CHEMOTHERAPY IN TUBERCULOSIS
(A Review of the Literature)

BY

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HISTORICAL

From time immemorial the search for a drug cure for tuberculosis has continued with but little success until about 1924 when Møllgard introduced sodium aurothiosulphate, though Koch had also used gold in tuberculo-therapy in 1890. The following ten years saw a widespread use of various gold preparations, but the accumulated experience of its toxic effects, and its relatively small value in the therapy of tuberculosis generally, led to its gradual abandonment; and since 1935 but few investigators have used chrysotherapy, although it probably still has a place in certain judiciously selected cases.

It was, however, the introduction of prontosil by Domagk in 1935 which gave a lively impetus to the search for chemotherapeutic substances with bactericidal or bacteriostatic properties against the M. tuberculosis. Rich and Follis (1938) reported that sulphonamides exerted an inhibitory action on the development of tuberculosis in laboratory animals, and recognition of this fact led to an increased interest in tuberculochemotherapy, which has continued to progress and develop since then. As a result sulphonamide and its derivatives were tried in man, but were soon found to be of little value (Ellman, Lawrence, and Cummings, 1941). Next the kindred class of sulphones were used by Feldman and his colleagues (1942) on laboratory animals and man and, though found to be more effective than the sulphonamides, they were considerably more toxic to man, especially on the blood-forming organs, and for this reason their use had to be abandoned. The most effective of these compounds was promine or promanide, and its greatest benefit was to be
found when applied locally either to laryngeal lesions (Heaf et al., 1943) or to tuberculous sinuses (Tytler and Lapp, 1942). The next drug to be used, also in the sulphone series, was diason which was reported by Petter and Prenzlau (1944) to be less toxic than promine, but later results have not shown that any greater benefit can be obtained than with the more recent chemotherapeutic agents. Finally the third member of this series, promizole, has been under investigation since 1944, and though by no means a satisfactory agent it is probably the best of the sulphones, though it may indeed be the progenitor of a new series of drugs, rather than the last member of the line of sulphones (Feldman, Hinshaw and Mann, 1944). All the sulphones can be given by mouth but they are toxic to man, and no adequate evidence has yet been adduced to justify the use of these drugs alone in the treatment of tuberculosis; although satisfactory results have been obtained when they are given with streptomycin in the treatment of tuberculous meningitis, further confirmation is still required (Crofton, 1950).

Meanwhile attempts had been made to extract chemical substances of microbial origin which would inhibit the growth or metabolic activities of bacteria, and such substances were called antibiotics by Waksman. Many so-called antibiotics have been recovered, but only a few are active chemotherapeutic agents, and these are derived from three main sources. Firstly from the higher fungi (Penicillia, Aspergilli) penicillin is the only substance produced which has any marked therapeutic efficacy, although, of course, it has no place in the treatment of tuberculous infections. The second source of antibiotics is a group of certain aerobic sporogenous bacilli but none are of any proven value because of their highly toxic effects on the kidney when given parenterally. It should, however, be noted in this connexion that B. mesentericus was used as an anti-tuberculous agent in 1912, though without any marked success. The third source is the more primitive group of fungi (Actinomycetes), and these have been found to yield three valuable antibiotics, streptomycin which was prepared in 1944, from Streptomyces griseus, chloromycetin which was formed from Streptomyces venezuelae in 1947, and aureomycin which was prepared in 1948 from Streptomyces aureofaciens. Of these the only effective anti-tuberculous preparation is streptomycin, which was isolated by Schatz, Bugie and Waksman (1944), and initially reported upon by Feldman and his co-workers (1945).

In 1946, the use of another synthetic organic compound was reported but this time belonging to the aromatic group of substances (Lehmann, 1946a). It had already been shown by Bernheim that salicylates and benzoates can increase the oxygen consumption of tubercle bacilli, and it was concluded that they play an essential part in the intermediate cell metabolism of the organism, though it was not clear whether they acted as catalysts or metabolites. Lehmann showed that this effect of salicylates and benzoates is true only in the case of pathogenic tubercle bacilli. On this basis he investigated, by competitive enzyme inhibition, the inhibitory effects on the growth of tubercle bacilli of more than 50 derivatives of benzoic acid in order to find a substance
possessing bacteriostatic properties. The most active substance he found which could be given by mouth or parenterally and was only mildly toxic to man was para amino-salicylic acid (Lehmann, 1946b).

At about this time Domagk and his co-workers (1946) introduced the thiosemicarbazones as chemotherapeutic agents with tuberculostatic properties. The most active member of this group was TB1–698, which is sold commercially in the U.K. as thioparamizone. The drug has been used extensively in Germany, but experience elsewhere is very limited. Mertens and Bunge (1950) have published a summary of their clinical trials, showing that it has tuberculostatic properties both in vitro and in vivo, but its toxic effects, especially on the bone-marrow and liver, are by no means inconsiderable. Its use is still in the experimental stage and its general employment can certainly not yet be recommended.

Finally the most recent agent to undergo trials in England is a further sulphone derivative. "Sulphetrone" was first produced in the Wellcome Research Laboratories in 1936, and the initial report by Brownlee (1948) suggested that its acute toxic effects were slight but the chronic effects were more marked. Clinical trials, which were encouraging initially (Anderson and Strachan, 1948), are still progressing, but it has been suggested (Morlock and Livingstone, 1949) that the end-results do not show any appreciable advantages over other agents, and in the opinion of these authors it has no place in the treatment of pulmonary tuberculosis.

Full reviews of the historical background of the chemotherapy of tuberculosis have been made by D'Arcy Hart in his Mitchell Lectures (1946) and by Feldman in the Harben Lectures (1946), both of which will well repay further study of this fascinating subject.

**Drugs Available**

It is thus clear that the drugs which have found a place in clinical use may be considered under two headings:

(a) Those still under investigation, and whose general use should not yet be implemented, including Promanide, Diasone, Thiosemicarbazones, Sulphetrone.

(b) Those in general use, and whose clinical application can be recommended, including streptomycin and its followers: Para-amino-salicylic acid and its derivatives; Promizole.

Of the drugs available for general use the most active is streptomycin, and this may be given in combination with one or other of the remaining drugs. In actual practice the chemotherapy of tuberculosis usually only involves the use of streptomycin and P.A.S. either singly or in combination. Both of these drugs produce startlingly beneficial results in suitable cases of tuberculosis but they possess two very marked drawbacks, first of all the possibility of developing drug-resistant bacilli and secondly severe toxic effects may be produced by the agent itself.
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Drug Resistance

Using streptomycin alone a high percentage of cases of pulmonary tuberculosis develop tubercle bacilli which become resistant to its action. These resistant organisms may emerge after only two or three weeks' treatment, but it is more common after about six or more weeks. This resistance when developed is usually a permanent and irreversible change.

It seems possible that resistant forms of bacilli arise by genetic changes, in the nature of a mutation, from streptomycin-sensitive organisms. In support of this is the undoubted fact that resistant organisms breed true, and also that an increase in the number of resistant bacteria in the presence of streptomycin occurs when the bacteria are in a medium which allows multiplication. A second factor allowing for the development of drug fastness is that in any bacterial population there is always a small proportion of organisms possessing an inborn drug insusceptibility. Thus, during the administration of the drug, the more sensitive organisms first of all cease multiplication because of the bacteriostatic effect, and secondly die off because of its bactericidal properties; and eventually the infection comes to be due more and more to drug-fast strains, which are resistant to both the bacteriostatic and bactericidal action of the antibiotic (Mitchison, 1950). The development of resistant strains must obviously, therefore, develop at a speed proportional to the rate of multiplication of the organisms.

But bacteria which have become streptomycin-resistant may become so in varying degrees, and this has led to the suggestion that there are a number of genetic forms of differing degrees of potency. A mutation in some genes will produce bacteria of low resistance, whilst a mutation in other genes will produce moderate or even very high degrees of resistance. It is considered that the low-potency genes are more numerous, and more likely therefore to produce by mutation bacteria with low degrees of streptomycin resistance, whilst only occasionally does a mutation occur in a high potency gene, producing highly resistant organisms. The obvious implication is that the larger the bacterial population the more rapidly it is multiplying, and the more suitable the medium for multiplication then the more likely it is that the rarer mutations to highly resistant forms will occur. It has also been shown (Crofton and Mitchison, 1948; Bignall et al., 1950) that the earlier that resistant bacilli are found after commencing treatment, the more highly resistant they eventually become, attaining their final level of resistance fairly rapidly.

Further, evidence is accumulating to suggest that there is some correlation between clinical factors and the development of drug-fastness. It has been demonstrated in three different investigations (Mitchell, 1949; Howard et al., 1949; Howlett et al., 1949) that in cases showing radiological evidence of caseation and cavitation which have been treated with streptomycin, about 60 per cent develop resistance, whereas in non-cavitated tuberculous disease the resistance rate is only about 8 per cent when similarly treated. Bignall et al. (1950) have shown that the more confluent the radiological picture, the sooner can resistant forms of tubercle bacilli be expected to appear. These
workers have also shown that there is a suggestive correlation between the
general severity of the infection and of the emergence of resistant forms.
Often very ill patients produce bacilli with very high degrees of resistance,
while those who are relatively well are less likely to do so. Thus cavitated and
confluent tuberculous lesions, in the very ill patient, with severe systemic
disturbances, are the more likely to produce resistant strains of *M. tuberculosis*.

It has also been shown that routine examination of the sputum in cases of
pulmonary tuberculosis undergoing streptomycin therapy often reveals an
initial fall in the degree of sputum positivity. If this initial fall does not occur,
it is usually an indication that highly streptomycin-resistant bacilli will emerge
although the converse is not entirely true. After this initial drop in positivity,
unless the patient becomes permanently sputum negative there is usually a
later rise, and when this occurs it is found that streptomycin-resistant organisms
have emerged (Crofton and Mitchison, 1948; Bignall et al., 1950).

The dangers then are, that patients carrying streptomycin-resistant
organisms may infect others and produce in them a streptomycin-resistant
tuberculous process. Such cases have already occurred. Therefore in order to
reduce the risk to a minimum, streptomycin should only be used when it is
most clearly indicated. The second implication of the development of strepto-
mycin-resistant tubercle bacilli is that any further response in the patient to
additional doses of streptomycin may decline, and may even go on to produce
absolute drug-fastness. Therefore it is imperative that the dosage of strepto-
mycin should be adequate and suitable throughout treatment.

Concerning the development of drug fastness during treatment with P.A.S.
alone, it was originally believed that resistance did not occur either *in vitro* or
*in vivo*. However, Karlson et al. (1949) have shown that prolonged therapy
does in fact produce P.A.S.-resistant organisms. This work has recently been
confirmed in England but it would appear that P.A.S.-resistance rarely occurs
in less than three months’ treatment.

The significance of the development of P.A.S.-resistance is that when this
occurs it may well prejudice the results of any combined course of therapy,
using streptomycin.

When P.A.S. is given in conjunction with streptomycin in adequate doses,
however, there is a marked reduction in the incidence of streptomycin-resistant
strains, and no reports have been published so far of P.A.S.-resistant strains
resulting from this therapy.

In a recent M.R.C. trial (1950) it is reported that in cases of acute bilateral
exudative disease, treated by chemotherapeutic agents for three months, of
those cases remaining sputum positive at the end of this period:

1) 60 per cent were streptomycin-resistant when treated with streptomycin
alone.

2) A slightly smaller percentage were P.A.S.-resistant when treated with
P.A.S. alone.

3) 10 per cent were streptomycin-resistant when treated with streptomycin
and P.A.S. in conjunction, but that no cases of P.A.S.-resistance were traced
in this series of cases undergoing treatment with the combined therapeutic course.

The development of streptomycin-resistant organisms in genito-urinary tuberculosis also occurs in a high proportion of cases, unless the urine is cleared permanently of tubercle bacilli. Therefore it is important that the whole of the urinary tract should be fully investigated, and the use of chemotherapeutic drugs should only be part of a planned attack on the disease.

In miliary and meningeal tuberculosis the development of resistant bacilli occurs much less frequently.

TOXIC EFFECTS

The second main disadvantage to the use of streptomycin is its toxic effects, particularly on the vestibular apparatus. This is more likely to occur the bigger the dose, and the more prolonged the course. The main symptoms are vertigo, tinnitus, and deafness, which usually come on after about three to seven weeks' treatment. If the treatment is stopped at once improvement will take place and the symptoms will usually disappear completely within two to three months, but if they come on after a large total dosage, or if the treatment is prolonged after the onset of the toxic symptoms, the vestibular damage may become permanent, though some degree of improvement is possible during the succeeding two years. For these cases it is important that their after-care is properly controlled. The giddiness from which they suffer is compensated for, and adjusted by, visual control. Therefore they should not be left unattended in the dark without adequate support, nor should they be allowed to drive motor cars, or cross roads busy with traffic, since under these circumstances their visual control may be lost, and they may suffer from severe though temporary giddiness, or vertigo, with perhaps disastrous results.

Other toxic effects include scarlatiniform rashes which may come on within a few days of starting treatment, or urticarial eruptions or other histamine-like effects which often commence within the first few weeks. These are usually controlled by anti-histamine drugs, and it is frequently unnecessary to discontinue the treatment. Rarely true exfoliative dermatitis or severe pyrexial reactions may occur, and these will usually necessitate termination of treatment. Quite often the injection itself will produce local pain, redness or swelling, or there may be anorexia, nausea or vomiting, but these are rarely severe enough to justify stopping the treatment, and are effectively controlled by the anti-histamine drugs. Eosinophilia may occur but it is unimportant. Streptomycin is excreted in the urine and if the urinary concentration is very high, in the order of 1,000 microgrammes per litre, a positive urinary Benedict's test may be obtained, due to streptomycin acting as a reducing agent.

The toxic effects of P.A.S. are very common though remarkably slight and usually consist of anorexia, nausea, vomiting, or diarrhoea, particularly at the start of treatment. These effects can often, however, be reduced if the drug is taken after a meal, or if it is preceded by an alkaline mixture. Drug
sensitivity reactions may occur with the production of a mild fever, skin rashes or localized pains, but these will often respond to anti-histamine drugs, or by cutting the dose to about one-tenth and then giving it in gradually increasing daily doses. Occasionally haematuria or albuminuria may occur, and in this eventuality the urine should be alkalinized before continuing the drug (Nagley and Logg, 1949). Hypoprothrombinæmia has been reported (Swanson, 1949) but it is probably of no clinical significance. In 30 consecutive cases of pulmonary tuberculosis undergoing P.A.S. therapy in the Connaught Hospital, all of whose prothrombin times were estimated, not one case of significant hypoprothrombinæmia was noted. No toxic effects have been reported on the blood, but like streptomycin P.A.S. is excreted in the urine and this may also have a reducing effect on Benedict’s solution.

Nurses handling streptomycin may become sensitive, and after some weeks or months they may develop sensitization rashes on the hands, flexures of the arms and around the eyes. It is therefore necessary that before the vials of streptomycin are opened, the handlers should wear rubber gloves until the whole operation of opening the containers, mixing the solution, and giving the dose is completed, and the syringes washed and the containers disposed of. Then the gloved hands should be thoroughly rinsed under running water, and after removing the gloves the hands themselves should be well scrubbed.

RATIONALE OF CHEMOTHERAPY

The first consideration for chemotherapy in tuberculosis is the proper selection of cases for which chemotherapy is suitable and indicated.

Secondly the giving of chemotherapeutic agents should not be counted an end in themselves, but should be considered as part of a planned course of treatment. They should not be expected to produce a lasting cure, but should be used in selected cases with the intention of achieving sufficient improvement to permit of the induction of collapse therapy or major chest surgery. The drugs must be continued until this objective is attained, be this weeks or months, and the collapse measures should be instituted at the most opportune moment while the patient is still under the protection of the drug, that is actually under treatment or immediately following completion of a course of treatment. Under no circumstances should a course of chemotherapy be terminated, and the patient left with unclosed cavities, for relapse is almost certain within a short time. Similarly chemotherapy should never be used as a temporizing measure, but only as part of a planned programme designed to arrest or cure the disease.

Thirdly they must be exhibited with a watchful alertness to the prevention of the development of resistant strains. This may be achieved by giving streptomycin intermittently or by giving it in combination with other drugs. In a study of 560 cases treated at the Fitzsimmons General Hospital, Denver, the report published by the Veterans Administration (1950) showed that when 1 gramme streptomycin is given daily for three months about 70 per cent of cases develop streptomycin resistance. When streptomycin is given in 1
gramme doses every three days, the resistance rate falls to 33 per cent, but when P.A.S. is given daily, in addition to streptomycin every third day, then no cases of resistance were reported after 120 days' treatment.

Fourthly the doses of streptomycin should be adequate in amount throughout treatment for the type of disease being treated. In those cases which are likely to produce resistant organisms quickly, the size of the dose must be effective from the very beginning of treatment. The object therefore should be to commence treatment at the earliest possible moment, while the number of innately resistant bacilli is still minimal, and to eradicate the infection as promptly as possible.

Fifthly due attention must be paid to the prevention, treatment and aftercare of any toxic effects which may arise from the drugs themselves.

Finally a recent M.R.C. investigation (1950) into the treatment of pulmonary tuberculosis with streptomycin and P.A.S. provides information on the relative values of these two drugs. The trials investigated the results of chemotherapy in comparable groups of cases with acute progressive bilateral pulmonary tuberculosis. One group was treated with P.A.S. 20 grammes daily only, a second group was treated with streptomycin 1 grammme daily only, a third group was given streptomycin and P.A.S. in combination, and a group of cases treated on bed rest only, in a previous similar investigation, was used as a control. Treatment was carried out for three months and observations were made for a further three months. The results of this investigation show that with P.A.S. alone far better results are seen than in the control group treated on bed rest alone, and this confirms earlier reports from Swedish authorities. Clinical improvement, when it takes place, occurs rapidly with a fall of temperature, reduction of E.S.R. and gain in weight though the radiological improvement was less impressive in its degree.

It was observed that P.A.S. alone, although producing better results than bed rest, was not as effective as streptomycin by itself. Comparing these two groups, more P.A.S. cases showed unchanging radiological appearances during six months' observation and fewer P.A.S. cases became sputum negative, while the rate of clinical improvement was less marked and occurred later whilst on P.A.S. only. Streptomycin alone thus produced considerably better all-round results than P.A.S. by itself.

Combined streptomycin and P.A.S. therapy showed somewhat more definite evidence of clinical and radiological improvement as compared with the cases only on streptomycin. About 30 per cent of the cases in the combined treatment group undergo sputum conversion in the first three months, compared to a maximum of 10 per cent in six months in the streptomycin only group. In those cases still remaining sputum positive a maximum of 9 per cent in the fifth month develop streptomycin-resistance in the combined treatment group, as compared to 70 per cent by the fourth month in the streptomycin-only cases.

P.A.S. resistance was observed in cases on P.A.S. only, but although accurate estimations are not available, it would appear that the development of P.A.S.-
resistance whilst on P.A.S. alone occurs only less frequently than the develop-
ment of streptomycin-resistance whilst on streptomycin alone. It was con-
sidered, however, that no significant difference in prognosis could be ascertained
between the patients from whom P.A.S.-resistant strains were isolated, and the
others. On the combined course of treatment no cases of P.A.S.-resistance
were found. Finally it was considered that:

(1) P.A.S. alone has a place in the treatment of cases which show
apparently complete streptomycin-resistance, and P.A.S. appears to be the
only chemotherapeutic agent in general use at present for streptomycin-
resistant cases.

(2) That when streptomycin is required to be given, it should always be
exhibited in conjunction with P.A.S.

(3) The greatest advantage obtained from combined therapy was the
considerable delay in the emergence of streptomycin-resistant organisms,
which allows effective administration of streptomycin possible for much longer
periods than previously, and may even permit of repeated effective courses.

A warning is sounded that neither P.A.S. nor streptomycin are without
toxic effects, and that the development of streptomycin-resistance is not
completely prevented by combined therapy, although drug resistance should
not be overstressed as a factor in prognosis.

INDICATIONS FOR CHEMOTHERAPY

The selection of cases suitable for chemotherapy calls for special skill
and experience in choosing the type of case wisely, adjusting the dose correctly,
and planning fully an adequate course of treatment, utilizing other therapeutic
procedures at the opportune times.

The indications for chemotherapy in the light of our present knowledge
can be summarized as follows:

(1) Absolute Indications.—(a) Tuberculous Meningitis: With chemotherapy
the survival rate in special centres is now about 40–50 per cent after six months’
treatment or longer.

(b) Acute Miliary Tuberculosis: After six months’ treatment recovery
can be expected in about 50 per cent of cases, but the possibility of the
development of tuberculous meningitis should be constantly borne in mind.

(c) Pulmonary Tuberculosis of the Following Forms: (i) Pneumonic
phthisis. Chemotherapy for three months or longer is often a life-saving
measure in these cases, and with the judicious use of a pneumothorax can
often render some of them suitable for major collapse measures. (ii) Acute
bronchogenic or haematogenous pulmonary spread. In the acute extensive
spreads chemotherapy should be instituted at once, since many of these
lesions show a propensity to cavitate early and it is necessary to commence
chemotherapy before this occurs, in order to be able to utilize collapse measures
in the future, to the best advantage.

(2) Relative Indications.—(a) Pulmonary Tuberculosis: (i) Recent pro-
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gressive exudative disease without much cavitation, with the intention of achieving sufficient improvement to allow the induction of suitable collapse measures. (ii) Tuberculous disease of the respiratory tract including the mouth, pharynx, larynx, trachea, and bronchi, especially in recent acute laryngeal or endobronchial lesions with slight parenchymal disease. (iii) Tuberculous empyema of recent origin, with or without sinus formation. Although the results to date are disappointing, yet when given intrapleurally as well as parenterally it almost certainly has a place in preparing such cases for major surgery. (iv) As an "umbrella" in major thoracic surgery for pulmonary tuberculosis especially pulmonary resection, with a view to reducing the incidence of post-operative spreads, and of tuberculous empyema.

(b) Extrapulmonary Tuberculosis: (i) Renal and genito-urinary tuberculosis, particularly of the bladder, as part of a planned course of treatment, involving surgical resection, convalescence, and a sanatorium regime. (ii) Severe tuberculous adenitis, especially if the glands have broken down and surgical treatment is contemplated. P.A.S. instillation following aspiration is particularly useful for tuberculous abscess formation from caseous glands. (iii) Cutaneous tuberculous lesions often show considerable benefit from chemotherapy, especially when used in combination with calciferol.

(3) Doubtful Indications.—(a) Tuberculosis of Bones and Joints: Although commonly used in these conditions the place of chemotherapy is still uncertain, though its value probably lies in making certain cases fit for operation.

(b) Tuberculous Peritonitis and Enteritis: It is difficult to assess the results of chemotherapy in these conditions owing to their tendency to spontaneous healing, but streptomycin is probably of some value.

(c) Primary Tuberculosis, by itself, is no indication for chemotherapy, which is useless in this condition, and there is no evidence that it has any effect whatsoever on the disease.

Clinical Application

There are three main ways in which chemotherapy may be employed in the treatment of tuberculous conditions.

Firstly it may be employed during domiciliary treatment of cases awaiting a sanatorium vacancy for the induction of collapse measures. A recent M.R.C. investigation (1948) into the effect of four months' treatment with 1 gramme daily of streptomycin on acute bilateral bronchopneumonic disease showed that considerable improvement occurred after three months, but compared with the control cases there was very little difference between them after an interval of twelve months. Thus streptomycin can be expected to produce relatively quick results by slowing down and arresting the progress of acute exudative disease and even producing considerable resolution of the lesions with marked clinical improvement. This improvement is usually most marked after about two months' therapy. These results have been confirmed in the latest M.R.C. investigation (1950). Therefore it is necessary that arrangements should be made to carry out some surgical procedure after two to three months'
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treatment with chemotherapy in order to consolidate the progress already
obtained and to lead to stability and healing. Streptomycin used in this way
will render a case fit for collapse measures much more quickly than could be
attained by prolonged bed rest only, and thus the main benefit is to be found
in the considerable shortening of the waiting period before the induction of the
collapse measures. Again, streptomycin may act to advantage in a case of
slowly progressive exudative disease in a person with little resistance by
producing a short period of quiescence which may allow with relative safety
the inception of collapse measures, which will tilt the scales in the patient's
favour and lead to progressive improvement and recovery. And thirdly it may
well be that on completion of a course of chemotherapy a much less drastic
surgical programme will be required than was originally contemplated.

Secondly chemotherapy should only be used as part of a planned course of
treatment whether it be carried out at home, or in an institution. In unilateral
disease it may be used with the intention of reducing the waiting time before
an A.P. can be safely attempted. Similarly in extensive bilateral disease it may
be used, first of all to arrest the progress of the lesion, then to produce a short
period of quiescence sufficient to allow the induction of a P.P. or even an A.P.,
and then later on to allow a major surgical procedure to be carried out on
one side with an A.P. on the other. It may also be used in those cases with
acute hematogenous or bronchogenic spreads with the intention of controlling
or arresting the spread and allowing the case to be dealt with by collapse
measures using standard indications. It is particularly of value in the planned
course of treatment for tracheo-bronchial disease. A recent investigation into
the streptomycin treatment of tracheo-bronchitis revealed two interesting
facts. Firstly that some cases which by reason of bronchial disease would be
considered unsuitable for collapse measures, may be made suitable by clearing
the bronchial obstruction initially with streptomycin. And secondly the use
of streptomycin much more certainly controls the activity of endo-bronchial
disease and this has led to a great reduction in the incidence of bronchopleural
fistula following resection, together with the reduction of morbidity and
mortality following resection procedure. In tuberculous pyopneumothorax or
tuberculous empyema in which all secondary infections have been controlled
and eliminated by penicillin, etc., streptomycin both intramuscularly and
intrapleurally plays a very considerable part in rendering these very ill patients
fit for major surgery.

Finally chemotherapy may be used as an adjuvant or as a precursor to
major surgery (Mullard, 1950). It is generally believed that the best cases for
thoracoplasty are those in good general condition with chronic upper lobe
cavituated disease which has shown no fundamental change for some months.
This type of case is unaffected by chemotherapy, but experience with strepto-
ymycin suggests that many of the so-called second-best cases, in which the
disease is unstable, or was recently acute and progressive, can be readily and
quickly prepared for thoracoplasty, and made much more suitable for major
surgery with relatively little risk by a preliminary course of chemotherapy
which should, however, be continued through the post-operative period. After a course of chemotherapy in preparation for major surgery, it often occurs that much less formidable procedures may be required than were originally contemplated.

The place of chemotherapy as "cover" during thoracic surgery is still awaiting final adjudication. An M.R.C. investigation on this problem in relation to thoracoplasty suggests that streptomycin does not in fact reduce the incidence of post-operative spreads or reactivation (Mullard, 1950). But it is quite effective in dealing with them when they occur. The effect of this has been to rely on the beneficial effects of thoracoplasty in allowing minimal contralateral non-cavitated infiltrations to harden and heal, once the main focus of the disease is controlled, or to rely upon streptomycin to control the contralateral disease should it show signs of activity during the course of major chest surgery, rather than induce a controlling A.P. prior to operation. The avoidance of a contralateral pneumothorax with the intention of preserving as much functioning lung tissue as possible is of course desirable, especially when one considers how much loss of pulmonary function may occur due to pleural fusion and obliteration as a result of maintenance of an A.P. for any length of time.

During resections, however, there is little doubt that chemotherapy plays a very useful part when used as an "Umbrella," during and after operation. With streptomycin cover complications following lobectomy such as post-operative spreads, bronchial fistulae, and tuberculous empyema have been very appreciably reduced, so that the main hazards attendant upon pulmonary resections have been largely removed, and this may allow of segmental resections instead of lobectomies. This is particularly noted in relation to the development of bronchopleural fistula following resection in tracheo-bronchial disease. It is interesting to note in this connexion that the efficacy of streptomycin when used as a cover for resection procedures seems to be unaffected by the presence of resistant strains. Tuberculous sinuses may be successfully treated by local daily injections of 20 per cent P.A.S. solution, after any secondary infection had been eradicated.

**Administration and Dosage**

Streptomycin was supplied originally as either a sulphate or a hydrochloride preparation. But these were found to contain a number of impurities, and now a much more purified double salt compound has been prepared which is the trihydrochloride-calcium chloride complex of streptomycin. This is readily soluble in water, remarkably free of impurities and is very stable, retaining its potency in powder form in sealed ampoules at room temperatures (85°F.) for many months, and in solution remains potent for several weeks if stored in a refrigerator.

Dihydrostreptomycin is a synthetic preparation obtained from the catalytic reduction of streptomycin in the presence of hydrogen. Like the parent substance it is capable of forming salts of which the sulphate and the hydro-
chloride are the commonest. It is undoubtedly less toxic on the vestibular apparatus than streptomycin but deafness appears to be slightly more common as the result of its use. Its lesser toxicity is, however, offset by its somewhat lesser therapeutic effectiveness, and the emergence of resistant bacilli are just as liable to occur as with streptomycin. Its use is therefore mainly confined to cases developing severe toxic reactions with streptomycin.

The adult dose of either of these drugs is 1 gramme daily which is now usually given in one daily intramuscular injection in 2-5 c.c. of sterile distilled water or normal saline. Phosphate buffers should never be used with the calcium chloride complex since precipitation will occur, nor should physiological salines containing calcium salts be used with dihydrostreptomycine sulphate for the same reason. Severe local pain due to the injection may be reduced by using 0.5 per cent procaine solution as the solvent. It should be noted that the technique of using less frequent injections or interrupted courses of treatment are likely to reduce appreciably the incidence of toxic manifestations.

In severe cases of pulmonary tuberculosis, genito-urinary tuberculosis, tuberculous meningitis and miliary tuberculosis the dose should be increased to 2 grammes daily given in two equally spaced doses. For children the dose should be 0.02 gramme per pound body-weight per day.

Para-aminosalicylic acid is generally supplied as the sodium salt which is given by mouth as a 20 per cent solution in tap-water. It has an unpleasant bitter taste which may be disguised by the addition of flavouring agents such as peppermint water, fruit syrups, liquid extract of liquorice, or chloroform water. But none of these are really satisfactory and many patients prefer the unflavoured solution. The usual dose in England is 5 grammes given three or four times daily, for six days in each week, but in America about half this dose is often given. For children, the dose can be calculated according to the usual formulae, or a daily dose of 0.25 gramme per kilo body-weight may be prescribed. For intrapleural injections a sterile 20 per cent solution is used, injecting about 20 ml. once a week. A similar solution may be used for tuberculous abscesses, using 1-3 ml. after weekly aspiration of the abscess and continued until pus formation ceases and the abscess becomes sterile.

In actual practice, however, when it is decided to use streptomycin in a suitable case, the opportune moment having arrived, and a suitable course of treatment designed, a course of chemotherapy to last six weeks to three months should be planned, using streptomycin 1 gramme daily in one intramuscular injection, and P.A.S. 15 to 20 grammes daily in four equally spaced doses for six days only in each week. von Leitner and Masson (1950) are of the opinion, after a considerable experience of P.A.S. therapy, that P.A.S. is useful not only in relatively favourable cases, but indeed should form the basic treatment in the more severe types of lesion. Further, they consider that streptomycin should be used mainly in a crisis situation, such as for an acute exacerbation or in preparation for operation, and that the mainstay of chemotherapy of the usual case should be with P.A.S. Therefore in less doubtful cases, where the indications for streptomycin are perhaps equivocal, but chemotherapy is
considered to be necessary, P.A.S. alone should be given in four daily doses of 5 grammes each.

**Summary**

1. A brief outline is given of the historical development of chemotherapeutic agents in the treatment of pulmonary tuberculosis.
2. The drugs now available are enumerated and the disadvantages of streptomycin and para-amino salicylic acid are discussed in detail. These are mainly concerned with drug resistance and toxicity.
3. The rationale of chemotherapy is noted and the indications for the exhibition of these drugs is discussed.
4. A scheme of dosage and the clinical application of chemotherapy is suggested. It is emphasized that streptomycin should never be used alone, but always in conjunction with P.A.S.
5. It is stressed that chemotherapy is not an end in itself, but only one part of a planned course of treatment, in which the use of chemotherapeutic agents must be integrated with the use of suitable collapse measures.

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**References**


——, (1946) *J. State Med.*, 9, 267, 297 and 343.


—— (1946b) *Lancet*, 1, 15.

Veterans Administration, Washington (1950) Transactions of the 9th Streptomycin Conference.
Chemotherapy in Tuberculosis: (A Review of the Literature)
G. F. Edwards

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