberc., 57:63-94 (1948).

33. Squibb, "Streptomycin Hydrochloride," phamphlet (E. R. Squibb & Sons, New York).

34. T. F. Su and M. Y. Wu, "Streptomycin and Promizole Combined Therapy in Tuberculous Meningitis in Children," J. of Peds., 36:295-305 (1950).

35. N. S. Tacket and G. S. Lovejoy, "Streptomycin Therapy of Tuberculous Meningitis," J.A.M.A., 142:648-650 (1950).

36. S. A. Waksman, Streptomycin, 224-226, 292-297 (The Williams & Wilkins Co., Baltimore, 1949).

Kenneth B. McDonough

Approved