STREPTOMYCIN: A VALUABLE ANTI-TUBERCULOSIS AGENT

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To find a specific therapeutic substance that will arrest or impede the progress of tuberculosis and permit the intrinsic factors of healing to operate successfully has been the goal of countless investigators since the beginning of the modern era of chemotherapy. Certainly the need for a specific drug treatment to assist in combating human tuberculosis has been and continues to be a compelling one.

During the past decade many infectious diseases have proved to be highly vulnerable to therapeutic attack by a variety of chemotherapeutic agents. Tuberculosis, however, has until recently resisted specific drug treatment successfully. In the quest for an effective substance in the treatment of tuberculosis little, if any, real basis for encouragement was evident until the advent of the sulphonamide compounds.* The observations that sulphanilamide had exerted a slight but definite deterrent action on the pathogenesis of tuberculosis in guinea-pigs prompted additional work with a large number of other sulphonamides in experimental tuberculosis. The results indicated that none of these drugs met the requirements of a therapeutic weapon sufficiently to justify their use in clinical tuberculosis.

Eventually drugs remotely related to sulphanilamide but chemically definitely dissimilar in certain important aspects were found to be greatly superior to any of the sulphonamide compounds in combating experimental tuberculosis. These latter drugs—known commonly as sulphone compounds—were derivatives of 4,4'-diaminodiphenyl sulphone. Among the better-known sulphone drugs that have figured in the recent revival of chemotherapy of tuberculosis are "promin" (known as "promanide" in Britain), "diasone," and "promizole."

Historical Résumé

Since the ability of certain of the sulphone compounds to suppress tuberculosis almost completely in the highly susceptible guinea-pig was so unprecedented, and since the significance of this phase of the recent development of tuberculo-chemotherapy to the present status of the drug treatment of leprosy is seldom recounted, a brief résumé of the development of the more recent antibacterial attack on tuberculosis seems appropriate.

As mentioned previously, the observations concerning the effects of sulphanilamide on the progress of tuberculosis in guinea-pigs suggested that the sulphonamide drugs and related compounds were worthy of further exploration. In October, 1940, Feldman, Hinshaw, and Moses reported the first experimental study of the use of promin in experimental tuberculosis induced by human tubercle bacilli.† The results when confirmed provided sound evidence that the drugs had exerted marked deterrent effects on the progress of a potentially lethal infection. With the recognition of this fact tuberculosis could properly be removed from the

list of infections previously considered resistant to the suppressive action of chemotherapeutic agents.

After this initial observation with promin the effectiveness of several other sulphone compounds as anti-tuberculosis agents was demonstrated (Feldman, 1946b). This phase of the work served to establish firmly the ability of a number of complex synthetic organic compounds to exert a measurable therapeutic effect on infections induced experimentally by human tubercle bacilli.

Parenthetically it is of interest to note that the work with the sulphone compounds, especially promin, in experimental tuberculous infections stimulated an important development in the chemotherapeutic attack on leprosy. Several reports now available indicate definitely that promin and subsequently promizole and diasone have ushered in an important new era in the specific drug treatment of this disease. An objective appraisal of the results up to the present time indicates that this newer therapy in leprosy is definitely encouraging (Faget *et al.*, 1946).

The advent of specific therapy with antibiotics which followed the development of penicillin again focused attention on the possibility of successful chemotherapy of tuberculosis with antibiotic substances. This was not a new approach to the problem of specific drug therapy in tuberculosis by the use of antagonistic substances of bacterial origin. As a matter of fact a report on this form of therapy had been published by Cantani in 1885. A review of the many subsequent reports of different investigators who have explored this approach to the treatment of tuberculosis discloses many antibiotic agents capable of antagonistic action against tubercle bacilli (Feldman, 1946a, 1946b, 1946c; Hart, 1946; Waksman, 1947). However, observations on the range of activity of the substances studied were, with few exceptions, limited to *in-vitro* tests. A notable exception is streptomycin, which, in addition to demonstrating its antagonism to tubercle bacilli in the test-tube, has demonstrated its effectiveness against tuberculous infections (Feldman and Hinshaw, 1944; Feldman, Hinshaw, and Mann, 1945; Youmans and McCarter, 1945). As the search continues, the possibility exists of eventually obtaining not one but perhaps several additional antibiotic agents that will be equal if not superior in potency to streptomycin.

As a result of the information that has accumulated since the first report on the use of sulphanilamide in experimental tuberculosis was published, a chemotherapy of tuberculosis

* For a review of the development of the chemotherapy of tuberculosis the lectures by Feldman (1946a, 1946b, 1946c), by Hart (1946), and by Waksman (1947) may be consulted.

† A few months previously Rist, Bloch, and Hamon (1940) had reported independently a definite antagonistic effect of 4,4'-diaminodiphenylsulphone on tuberculosis of rabbits and guinea-pigs infected with avian tubercle bacilli.

of practical significance has been evolved. At last, after countless disappointments, the practical therapeutics of tuberculous infections has been advanced by a drug of considerable specificity and usefulness. By the use of streptomycin it is now possible for the first time to arrest by specific chemotherapy the progress of several different clinical types of potentially fatal tuberculosis.

Streptomycin in Experimental Tuberculosis

Therapeutic Efficacy.—The effect of streptomycin on the course of experimental tuberculosis in guinea-pigs and in mice is striking. Under prescribed conditions the potency of this antibiotic is sufficient to alter to a marked degree the usual pathogenesis of infections established by fully virulent tubercle bacilli of the human and of the bovine types. It is of much significance that guinea-pigs inoculated subcutaneously with an effective dose of tubercle bacilli will respond to treatment usually in a dramatic manner. Compared with untreated controls, such animals have an extended longevity, and the residual signs of infection either are not demonstrable grossly or microscopically or, if present, are usually inactive lesions characterized by fibrosis, calcification, or other signs of quiescence. In the experimentally infected animals the tempo of the therapeutic effects is relatively rapid. Evidence of deterrent action may be observed after three weeks' treatment.

The specificity of streptomycin for tubercle bacilli and its ability to alter the course of otherwise irreversibly fatal infections are convincing as shown by experiments wherein guinea-pigs are inoculated intravenously with large doses (1 mg.) of virulent tubercle bacilli. Tuberculosis established by this procedure usually becomes a rapidly fulminating process within a short time. However, if treatment with streptomycin is started within three to four days after the animals have been inoculated the treated animals will live many months longer than those not treated (Feldman, Karlson, and Hinshaw, 1947). The same therapeutic restraints can also be observed in white mice inoculated intravenously with virulent tubercle bacilli and treated with streptomycin (Youmans and McCarter, 1945).

Considering the exceedingly formidable character of the widely disseminated infection that follows the introduction of tubercle bacilli direct into the venous circulation, one cannot avoid the conclusion that streptomycin is an anti-tuberculosis agent of considerable potentiality (Feldman, Karlson, and Hinshaw, 1947). It is suggested that in the future new substances antagonistic to tubercle bacilli be subjected to trial in tuberculous infections induced intravenously. Such a procedure should provide valuable data for comparison with the effectiveness of streptomycin.

Dosage.—The therapeutic range of streptomycin in the treatment of tuberculous guinea-pigs appears to vary within rather wide limits. In our experience a daily dose of 4 to 6 mg. administered subcutaneously is therapeutically effective for animals weighing 500 to 800 g. Much larger doses do not seem to be more effective. We have found daily doses of 2 mg. inadequate. However, in many infected animals this smaller dose does exert a definite deterrent influence, but the results are, generally speaking, inferior to those produced by doses of greater magnitude. In the treatment of tuberculous mice with streptomycin a daily dose of 3 mg. divided into four injections has proved effective (Youmans and McCarter, 1945).

Frequency of Medication.—In our earlier studies on streptomycin in experimental tuberculosis we administered the daily dose of the drug in four equally divided injections six hours apart. Later, as a result of experimental observations (Feldman, Hinshaw, and Karlson, 1947), we found that the frequent administration of streptomycin was not

essential to a satisfactory therapeutic effect. It was observed that daily doses of 6 mg. divided into two equal injections twelve hours apart were adequate. Furthermore, we observed that animals treated every alternate week appeared to receive essentially the same therapeutic benefit as those on a daily schedule of treatment.

We now prefer to administer the drug every twelve hours. However, it is our impression that streptomycin can be given to tuberculous guinea-pigs, with satisfactory results, once daily or perhaps once every second or third day. There is no evidence indicating that its therapeutic effectiveness in experimental tuberculosis is dependent on frequent administration of the drug. Certainly it is not necessary to administer streptomycin every two to three hours to obtain the desired effects.

Toxicity for Animals.—Although the administration of streptomycin to tuberculous human beings usually provokes certain objective signs of toxicity of varying severity, this drug is well tolerated by guinea-pigs and by mice in doses within the therapeutic level. Guinea-pigs treated daily for five to six months have shown a normal increase of weight and size and have at the end of the experiment the appearance of normal healthy animals. What the maximal tolerated dose for guinea-pigs may be is uncertain. So far as we know, doses of streptomycin even in excess of the therapeutic effective dose do not induce demonstrable damage in the liver or kidneys of guinea-pigs or mice.

In some animals, particularly monkeys and dogs, signs of toxicity have been reported (Molitor *et al.*, 1946). In these animals toxicity was indicated by transient anaemia, mild to severe proteinuria, and casts and blood cells in the urine. Dogs receiving streptomycin have been noted to manifest signs of vestibular dysfunction. Disturbance of metabolism of fat in the liver and kidneys of monkeys and dogs has been reported (Molitor, 1947).

Summary of Evidence in Support of Clinical Trials

In reviewing the evidence to justify the use of streptomycin in the treatment of tuberculous patients several facts of considerable significance may be recounted:

- (1) The experimental animal used was the highly susceptible guinea-pig, which has a minimum of intrinsic resistance to infection by virulent mammalian tubercle bacilli.
- (2) The beginning of treatment was delayed usually from two to seven weeks after the animals had been inoculated with tubercle bacilli. Thus the conditions of the experiments were severe. Furthermore, the conditions were those of therapy and not of prophylaxis.
- (3) Treatment extended the lives of the infected animals indefinitely.
- (4) In many treated animals there was a reversal of a previously positive to a negative reaction to tuberculin.
- (5) As a consequence of treatment the usual course of the disease was dramatically modified even though the animals had been infected by intravenous inoculation.
- (6) There was a marked tendency for infected tissues to mobilize factors of repair and resistance, and as a result lesions resolved, fibrosed, hyalinized, or calcified. In a word, under the influence of treatment with streptomycin the tuberculous lesions in an infected animal were converted from an advancing destructive process to one of regression and arrest.

The evidence obtained from the experimental studies amply justifies the conclusion that streptomycin is a highly potent antagonistic agent against tuberculous infections in animals.

The favourable therapeutic index of streptomycin in tuberculous guinea-pigs and the further fact that the drug was well tolerated by these animals provided acceptable reasons for extending the investigation to tuberculous patients.

Residual Infectivity after Treatment.—It is our impression that in tuberculous guinea-pigs streptomycin in most

instances exerts its beneficial effects by suppressing the normal growth-progression of the tubercle bacilli rather than by acting in a bactericidal capacity. We have, however, observed infected guinea-pigs, treated for a prolonged period with streptomycin, in which no residual infection could be demonstrated in the spleen by *in-vivo* tests. In addition the same animals failed to react to tuberculin, although at the beginning of treatment sensitivity to tuberculin had been noted (Feldman, Hinshaw, and Mann, 1945).

Although the question is difficult to decide with finality, it seems likely that at least in some infected animals most if not all of the infective bacteria are eventually eliminated as a direct or an indirect consequence of treatment. However, in our experience this is not true in the majority of instances. Even after treatment for many months and in the absence of recognizable alteration of tissue the presence of fully virulent tubercle bacilli can be demonstrated in the guinea-pigs by suitable procedures. For this reason it must be concluded that the major effect of streptomycin on tubercle bacilli is that of a bacteriostatic agent.* It appears that the concentrations of streptomycin which are attained in the blood and tissues of animals and man are too low to have a direct bactericidal effect.

Streptomycin in Clinical Tuberculosis

The bacillus of tuberculosis produces a number of different diseases in human beings. With this fact recognized, it should not be anticipated that any one form of treatment should be equally applicable to all these diseases. However, these several diseases are all caused by the same micro-organism, *Mycobacterium tuberculosis*, and if the organism is so situated as to be exposed to the antagonistic action of streptomycin the suppressive action of the drug should have a certain degree of effectiveness. Studies have shown that streptomycin is not distributed through all tissues of the body in equal concentration (Baggenstoss, Feldman, and Hinshaw, 1947). Furthermore, the mechanical defects which are produced in different structures by the destructive action of tuberculosis will create special clinical and surgical problems which cannot be met completely with any antibacterial agent, regardless of its efficacy (Hinshaw, 1947a).

Miliary and Meningeal Tuberculosis

Generalized haematogenous tuberculosis of human beings most closely resembles the form of tuberculosis which is produced in guinea-pigs and mice experimentally. Such haematogenous forms of tuberculosis as miliary tuberculosis and tuberculous meningitis have in the past been totally refractory to all therapeutic efforts and have had a mortality rate approaching 100%. Until the advent of streptomycin there was no method of treatment which produced even temporary suppression of these diseases or amelioration of the distressing symptoms caused by them.

It is now well established that streptomycin treatment may be effective in bringing about a clinical remission in a considerable percentage of cases of miliary tuberculosis and of tuberculous meningitis (Hinshaw, Feldman, and Pfuetze, 1946; Council on Pharmacy and Chemistry, 1947). It remains to be seen how often these remissions may be prolonged and extended to the point at which one is justified in regarding the disease as cured. We have observed remissions which have lasted for more than two years, and we have patients now under observation who apparently remain well and who eventually can be pronounced essentially cured if this favourable progress continues. When miliary tuberculosis and tuberculous meningitis have been diagnosed at an early stage of the disease and have been treated promptly and adequately, more than 50% of these patients may enjoy a complete remission of all symptoms and of all radiographic and bacteriological evidence

of the infection. Unfortunately, some of these patients will suffer from recurrence of the disease process. In those instances in which the recurrent disease is due to a streptomycin-resistant strain of tubercle bacilli no hope of recovery from the second attack should be entertained. It will probably be at least five years before it can be known to what degree streptomycin treatment will reduce the formerly almost universal mortality rate from these diseases. In the meantime, we would emphasize the importance of starting treatment with streptomycin at the earliest possible moment after the diagnosis of miliary tuberculosis or of tuberculous meningitis has been made.

Pulmonary Tuberculosis

This constitutes the cause of more than 90% of all the deaths from tuberculous infection. The wide variability of tuberculous lesions produced in the lungs and the frequency with which spontaneous recovery from pulmonary tuberculosis is realized make the evaluation of any remedy in this form of disease most difficult (Hinshaw and Feldman, 1944).

Several hundred patients with varying forms of pulmonary tuberculosis have received treatment with streptomycin during the past three years in various American hospitals, and certain conclusions are now tenable (Council on Pharmacy and Chemistry, 1947; Hinshaw, 1947b). All physicians who have employed streptomycin extensively in the treatment of pulmonary tuberculosis have agreed that patients with progressive disease whose symptoms have been marked often enjoy relatively prompt improvement of symptoms, with reduction in the amount of expectoration. There are also a decrease of fever and an improvement of the systemic manifestations of pulmonary tuberculosis. Previously progressive disease becomes at least temporarily quiescent under the influence of streptomycin therapy, and this suppression of the acute disease process is quite uniform during the first few weeks of treatment.

The clinical trend after the first few weeks of treatment depends on whether or not the tubercle bacilli are resistant to the effects of streptomycin and whether or not the destructive nature of the disease is such as to prevent its arrest and the disappearance of bacilli during this period of effective action. Some patients continue to improve for many weeks or months, whether or not streptomycin treatment is continued. The physician is occasionally disappointed to observe a reactivation of the disease within a short time after streptomycin treatment has been discontinued. This tendency to reactivation of previously progressive tuberculosis constitutes strong evidence in favour of the thesis that the drug *in vivo* is a truly effective suppressive agent. There is increasing evidence that streptomycin combined with collapse therapy and other forms of treatment may be effective when either one alone would probably fail.

Tuberculous Laryngitis and Endobronchitis

Tuberculous Laryngitis.—Streptomycin has also been found to be useful in some of the most distressing complications of pulmonary tuberculosis which had previously been refractory to nearly all therapeutic efforts. Tuberculous laryngitis has responded to streptomycin treatment (Figs and Hinshaw, 1946) in a very large percentage of cases, and it is now widely believed that use of the drug is clearly indicated in the more severe and acute phases of this tuberculous disease, even when such treatment is likely to achieve only palliative results. Other ulcerating lesions about the oropharynx and tongue respond to streptomycin in a similar manner. In our experience the most spectacular results with streptomycin treatment of lesions in the larynx have been in those patients with maximal laryngeal involvement and with acute forms of pulmonary tuberculosis without extensive cavitation, and in those patients who have tuberculous laryngitis with minimal evidence of pulmonary tuberculosis.

Endobronchial Tuberculosis.—Active ulcerating lesions of the tracheo-bronchial tree, which are being observed with increasing frequency in the United States, have also responded in a uniform manner to streptomycin treatment (Hinshaw, Feldman, and Pfuetze, 1946; Council on Pharmacy and Chemistry, 1947). The serious potentialities of this type of tuberculosis would justify streptomycin treatment under many circumstances. The end-result of tracheo-bronchial tuberculosis is often a bronchial

* The question of the action of streptomycin on tubercle bacilli *in vitro* was the subject of a recent report by Smith and Waksman (1947).

stricture as a result of peribronchial fibrosis. It is immediately obvious that bronchial strictures of this type cannot be precluded and will not yield to any type of antibacterial treatment, and if the degree of obstruction is considerable, pulmonary resection is likely to be required if the stricture is so situated as to make such operation feasible.

Tuberculous Sinuses, Lymph Nodes, Bones, and Joints

Tuberculosis of lymph nodes, of bones and joints, and other types of tuberculosis that produce draining cutaneous sinuses have been treated with streptomycin in a sufficient number of cases to indicate that clinical results are satisfactory in a very high percentage of cases (Hinshaw, Feldman, and Pfuetze, 1946; Council on Pharmacy and Chemistry, 1947; Hinshaw, 1947b). Within a few days to a few weeks after starting treatment the drainage of pus ceases and a scab forms over the sinus, and within a few more weeks, when this scab is dislodged, the sinus appears to be healed. If the sinus tract leads to some large accumulation of pus, such as a cold abscess or an empyema cavity, healing is much less likely to occur, and if it does occur there is much greater danger of a recurrence of drainage of pus. It begins to seem probable that large accumulations of tuberculous pus should be drained by wide-open incision as soon as possible after streptomycin treatment has been instituted. This is in contrast to previously accepted surgical practices. It is probable that tuberculous suppuration may be treated in much the same way as suppurative diseases due to pyogenic bacteria have been treated in the past, provided streptomycin treatment is combined with such surgical intervention.

Cutaneous tuberculosis has not been studied sufficiently to warrant the formation of conclusions, except in the case of scrofuloderma which is associated with tuberculous draining sinuses (O'Leary *et al.*, 1947). This has been discussed in the preceding paragraph. A few patients with lupus vulgaris have been treated, and have appeared to respond sufficiently well to indicate the need for further studies.

Tuberculosis of bones and joints involves a series of problems almost as complicated as those afforded by pulmonary tuberculosis. It is immediately evident that no antibacterial drug can promote the regeneration of destroyed structures, and a comparison with chronic osteomyelitis appears logical. Experience gained thus far has indicated that the principal uses of streptomycin for treatment of tuberculosis of bones and joints are to prevent progression of the disease and to afford protection during and after surgical procedures on the tuberculous joints. In early forms of tuberculosis of joints involving the synovial membrane alone, streptomycin treatment in itself may be adequate to arrest the tuberculous process and hence to avoid subsequent destructive changes, crippling deformities, and the need for surgical treatment.

Tuberculous Enteritis and Peritonitis

Tuberculous enteritis is another most distressing complication of pulmonary tuberculosis. It now seems that streptomycin treatment of this disease yields a gratifying degree of symptomatic relief very promptly in a large percentage of patients. It remains to be determined how permanent these effects may be, but, even if the results prove to be merely palliative, treatment is well worth while, and in some other instance may be the crucial factor in permitting the eventual recovery of the patient.

Tuberculous peritonitis has appeared to respond to streptomycin treatment in the small number of cases in which this treatment has been applied thus far. Judgment of therapeutic results in this disease is more difficult than in other forms of tuberculosis because of the fact that the diagnosis has usually been arrived at as a result of surgical exploration and because of the fact that surgical exploration in itself is thought frequently to exert a beneficial effect on tuberculous peritonitis.

Use of Streptomycin Before and After Surgical Procedures

The prophylactic use of streptomycin in conjunction with radical types of thoracic surgical treatment is being put to test in a number of institutions in the United States (Council on Pharmacy and Chemistry, 1947; Glover, Clagett, and Hinshaw, 1947). It has already been determined that streptomycin is of little value in the treatment of advanced and chronic tubercu-

lous empyema (Hinshaw, Feldman, and Pfuetze, 1946). Whether better results will be achieved by surgical treatment of tuberculous empyema in combination with streptomycin remains to be ascertained. There is reason to hope that streptomycin treatment may prevent the development of tuberculous empyema; our surgical colleagues have not witnessed tuberculous empyema following intrathoracic operations for tuberculosis when operation was performed in combination with streptomycin treatment, except in a few instances in which operation was carried out after the tubercle bacilli had become resistant to the effects of streptomycin.

Clinical Toxicity.—Streptomycin is a drug of moderate toxicity when compared with such drugs as the sulphonamide compounds, but it is definitely more toxic than penicillin. The toxicity of streptomycin is negligible when the drug is used for brief periods in the treatment of non-tuberculous infections. However, when tuberculosis is treated with streptomycin it probably is necessary to utilize the drug for many weeks, and this results in neurotoxic manifestations which are described later. Our colleague Dr. Karl Pfuetze (Medical Director, Mineral Springs Sanatorium, Cannon Falls, Minnesota) has been interested especially in toxicity of streptomycin and the efficacy of the drug when given in small doses. His studies, which have now been in progress for at least two years, have shown clearly that streptomycin is effective in doses as small as 1 g. a day, and perhaps the dose may be still further reduced in many clinical circumstances. When the total daily dose is 1 g., fewer than 50% of patients experience any toxic manifestations whatsoever, and only a few of these complain to any considerable degree. Even these usually recover when treatment is discontinued (Pfuetze, personal communication).

Dosage

The minimal effective dose of streptomycin has not been determined for the various clinical types of disease, but we would suggest that in tuberculosis the average daily dose be approximately 1 g. for a patient of average weight. McDermott (personal communication) has suggested a dose of 20 mg. per kilogram of body weight, which appears to be a reasonable and effective dose and one which will yield minimal toxic results. In previous communications we have recommended that streptomycin be injected at frequent intervals so as to maintain a constantly elevated blood level of the drug. However, as a result of experiments carried out on guinea-pigs (Feldman, Hinshaw, and Karlson, 1947), mentioned above, we have modified this conclusion, and in recent months we have been treating patients by giving the daily dose in a single injection or by dividing the total dose into two injections administered at intervals of twelve hours. The results seem to be equally satisfactory, and this has greatly simplified the clinical use of streptomycin. It remains to be determined whether these infrequent injections and lower doses will be adequate to produce and maintain remissions in such malignant forms of tuberculosis as tuberculous meningitis and miliary tuberculosis.

In previous publications we recommended that in treatment of tuberculous meningitis streptomycin be administered intrathecally as well as intramuscularly (Hinshaw, Feldman, and Pfuetze, 1946). Studies have not been completed to ascertain whether intrathecal injection alone or intramuscular injection alone may possibly suffice. In view of the severe reactions which have occasionally followed the intrathecal administration of streptomycin in doses of 100 to 200 mg., which we recommended previously, we have recently reduced the amount of streptomycin injected intrathecally to 25 to 50 mg. a day. It seems probable that such intrathecal injections every alternate day may suffice.

In the treatment of lesions of the larynx and tracheo-bronchial tree streptomycin administered by either aerosol or atomizer has often been employed in addition to intramuscular treatment. Recent observations make it seem possible that intramuscular administration of streptomycin alone is adequate for the treatment of these forms of the disease. In the treatment of tuberculous enteritis intramuscular administration of streptomycin is recommended, and it is doubtful if any advantage is gained by the addition of orally administered streptomycin. However, this phase of streptomycin therapy is worthy of further investigation.

Therapeutic Limitations of Streptomycin

Streptomycin, like all other substances of value in chemotherapy, has certain definite shortcomings or limitations.

Antibacterial Potency

Compared with other antagonistic agents effective against tubercle bacilli the antibacterial efficacy of streptomycin against tubercle bacilli is amazingly high. Yet, as was mentioned previously, the major influence of streptomycin on tubercle bacilli in tuberculous infections appears to be that of suppression of the normal pathogenic activities of the organisms. Sterilization of the infective process, even when observed, cannot be attributed to the direct antibacterial action of streptomycin alone. In many instances in clinical tuberculosis during the treatment with streptomycin a marked diminution and eventual disappearance of tubercle bacilli in sputum or other discharges may occur. However, the final elimination of tubercle bacilli from the infected tissues may be dependent only indirectly on the specific action of streptomycin. Most human beings are intrinsically capable of mobilizing mechanisms of resistance and repair which are effective in disposing of tubercle bacilli or inhibiting their aggressive action.

While it would be desirable in the treatment of tuberculosis to have a chemotherapeutic substance of such potency and safety that all tubercle bacilli could be eliminated from the infected host immediately or soon after the administration of a single dose of the drug, the probable results would still be inadequate. In other words, we should distinguish the specific antagonistic effect of the therapeutic substance on the bacterial parasites from the anatomical and purely mechanical factors that were created as a result of the infection. It is illogical to assume that a chemotherapeutic substance, no matter how potent and effective its antibacterial properties may be, can cause in some incredible manner the immediate and complete restoration of tissues that have been irreversibly damaged or destroyed as a consequence of the pathogenicity of the infective agents.

Toxicity*

Toxicity must also be considered as another of the limitations of streptomycin as a specific agent in tuberculosis. Like all other agents used in chemotherapy, streptomycin has certain toxic potentialities. However, compared with most other chemotherapeutic agents streptomycin has a reasonable margin of safety when the treatment of severe types of tuberculous diseases is considered. The most important toxic manifestation associated with streptomycin therapy in clinical tuberculosis is the unusual neurological reaction giving rise to dysfunction of the vestibular apparatus. Rarely, auditory function is impaired when large doses are given for prolonged periods or when impaired renal function interferes with the excretion of the drug. Other toxic reactions that have been noted include erythematous rash, fever, eosinophilia, and abnormal urinary sediments.

The toxic reaction to streptomycin referable to the eighth cranial nerve or its end-organs which results in a reduction of the vestibular function is the most serious and was one of the first evidences of toxicity described (Hinshaw and Feldman, 1945; Brown and Hinshaw, 1946; Fowler and Seligman, 1947). The incidence of occurrence of this untoward effect is rather high. At least 90% of patients receiving a daily dose of 2 g. of streptomycin for more than one month will exhibit symptoms of vestibular dysfunction. If the dose is reduced to 1 g. a day fewer than 30% of patients will experience any subjective symptoms or exhibit any objective signs of vestibular dysfunction. Fortunately in most cases the symptoms largely disappear within sixty to ninety days or longer after treatment has been stopped. The most severe symptoms of decreased vestibular function occur in patients receiving doses of 3 g. or more of streptomycin daily. Restoration of vestibular function or compensation phenomena occur more rapidly and more completely in children and young adults than in persons beyond the age of 50 (Hinshaw, Feldman, and Pfuete, 1946).

While the possible toxic effects of streptomycin should be recognized and carefully considered, extensive clinical trials indicate that in cases of tuberculosis in which the prognosis is

unfavourable or uncertain the possible toxic effects of streptomycin do not constitute a valid contraindication to its use (Hinshaw, 1947b). In cases of tuberculosis in which the prognosis is favourable under conventional forms of treatment streptomycin therapy should be used only in exceptional circumstances, if at all.

Streptomycin Resistance

One of the most serious obstacles to the achievement of maximal therapeutic benefits from streptomycin in clinical tuberculosis is the problem of streptomycin-resistant tubercle bacilli. Although the problem of drug-resistant micro-organisms is not entirely understood there is evidence that this phenomenon represents a selective process dependent on the capacity of bacteria to undergo spontaneous variation or mutation (Demerec, quoted by Selbie, 1946).

In clinical tuberculosis, while the largest proportion of the bacterial population is sensitive to streptomycin before treatment is started, a few variants are present that are drug-resistant in varying degrees (Pyle, 1947). During treatment with a sufficiently potent antibacterial substance such as streptomycin the more sensitive bacterial cells are gradually inhibited and eventually eliminated, while the more resistant cells continue to be propagated. Eventually, if treatment is long continued, there frequently occurs a gradual replacement of the population of tubercle bacilli from one that was predominantly sensitive to streptomycin when treatment began to one that is predominantly streptomycin-resistant. The degree of resistance may be several thousandfold greater than is true of tubercle bacilli sensitive to streptomycin.

In clinical tuberculosis the exact significance of the appearance of varying percentages of streptomycin-resistant tubercle bacilli is somewhat uncertain at the present time. Evidence obtained by animal experimentation shows definitely that infections induced in guinea-pigs by apparently pure cultures of highly streptomycin-resistant strains of tubercle bacilli are not amenable to the therapeutic action of streptomycin (Feldman, Karlson, and Hinshaw—unpublished data; Youmans and Williston, 1946). However, clinically the occurrence after weeks of therapy of some tubercle bacilli highly resistant to streptomycin does not necessarily indicate that the preponderant bacterial population is resistant, and must not be accepted as an indication that treatment may be of no benefit if the need for treatment continues to exist. The fact that patients may continue to improve spontaneously after administration of streptomycin has been discontinued and eventually may become bacteriologically negative (by guinea-pig tests) for tubercle bacilli indicates that treatment may not be required for extended periods.

The time required for the appearance of streptomycin-resistant tubercle bacilli after the beginning of treatment with this substance is variable. Ordinarily, however, the drug-resistant bacteria cannot be demonstrated in appreciable numbers until treatment has been in effect sixty to ninety days. While it is desirable to obtain cultures for the purpose of bacteriological assays for the determination of streptomycin sensitivity* at regular intervals after treatment has been started, there is no adequate practical quantitative method of determining when resistant organisms have gained ascendancy. All available tests are only qualitative, and merely indicate that at least a few resistant bacilli are present. This must not be accepted as convincing proof that the end-point of practical treatment has been reached.

Whether or not the administration of streptomycin should be continued after the bacterial population has become predominantly drug-resistant is at the present time a controversial question. It is our opinion, however, that when the vast majority of bacterial cells are no longer susceptible to the antibacterial action of streptomycin further administration of the drug is unwarranted and may even be deleterious. If at a later time streptomycin-sensitive tubercle bacilli again predominate, and other indications are favourable, treatment with streptomycin may be resumed.

How best to meet the problem of streptomycin-resistant tubercle bacilli is at present one of the most important of

*A method for the determination of sensitivity of tubercle bacilli to streptomycin *in vitro* has been described by Karlson and his associates (1947).

*A report on the toxicity of streptomycin in human beings has been given by McDermott (1947).

the many unsolved problems that confront the experimentalist and the clinician. A logical approach would seem to be to use as the therapeutic regimen a combination of two or more drugs each having a high antagonistic efficacy for tubercle bacilli. Streptomycin utilized simultaneously with some other (as yet unknown) antibiotic might prove effective. Streptomycin combined with sulphone compounds or with other synthetic anti-tuberculosis drugs offers possibilities that are now being explored.

Final Comment

During recent years studies in the antibacterial attack on tuberculosis have yielded results sufficient to change to a considerable degree many of the previously held therapeutic concepts of tuberculosis. Most important, it has been adequately demonstrated that this disease is no longer beyond the range of specific drug therapy. Instead, the vulnerability of tuberculous infections to a chemotherapeutic attack has been established experimentally and clinically. While to date the completely ideal anti-tuberculosis drug has not been reported it seems probable that substances equal or superior in effectiveness to known agents may be found. These possibilities warrant expenditure of great effort, and this search may become one of the most important and exciting adventures in medical research.

In the meantime streptomycin seems likely to become generally accepted as a useful drug in certain types of clinical tuberculosis. It must, however, be used intelligently, with full recognition of its shortcomings and limitations. It should frequently be used in combination with other effective methods of treatment, rather than as a substitute for such proved therapeutic procedures as care in a sanatorium, collapse therapy, and surgery.

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CANCER OF THE STOMACH IN ADDISON'S ANAEMIA

BY

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Among some clinicians there is a feeling that patients suffering from pernicious anaemia are more liable to gastric carcinoma than normal individuals of the same age groups. Kaplan and Rigler (1945) suggested that this feeling had statistical backing, and reported (Kaplan and Rigler, 1947) 18 cases of cancer and 17 simple tumours in 259 cases of pernicious anaemia. During the past two years 15 of my own cases have been observed by radiograph and gastroscopy in the hope of detecting carcinoma of the stomach at an early stage. Occasional estimations of the blood sedimentation rate have also been made, since Whitby and Britton (1946) state that the test is of great value in suggesting the onset of carcinoma. Cases were not selected, and there can be no pretence that they form a series. These observations have resulted in the discovery of three cases of carcinoma in patients free from symptoms and clinical signs: one was certainly operable and one probably operable when first detected. One further case has been found to have a leiomyoma. Two others are under particular observation because of a persistently high blood sedimentation rate; one of these has a nodule of uncertain nature in the pyloric antrum.

The cases observed are here tabulated. The total is made up of 11 females and 4 males. Radiological examination consisted of a barium swallow, fluoroscopy, and, usually, a film. Gastroscopy was performed with the Hermon Taylor

Case No.	Sex	Age	Duration of Anaemia	X-ray Film	Gastroscopy	E.S.R.	Conclusion
1	F	41	3	Normal	—	—	—
2	F	41	7	—	—	20	—
3	F	47	2	"	—	1	—
4	F	49	4	"	Normal	40	—
5	F	50	11	"	—	—	—
6	M	52	1	"	—	—	—
7	F	55	11	"	—	26	—
8	F	60	4	"	Polyp	—	Leiomyoma
9	M	65	10	Abnormal antrum	Abnormal antrum	—	Carcinoma
10	F	70	13	Normal	—	—	—
11	M	70	13	Abnormal antrum	Carcinoma	—	Carcinoma
12	F	73	6	Normal	—	—	—
13	F	75	2	"	—	—	—
14	F	75	12	Abnormal antrum	Abnormal angulus	—	Carcinoma
15	M	77	1	Normal	Nodule in antrum	30	Solitary polyp

or Schindler instrument if the radiological report was doubtful, if there was failure to improve clinically, and once when there was a persistently high sedimentation rate in the absence of abnormal radiological findings. The sedimentation rate was determined by Wintrobe's method corrected for anaemia, and was asked for quite at random. It must be emphasized that no patient had dyspepsia when examined.

Case 9

A retired jockey aged 65 was diagnosed as suffering from pernicious anaemia in Berlin in 1937, and had been on liver treatment with satisfactory results thereafter. Though asymptomatic he was x-rayed on Sept. 18, 1945, and the report stated: "There is some rigidity in the prepyloric region which is somewhat suggestive of early scirrhus carcinoma, but it may be due only to fibrosis. If other signs are equivocal, a repeat examination in a few weeks' time would be advisable for comparison." Gastroscopy on Oct. 31 showed that the lower third of the stomach was fixed and pale, with no peristalsis. Laparotomy was performed on Feb. 27, 1946. At this time he