Streptomycin in the Treatment of Human Tuberculosis

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Following the demonstration by Hinshaw and McDermott that streptomycin affects favorably the course of human tuberculosis, the Veterans Administration, in collaboration with the Army and Navy, organized one year ago a cooperative investigation to study these effects. This was to be carried out simultaneously in nine service hospitals, but since that time the study has been enlarged to include 22 hospitals. The present report will summarize the results of treatment in 650 cases of various types of tuberculosis treated in 20 Veterans Administration hospitals.

Approximately 80 per cent of the patients were treated uniformly and according to the terms of protocols designed by the streptomycin committees of the organizations concerned. The remainder were what we have chosen to call "panic" or "unusual" types of tuberculosis and were not observed in as uniform a manner.

The vast majority of cases were required to have either pathologic or bacteriologic proof of the diagnosis before treatment was started—the exceptions to this requirement will be remarked upon. The patients treated in accordance with the terms of the protocols were selected and observed in a consistent fashion. Adequate and periodic notations of blood, kidney, and otologic functions were made before and during treatment and frequent bacteriologic, roentgenographic, and clinical examinations were recorded.

Results of streptomycin therapy will be described in the following types of tuberculosis: Pulmonary, 306 cases; draining cutaneous sinuses, 82 cases; upper respiratory ulcerations including tracheobronchial and laryngeal lesions, 73 cases; meningitis, 71 cases; acute disseminated miliary tuberculosis, 24 cases; genito-urinary, 38 cases; bone and joint, 25 cases; enteritis, 7 cases; peritonitis, 9 cases; pericarditis, 8 cases; tongue, 10 cases; and eye, 4 cases.

The dosage of streptomycin in most instances was 1.8 to 2 grams

*A speech delivered by Dr. Paul A. Bunn, member of the Veterans Administration Committee on Streptomycin, before the American College of Chest Physicians in Atlantic City on June 8, 1947. The cases referred to in its text are amongst the group described in a report to the Council on Pharmacy and Chemistry of the American Medical Association and published in the Association's Journal on November 8, 1947.

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daily, injected intramuscularly in 5 or 6 doses, and the duration of treatment varied from 7 to 150 days, although the extremes of this variation concern only the less common types of tuberculosis. In the pulmonary cases, which comprise one half of the total number, the duration of treatment was 120 days unless some toxic manifestation altered that regimen.

The results of treatment can be divided into 3 categories. (1) The group of tuberculous lesions in which the effect of streptomycin seems clear cut and impressive; namely, in cases with draining cutaneous sinuses, upper respiratory ulcerations, glossitis, ileocolitis, and peritonitis. (2) The group of tuberculous lesions in which the therapeutic efficacy of streptomycin is less well defined; namely, in pulmonary, genito-urinary, orthopedic, pericardial, and ophthalmologic. (3) The group of disseminated tuberculous lesions, i.e., miliary and meningeal tuberculosis, in which the place of streptomycin is not only well defined and impressive but also in which it is the only known therapy of any effectiveness.

GROUP I.

Cutaneous Sinuses: The data in Table I indicates the profound effect that streptomycin exerts upon tuberculous cutaneous sinuses. In over 80 patients, with an average of 3 to 4 sinuses in each, a "cure" rate of 80 per cent occurred. The lesions treated were all over 3 months' duration and many had been open and draining for as long as 5 years. In the table, the good results are, if anything, underestimated, for in the group of 10 per cent listed as improved, there were favorable changes, unexpected from any previous experience by physician or patient, but little short of complete healing. In every patient with multiple sinuses, at least one healed.

During the treatment period, no major accessory surgical procedure or local therapy was employed. Many of the sinuses were incised to allow better drainage of underlying collections of pus, but no radical incisions and drainages were attempted.

<table>
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<th>TABLE I</th>
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<tr>
<td><strong>TUBERCULOUS SINUSES WITH CUTANEOUS DRAINAGE TREATED WITH 1.8 GRAMS STREPTOMYCIN DAILY FOR 120 DAYS</strong></td>
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<tr>
<td>Number of Patients, Majority had Multiple Lesions</td>
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<td>Duration of Lesion, Months</td>
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<td><strong>Results:</strong></td>
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<tr>
<td>Complete Healing</td>
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<td>Improved</td>
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The speed with which improvement occurred must also be mentioned. Many sinuses healed within a month and a majority within 60 days.

**Other Tuberculous Ulcerations:** Tuberculous ulcers of the upper respiratory tree and alimentary tract, including pharynx, larynx, trachea and bronchi, tongue, ileum, and colon, responded well to streptomycin, following treatment for from 7 to 90 days. All of these benefited considerably more from intramuscular injections of streptomycin than from its use by other routes such as aerolization, nebulization, local, or oral. Although symptomatic benefit often resulted from the use of these latter routes, adequate blood serum concentrations cannot be attained by them and complete benefit could not be expected.

Regardless of the extent, type and response of the pulmonary tuberculosis accompanying the laryngeal, pharyngeal, and tracheobronchial lesions under observation, complete and lasting healing of the ulcers occurred in a vast majority of the 73 patients treated with streptomycin. The rapidity of this healing was remarkable; some cases showed repair of ulcerations within 7 days, and most were healed within 30 days.

A majority of the patients in this group were treated at the San Fernando Veterans Administration Hospital under the direction of Doctors Emil Bogen and Lyman Brewer. All of these patients were bronchoscooped at least twice before streptomycin was started and at bi-weekly intervals during the treatment period, so that the trend of disease was well recorded. No case was given streptomycin if there was any tendency of the lesion to heal during the pre-treatment observation period.

Seventeen cases of alimentary tract disease have been treated, 10 cases of tongue ulcerations and 7 with enteritis. As in the group previously described, the intramuscular route of administration has proved to be the best method to produce satisfactory response. Both local therapy to the tongue and ingested streptomycin have been tried in some patients, prior to a shift to the parenteral route, but in each instance the rapidity and completeness of the response have appeared significantly better by the latter method of administration.

There has been a dramatic symptomatic improvement in all cases of enteritis treated with streptomycin. No case has been included in the series unless he had had a positive sputum and severe gastro-intestinal symptoms. It was not possible to obtain specific bacteriological or pathologic proof of diagnoses in these individuals but, in most, typical roentgenographic observations were recorded so that the clinical impression of ulcerative tuber-
culous enteritis could be reasonably well supported. Very rapid relief of diarrhea, distension, and flatulence was noted, and the stools became normal in consistency and amount. X-ray evidence of healing has not matched the clinical response. However, a majority of these cases have been treated since January 1947 and it is quite possible that sufficient time has not elapsed for the changes to have become obvious by x-ray.

Nine cases of peritonitis, proved by biopsy at laparotomy, have improved symptomatically and the patients have lost all signs of infection following a course of streptomycin. The dosage of 2 grams daily has been continued for 80 days in most, as was done in the cases of enteritis. It would be difficult to describe the pathological changes coincident with this improvement because only by a second exploration could the investigator observe objectively what had taken place within the abdomen. This procedure has not been performed.

GROUP II.

The place of streptomycin in the treatment of bone, joint, genito-urinary and pulmonary tuberculosis is less well defined although its use is accompanied in most instances by some type of improvement. The greatest efforts in the Veterans Administration studies have been and are being directed toward defining precisely the position of streptomycin in the therapy of these commonest types of human tuberculosis.

In all three groups, a daily dose of 1.8 or 2.0 grams has been used and most patients have received the drug for 120 days. No local or accessory therapeutic measures have been employed during streptomycin treatment.

Pulmonary: The protocol allowed only those patients to be treated whose tuberculosis had been under observation for at least two months and in whom the tuberculous process had proved to be progressive or, at best, stationary. Other forms of therapy including the amount of bed rest, were maintained at levels similar to those existing prior to the administration of streptomycin.

The most important measurable effect that streptomycin could be expected to exert on the course of tuberculosis should be demonstrable in x-ray films. Films from 157 cases in which treatment had been completed were reviewed by a jury of 12 physicians at the third streptomycin conference in St. Louis early in May 1947. The jury, composed of physicians whose experience in clinical tuberculosis and roentgenology well qualified them, and who had not previously seen the cases, was asked to answer specific ques-
tions, on score cards, about the x-ray films after a review of each patient's series of films, taken before, during, and after streptomycin.

The opinion of the jury and that of the individual investigator who managed the cases can be summarized briefly. The effect of streptomycin on proliferative lesions was negligible. A majority of the jury voted that 81 per cent of exudative lesions improved, i.e., became smaller in extent, harder in type, or disappeared. They indicated that visualized cavities, either old or new, became smaller or closed in 65 per cent of the cases. The most remarkable vote concerned the question of whether, in the juror's opinion, the frequency with which the observed changes could have been expected to occur with bed rest alone. In the judgment of the jury, 50 per cent of the cases showed improvement following streptomycin which it had rarely or never seen before.

In the observations upon the entire group of 306 cases by the responsible investigators, over 70 per cent showed some evidence of improvement either clinical or by x-ray, regardless of the type of pulmonary disease under consideration.

The conclusion to be drawn from a review of x-ray films alone is that while streptomycin has the ability to reverse the trend of unfavorable disease and to aid in the unusually rapid resolution of exudative disease, it has not been seen to "cure" any pulmonary lesion. It must be emphasized that, in this series of 306 cases, streptomycin was given to a group of patients whose previous tuberculous history showed an unfavorable course and whose treatment was unchanged in other respects.

Streptomycin is an antibacterial agent—it has the ability to inhibit the growth of tubercle bacilli in the human to a degree never before observed with any agent. It has been shown in this series of cases that it does everything that could be expected of such an agent. This or any other antibiotic cannot be expected to alter permanent pathological changes in the lung. The improvement observed in these patient's x-ray films is the result of the body's ability to heal or resolve the inflammatory lesions during the period when the infecting organisms are not capable of active growth. It could have been predicted that caseous tissue, fibrosis and cavernous disease would be far less affected than reversible exudative lesions. This prediction is borne out by our series.

There are other effects of streptomycin in the course of pulmonary tuberculosis, more difficult to summarize and probably of less overall importance. Fever, when present, was reduced in most instances, cough lessened in severity and frequency, sputum became less purulent and less in amount, sedimentation rates tended to become lower, gain in weight varied considerably but
was striking in many, and the subjective improvement was marked in the majority of patients.

During the treatment period, less than 10 per cent of the individuals showed progression of their disease, and this occurred usually in the fourth month of therapy. Whether or not these treatment failures have been due to the organisms' gaining resistance is unknown, as the bacteriological data on them are not yet complete. It is to be anticipated, however, that the failures during treatment, can be explained by this mechanism.

Relapses occurred in the post-therapy period in 20 per cent of the cases. In a few, re-treatment failed to produce a second improvement and in these instances, where the information is available, the organisms were found to be resistant to streptomycin. In other instances, when re-treatment produced further improvement, the organisms proved to be still sensitive. Despite these examples that clinical response parallels the sensitivity of the organism, the cases are too few to warrant drawing any conclusion on this point from the Veterans Administration series. It is necessary to await further bacteriological and clinical correlations.

Bone and joint, pericardial, and ophthalmic tuberculosis have been treated with streptomycin in our hospitals. The information from the results of this therapy is too meagre to permit any conclusions. Certainly there has been no profound change in any case thus far treated, and although the various lesions have not progressed during therapy, there is nothing to indicate that any degree of benefit can be expected from streptomycin alone. It must be emphasized, however, that very few patients in these categories have been treated, and that the period of observation is too short to determine whether a favorable response will be obtained.

In the treatment of genito-urinary tuberculosis, a prompt and impressive improvement in symptoms, such as distressing urgency, frequency and pain of urination, has been commonplace following the use of streptomycin. Cystoscopic examinations, performed at routine intervals before and during therapy, have revealed that bladder ulcerations heal rapidly and that the degree of tuberculous cystitis is reduced considerably in the majority of patients. Pyelograms, on the other hand, have failed to disclose appreciable improvement in kidney defects due to tuberculosis.

GROUP III.

The most exciting and the most remarkable effect that streptomycin exerts on the course of human tuberculosis has been demonstrated in miliary and meningeal tuberculosis. In the past, the mortality rate of acute disseminated miliary tuberculosis and
tuberculous meningitis has been 100 per cent or very near that figure. With adequate dosage and with the proper administration of streptomycin, an appreciable reduction in this mortality will occur.

Of 25 cases of miliary tuberculosis which have been treated, 20 are living. Nine of these have been observed for from 2 to 20 weeks, following completion of treatment; they are in good health and all evidences of the miliary dissemination have disappeared both by clinical and roentgenographic signs. Three others are about to discontinue treatment and all of them are similarly and remarkably well.

In many of these cases, the focus from which the widespread dissemination originally occurred continues to be active, but the fatal complication has apparently been controlled by streptomycin.

Five cases have died, 3 of them within 6 weeks following the beginning of treatment. All 3 were moribund when streptomycin was started and streptomycin had no obvious effect on the course of their disease. Two others died after 110 and 120 days' treatment. Both had had an initial profound improvement, including the disappearance of x-ray lesions, but despite continuation of therapy, re-dissemination occurred and the patients died. Presumably, these are instances in which the organisms became resistant to streptomycin and the individual, despite the initial help of the antibiotic, could not control the infection when its antibacterial effect was lost.

Although this survival rate (I question the advisability of using the term “cure rate”) of 80 per cent is remarkable, it may produce a sense of false security in the physician treating the case. A serious hazard has been noted, during or after therapy, which makes it unwise to declare that streptomycin is a wonder drug in this type of tuberculosis. Five cases have developed fatal meningitis during therapy for miliary tuberculosis and two others have developed meningitis 3 months after cessation of streptomycin therapy, originally given for acute miliary tuberculosis. All seven of these individuals will die or have died, and presumably the lack of response during re-treatment has been due to the organisms' having become resistant to streptomycin.

The treatment of meningitis with streptomycin is similarly remarkable even though the mortality rate will still, apparently, be in the neighborhood of 90 per cent. Of the 71 cases of meningitis, with or without evidences of acute miliary dissemination, 28 are still living and of the 43 who died, 29 (70 per cent of deaths or 40 per cent of total) expired within 6 weeks without streptomycin having had any effect on their course. All 29 were in coma when treatment was started.
Eight individuals have finished a course of treatment and have remained more or less free of central nervous system infection for periods of from 30 to 110 days. Three of these, however, are in terminal stages of tuberculosis elsewhere in the body or have become decerebrate. The other five are in good health although four of them continue to have abnormal spinal fluid.

There are 20 others still under treatment. Most of these will probably die but hope for a "cure" is being held out for a few. Even though all should die, however, the very fact that 5 out of 71 individuals, all with proved tuberculous meningitis, have not only survived for periods of 4 to 8 months after the onset of the disease, but are in relatively good health, indicates the definite effect that streptomycin exerts on the course of this fatal type of human tuberculosis. That 7 to 10 others may also survive, merely adds prestige to that statement.

Toxicity: Streptomycin is not free of toxicity; in fact, the vast majority of patients receiving it for periods longer than 3 weeks in the dosage we have employed will experience one or more untoward side reactions. Fortunately, few of these require the cessation of treatment, provided, of course, the proper indications for its use are present; reactions are rarely severe enough to endanger the patient's life.

The toxic reactions fall into three distinct categories. The first concerns the unique ability of streptomycin to injure the 8th cranial nerve. In the Veterans Administration series of 650 cases, over 95 per cent completely lost the function of their vestibular apparatus. This syndrome is characterized by the onset of dizziness and vertigo between the third and fifth week of continuous therapy. The vertigo and loss of balance cause the patient considerable discomfort during the first few days, but thereafter is noted only when he attempts to use his balancing mechanism. As evidenced by many tests of vestibular function, the entire labyrinthine apparatus dies, for a return of function does not occur following termination of the administration of the antibiotic. Although in the young individual, the cerebellum and muscles of the eye allow reasonably adequate accommodation for this loss, there is no question but that an absent vestibule comprises a distinct hazard to normal existence.

The auditory branch of the 8th nerve is involved only when high concentrations of streptomycin are present in the brain for relatively long periods of time. Loss of hearing, progressing to total deafness occurs, then, only in cases receiving streptomycin intrathecally, or when excessive doses are given intramuscularly, or when kidney function is so reduced that high blood levels, above 80 mcg/cc., are being maintained. Fortunately,
the loss of hearing is slowly progressive so that the necessary laboratory procedures, performed over several days to a few weeks' time, allow treatment to be continued until the cause of the complication can be determined. A return of hearing is expected, in those instances in which the loss has not been complete, as soon as the irritant is removed. Complete deafness, on the other hand, is permanent when it becomes established.

Streptomycin, like many other chemotherapeutic agents, can be antigenic and cause a variety of delayed anaphylactic phenomena. The worst of these is exfoliative dermatitis. It is rare, but sufficiently common to force the clinician to perform those laboratory procedures which demonstrate the patient's sensitization. Cessation of treatment is of course imperative whenever such lesions develop.

Other hypersensitivity phenomena are commonly observed. Skin rashes, eosinophilia, circumoral paresthesias and other minor ones are examples. There have also been many instances of contact dermatitis among those who handle the antibiotic.

Streptomycin has been shown to be a kidney irritant. If affects the proximal convoluted tubules somewhat like a heavy metal and may produce irreparable damage to renal function. Casts are commonly observed shortly after streptomycin is first administered but in most instances further evidences of its irritant effect do not occur. In some cases, however, there are progressive urinary sedimental changes such as albuminuria and the presence of red or white blood cells. Whenever this sequence of events occurs, caution should be exercised in continuing treatment, for a reduction in renal function as evidenced by lowered PSP and urea clearances may follow.

There have occurred two instances of bone marrow depression, one in the Veterans Administration series, which developed during long-term streptomycin therapy. As this complication is so rare and as the depression is not permanent, mere mention of its possibility is sufficient.

SUMMARY

1) The Veterans Administration has undertaken a large scale investigation into the clinical and toxicologic effects of streptomycin in the treatment of human tuberculosis. The treatment was given in accordance with the terms of protocols designed by representatives of the Veterans Administration, Army, and Navy, and was carried on in 20 cooperating Veterans Administration hospitals.

2) The results of treatment of 650 cases of various types of
tuberculosis have been described. Because these are indicative of the fact that streptomycin exerts a favorable effect upon many types of tuberculosis, the present investigations are being continued and enlarged.

3) In some types of tuberculosis, namely, sinuses with cutaneous drainage, tracheo-bronchial, laryngeal and pharyngeal ulcerations, ulcers of the tongue and enteric tract and peritonitis, streptomycin has proved to be adequate and effective therapy when given by the intramuscular route.

4) In genito-urinary and in certain types of pulmonary tuberculosis, streptomycin has favorably altered the course of the infection in a majority of the cases.

5) The most beneficial effect in pulmonary disease occurred in exudative lesions. Less benefit was observed in fibrous, caseous, and cavernous lesions. No case was cured.

6) Bone and joint, ophthalmic and pericardial tuberculosis do not appear to be particularly benefited by streptomycin but experience with these lesions is meagre.

7) The expected mortality of meningeal and miliary tuberculosis has been lowered by the administration of streptomycin.

8) Toxic reactions upon the eighth nerve, kidney and organs of blood formation, and the delayed anaphylactic complications caused by streptomycin, preclude its use in all patients with tuberculosis. Its long term use must be accompanied by frequent and accurate laboratory procedures, and the disease under treatment must carry a prognosis sufficiently serious to justify the hazard of toxic effects from the drug.

9) Tubercle bacilli exposed to streptomycin eventually develop an overwhelming resistance to the antibiotic, so that the maximal therapeutic benefit to be anticipated will probably have taken place within 90 to 120 days in most cases. After resistance develops, further antibacterial therapy is probably useless, although this statement has not been decisively proved as yet.

10) It seems clear that streptomycin is capable of healing certain tuberculous lesions and of serving as an adjuvant to existing forms of therapy in other types of the disease. The precise indications for its use and the optimal dosage regimen have still to be learned in pulmonary, genito-urinary and bone and joint tuberculosis. The dosage schedule for treatment of respiratory, enteric and cutaneous ulcerations and disseminated tuberculosis is better defined. Further intensive and long term studies are necessary to learn how streptomycin can be most wisely and effectively used.

11) I should like to close by emphasizing, what I hope I have already made clear, that the work which has been described has
been carried out by investigators in many Veterans Administration hospitals and that my function here today is simply that of a reporter of what I believe to be good deeds.

RESUMEN

1) La Administración de Veteranos ha emprendido una investigación en grande escala sobre los efectos clínicos y toxicológicos de la estreptomicina en el tratamiento de la tuberculosis humana. Se administró el tratamiento de acuerdo con las estipulaciones de protocolos concebidos por representantes de la Administración de Veteranos, del Ejército y de la Marina, y se llevó a cabo en 20 hospitales cooperantes de la Administración de Veteranos.

2) Se han descrito los resultados del tratamiento de 650 casos de varios tipos de tuberculosis. Debido al hecho de que estos resultados indican que la estreptomicina ejerce un efecto favorable sobre muchos tipos de tuberculosis, se están continuando y amplificando las presentes investigaciones.

3) En algunos tipos de tuberculosis, tales como las fistulas cutáneas, las ulceraciones tráqueobronquiales, laringeas y faríngeas, las úlceras de la lengua y de los intestinos y la peritonitis, se ha comprobado que la estreptomicina, administrada por la vía intramuscular, es una terapia adecuada y eficaz.

4) En la tuberculosis génito-urinaria y en ciertos tipos de tuberculosis pulmonar la estreptomicina ha alterado favorablemente el curso de la infección en la mayoría de los casos.

5) En lesiones pulmonares el efecto más beneficioso ocurrió en las de tipo exudativo. Se observó menos beneficio en lesiones fibrosas, caseosas y cavernosas. No se curó a ningún caso.

6) No parece que la estreptomicina sea beneficiosa en la tuberculosis de los huesos y las articulaciones, de los ojos y del pericardio, aunque no se tiene mucha experiencia con estas lesiones.

7) La esperada mortalidad de la tuberculosis meningea y miliaria ha sido reducida mediante la administración de la estreptomicina.

8) Las reacciones tóxicas sobre el nervio octavo, sobre los riñones y los órganos de formación de la sangre y las complicaciones anafilácticas tardías causadas por la estreptomicina impiden que se use en todo paciente con tuberculosis. Su empleo por un tiempo prolongado debe estar acompañado de procedimientos de laboratorio frecuentes y exactos, y la enfermedad bajo tratamiento debe llevar un pronóstico lo suficiente grave para justificar el riesgo de los efectos tóxicos de la droga.

9) Los bacilos tuberculosos expuestos a la estreptomicina desarrollan con el tiempo una resistencia abrumadora al antibiótico, de manera que el beneficio terapéutico máximo que se puede
esperar en la mayor parte de los casos probablemente tendrá lugar en los primeros 90 a 120 días. Después de haberse desarrollado la resistencia la terapia antibacterial probablemente no tiene valor, aunque esta declaración no ha sido comprobada decisivamente todavía.

10) Parece evidente que la estreptomicina puede curar ciertas lesiones tuberculosas y puede servir de coadyuvante a las terapias existentes en otros tipos de la enfermedad. No se han determinado todavía ni las precisas indicaciones para su empleo ni la dosis óptima en la tuberculosis pulmonar, génito-urinaria y de los huesos y las articulaciones. Se ha definido mejor la dosis necesaria para el tratamiento de las ulceraciones respiratorias, entéricas y cutáneas y de la tuberculosis diseminada. Precisa que se lleven a cabo estudios más intensos y prolongados a fin de descubrir la manera de emplear la estreptomicina en la forma más prudente y eficaz.

11) Para terminar, quiero recalcar lo que creo que ya he explicado claramente, es decir, que la labor aquí presentada ha sido realizada por investigadores en muchos hospitales de la Administración de Veteranos y que yo solamente he relatado lo que considero ser buenos resultados.

REFERENCES


Since this paper was delivered, many articles have appeared in the American literature concerning the place of streptomycin in the therapy of human tuberculosis. Information from these indicates that the dosage and duration of its administration described herein are undoubtedly too great. The Veterans Administration in its study now recommends, for most types of tuberculosis, one gram of streptomycin daily given in two doses of ½ gram 12 hours apart. Only in those cases of truly acute tuberculosis should more be used. Proper duration of therapy cannot yet be defined but it is probable that in most instances less than 120 days' continuous therapy is required.

Recent publications arising from the cooperative study include:

I would first like to congratulate Dr. Bunn on his excellent paper. His report of the combined experiences of the Veterans Administration Tuberculosis Service with streptomycin in tuberculosis during the past year is particularly welcome and timely. We are deeply indebted to him and to all the physicians of the Veterans Administration whose research and clinical investigation made this splendid report possible.

It has been my unusual privilege and opportunity to work in close collaboration with Drs. Hinshaw and Feldman of the Mayo Clinic and Mayo Foundation in their investigation of streptomycin since it was first used clinically for human beings at Rochester, Minnesota in October 1944. During the past two and a half years we have used the drug in treating more than 150 patients suffering from various forms of tuberculosis. It is especially gratifying to us that this report of the Veterans Administration based on such a large series of patients, confirms our clinical impressions gained from our earlier investigations on a much smaller scale. Information and data from other investigators show the same general results.

I believe we now can state definitely that streptomycin has proved to be a valuable adjunct in the treatment of certain forms of tuberculosis. It has already become a “must” in treatment of tuberculous meningitis and miliary tuberculosis. It is the treatment of choice in such forms of the disease as tuberculous laryngitis, ulcerative tracheobronchial tuberculosis, draining cutaneous sinuses and tuberculous enteritis.

In pulmonary tuberculosis it is most effective in the treatment of soft exudative lesions of recent origin. Old chronic fibrocaseous lesions are benefited little if any by its use.

The optimal daily dosage, frequency of administration and duration of treatment have not been established as yet. In our earlier investigations we used large doses, 2 to 3 gm. daily in divided doses given every three hours day and night. In December 1945, we began to use 1 gm. daily in divided doses, given every six hours, for 120 days. We wanted to determine whether a lower daily dose would be effective therapeutically and whether the toxic manifestations would decrease with the smaller dosage. To date we have used this schedule of doses for nearly forty patients. The therapeutic results in this series were comparable to those obtained previously with the higher doses. We also noted a sharp decrease
in toxicity in the patients receiving the smaller doses. It is our impression the 1 gm. daily is preferable to the larger dose (2 to 3 gm. daily) in the great majority of patients with the exception of those who have miliary or meningeal tuberculosis. However, not enough work has been done as yet on the problem of dosage to warrant anyone being arbitrary on this point. With so many workers investigating streptomycin throughout the country, this whole question of optimal dosage, frequency of administration and duration of treatment undoubtedly will be determined in due time.

The phenomenon of strains resistant to streptomycin which are noted not infrequently during the third and fourth months of treatment is incompletely understood. Unpublished data by Dr. Pyle, as associate of Drs. Feldman and Hinshaw in the Mayo Foundation, indicates that certain streptomycin-resistant strains of the organism are demonstrable before treatment is started. A vast amount of research must be done, both by clinicians and laboratory men, before this part of the puzzle can be fitted into the whole clinical picture.

One thing should be strongly emphasized. Streptomycin is not an overnight cure-all for tuberculosis. Like other valuable drugs, such as penicillin and sulfonamides, it has its assets, limitations and liabilities. It must not be considered as a substitute for sanatorium care, rest in bed and other well established methods of treatment, such as collapse therapy and other surgical procedures. Streptomycin should be welcomed as a valuable weapon to our armamentarium. We, as physicians, have a solemn obligation to learn its value and shortcomings, so that we may use it intelligently for the right patient at the right time, and in combination with such other therapeutic measures as may be necessary to achieve a good end result.

Discussion

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Dr. Bunn's report is of great value to each of us. Our discussion is based on 100 cases of pulmonary tuberculosis treated with streptomycin. The only protocols for treatment were: that the patient receive one gram of streptomycin daily, divided into 12 hypodermic doses for a period of eight weeks with periodic laboratory studies.
In these 100 cases there was no eighth nerve damage and the same results were achieved with one gram a day for 8 weeks, as when giving two to three grams daily for a period of three months or longer. One-twelfth of a gram given hypodermically every two hours maintains a blood serum level of approximately 10 to 15 micrograms per cubic centimeter of blood serum depending on kidney function. This is adequate to inhibit the growth of tubercle bacilli as only 5 to 7.5 micrograms are necessary, and yet this is not enough streptomycin to damage the eighth nerve, nor is it enough to develop eosinophilia or to produce abnormal urinary sediments. The drug is given for only eight weeks, because we have observed maximum effect from the drug in the first 6 to 8 weeks.

The results in these 100 cases agree with those presented by Dr. Bunn. It shows that in 80 per cent of individuals there was a striking change in the progress of the disease. Seventy-five per cent of these cases showed improvement in their x-ray films. In the clinical picture, there was lowering of the sedimentation rate, marked increase in appetite and hence weight gain, marked reduction of fever, less cough and expectoration, and each patient showed subjective improvement. We agree with Dr. Bunn that we must maintain collapse therapy along with the streptomycin in order to achieve the best end results possible. We do not agree with the Veterans Administration Protocols in allowing the patient to remain under observation for 60 to 90 days in order to decide whether the disease is progressive or regressive. It is believed that we should begin treatment immediately with the correct form of collapse therapy and streptomycin.

In our 100 cases each individual was taught to prepare his own streptomycin dilution, syringes, needles—and do it sterily; to inject himself as a diabetic is taught to take insulin; and to keep an accurate daily chart. The youngest patient was 14 years and the oldest 81. By this method we saved these patients $90,000 of hospital expenses and an untold amount of nursing service. This is important today when our hospitals are overcrowded and with our shortage of nurses.

Now let us compare the results of these 100 cases with those 600 treated by the Veterans Administration:

1) All types of tuberculosis were treated and no case was allowed to be observed to see whether the disease was progressing or regressing.

2) Collapse therapy was instituted immediately with streptomycin therapy.

3) (a) One hundred cases were treated with no eighth nerve damage, i.e., in not one of these did we see a spontaneous nystag-
mus or deafness. Only 4 per cent developed vertigo, three of whom were definite cardilacs and one had previous kidney damage.

(b) Only 3 per cent developed a skin rash which disappeared by changing the lot numbers—that is to a different batch of the drug.

(c) Only 1 to 2 per cent showed abnormal urinary sediments.

4) Clinical changes were observed within 4½ days and later improvement was seen in 80 per cent of the x-ray films and in 30 per cent the sputum was converted from positive to negative.

Discussion

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There are two subjects to be mentioned further regarding streptomycin therapy:

1) We noted among the urinalysis reports on 100 cases treated with streptomycin that a trace of sugar was common. It was suspected that streptomycin might be a reducer of copper solutions and the suspicion was confirmed by dropping a tiny amount of streptomycin solution, remaining in a syringe after it had been used for streptomycin injection, into the usual test tube of Benedict solution. The copper was promptly precipitated.

2) Many cases who found the hypodermic of 1/12th of a gram of streptomycin locally, painful and with swelling and redness at the site of injection, when the streptomycin was dissolved in physiological solution, had no local reaction or pain when it was dissolved in sterile distilled water. This lead to investigation which indicated that streptomycin dissolved in water in the proportion used in this Clinic (one gram of streptomycin to 6 cc. of solvent) was one-third stronger in osmotic pressure than body fluids, but when the same dilution was made using physiological saline solution as a diluent the osmotic pressure of the resultant solution was over two times as great as in body fluids; high enough to cause pain on injection.