THE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

By J. G. Scadding, M.D., F.R.C.P.

From the Institute of Diseases of the Chest, Brompton, London, S.W.3

Many attempts have been made in the past to find chemotherapeutic agents active against the tubercle bacillus, and some agents alleged to have had such action, notably gold compounds, have had a considerable vogue. The discovery of the antibacterial action of the sulphonamides stimulated a search for compounds of related constitution having an action against the tubercle bacillus, and this resulted in the investigation of the effects of the various sulphone compounds. The therapeutic activity of these compounds, however, was so slight, especially in relation to their rather severe toxic effects, that it is doubtful whether, even had no more active agent been discovered, they would ever have entered into general use. It was with the discovery of streptomycin that the first really effective and practicable antibacterial therapy of tuberculosis became available. No other agent comparable with streptomycin as a clinically useful antibacterial agent in tuberculosis has been discovered. Para-aminosalicylic acid (PAS) has an undoubted, but less potent, antibacterial effect, and has found its principal place as an adjuvant to streptomycin. The thiosemicarbazones appear to be about as active as PAS against the tubercle bacillus, but their effectiveness as an adjuvant to streptomycin has not yet been fully explored; they certainly have more serious toxic effects than PAS.

Streptomycin in Pulmonary Tuberculosis

The literature on streptomycin has become so enormous that any attempt at a formal review would be tedious and possibly confusing. Moreover, knowledge about the practical application of the drug is accumulating so rapidly that it would be misleading to suggest that a definitive account of its place in the management of pulmonary tuberculosis is possible. A much truer impression can be given by describing the development of our knowledge of this subject. The investigations organized by the Medical Research Council's Streptomycin in Tuberculosis Trials Committee give a framework of logical order in which this development may be outlined, and will be described briefly for this purpose.

M.R.C. Trials

The first of these trials, conducted during the earlier part of 1947, was designed primarily to demonstrate, by observation of parallel series of treated and 'control' patients, whether streptomycin had any favourable effect in pulmonary tuberculosis. For this purpose patients with acute bilateral bronchopneumonic tuberculosis, not regarded as suitable for collapse therapy, were chosen. At the end of this trial certain conclusions could be drawn. There could be no doubt that recent exudative lesions might clear remarkably as a result of streptomycin treatment. On the other hand, the effectiveness of streptomycin in patients with considerable cavities, or with disease of older standing, was considerably less, and it was only rarely that cavities of any considerable size were healed as a result of streptomycin treatment alone. However, even in the presence of large cavities, streptomycin, by causing resolution of acute exudative lesions, might convert a case in which active treatment had not originally been feasible into one suitable for collapse therapy, or even surgical excision of the diseased parts of the lung.

Against these favourable findings had to be placed certain disadvantages. Streptomycin was clearly not as effective against the tubercle bacillus as, for instance, penicillin is against staphyloccoci; some patients with very acute disease might show a very poor response to streptomycin, and the disease might even spread whilst they were receiving the drug. The appearance of strains of tubercle bacilli having a high resistance to streptomycin soon became evident as a limiting factor. In this first trial strains with a resistance ratio greater than ten (i.e. able to grow in a concentration of streptomycin ten times that which is sufficient to inhibit the growth of the standard strain H37Rv) developed in 85 per cent. of patients, the mean
date on which the resistant strain was detected being the 53rd day from the beginning of treatment. Certain unfavourable factors, such as the presence of large cavities, a severe degree of illness at the beginning of treatment and delay in clinical response to the drug seemed to be related in a general way to the early appearance of highly resistant organisms. After the emergence of such organisms, a patient who had initially shown a favourable response might deteriorate in spite of continued administration of streptomycin. The toxic effects of streptomycin might also be serious. In this first trial the standard dosage was 2 g. daily; on this, disturbances of vestibular function were frequent. Nausea, vomiting and dizziness were often troublesome and, in general, were more severe in the older patients; skin rashes and drug fever were rarer complications.

A very important point which became evident during the course of this trial was not directly related to streptomycin. It was the absolute need for controlled trials of new therapeutic agents in pulmonary tuberculosis. Among the patients who were observed as control cases, there were some who showed improvement in every way comparable with that shown in the treated cases; and, moreover, as noted above, some of the streptomycin-treated patients failed to improve. Thus it was only by the careful analysis of data on a statistical scale that scientifically valid conclusions could be drawn.

Soon after this trial was completed a trial of the effectiveness of streptomycin in tuberculous lesions of the main bronchi was started. It has become generally recognized that tuberculous lesions of the main bronchi are frequent in the course of pulmonary tuberculosis, and that, when present, they may exercise a controlling influence over the progress of the disease. The especially baneful effect of tuberculosi of the larger bronchi arises chiefly from two causes. First, an active tuberculous ulceration gives rise to persistence of tubercle bacilli in the sputum, and this cannot be controlled by collapse therapy; and secondly, although such ulcerations may heal naturally, they do so with stenosis which leads to the same deleterious effects on the portion of the broncho-pulmonary system beyond the obstruction as does any other form of obstruction, together with others due to the specific tuberculous nature of the infection—secondary bronchiectasis, cavity-formation, sometimes of tension type, atelectasis and, eventually, complete disorganization of the lung. Streptomycin was shown to have very great value in the treatment of such lesions. In most cases ulcerations and granulation tissue healed; but where the lesion had progressed to the stage of stenosis, this was, of course, permanent, and in some instances stenosis developed during treatment pari passu with the healing of the more active lesions. It had already been observed that a similar favourable response might be obtained in cases of tuberculous laryngitis.

The next step consisted of a trial designed to determine whether liability to the emergence of streptomycin-resistant organisms could be diminished by modified schemes of intermittent dosage. These were unsuccessful and need not be examined in detail.

At this stage, therefore (i.e. about the end of 1948), the position was that streptomycin had to be regarded as an agent which could normally be used effectively once, and once only, in the often prolonged treatment of pulmonary tuberculosis. It was obviously unwise to use it alone in the treatment of chronic lesions, in which persistence of cavitation, with continued excretion of probably streptomycin-resistant organisms, was a likely result of prolonged administration of the drug. It was clearly indicated in cases of acute bilateral disease in which no other form of treatment was possible; even in these it had to be regarded mainly as a preparation for some more definitive form of treatment. Active tuberculous bronchitis and acute spreads of disease occurring in the course of recognized cases of pulmonary tuberculosis were known to respond well, and constituted other clear indications for streptomycin. In short, it seemed likely that the correct place of streptomycin in pulmonary tuberculosis was as a means of salvaging a certain number of patients with otherwise hopeless active disease; as a preparation for and adjuvant to collapse therapy and lung resection; to treat acute spreads of disease in patients with previously inactive disease or under treatment by other methods; and to treat active tuberculous bronchitis and laryngitis.

Para-amino-salicylic Acid

The action of PAS against the tubercle bacillus was first reported by Lehmann in 1946, and in the years immediately after this many claims for the beneficial effect of the drug in human tuberculosis were made. Accordingly, in December 1948, a clinical trial was started in which the effects of PAS, of streptomycin, and of PAS and streptomycin combined were compared in the treatment of cases of acute pulmonary tuberculosis similar to those investigated in the first trial. Streptomycin was given in a single intramuscular dose of 1 g. daily and PAS in a dosage of 20 g. daily by mouth, divided into four doses of 5 g. each. The object of this trial was twofold; first, to compare the clinical response in the three groups and, secondly, to find whether the addition of PAS had any effect in delaying the emergence of strepto
mycin-resistant strains. The reduction of the dose of streptomycin to 1 g. daily was the result both of experience gained in the trials of various schemes of dosage, mentioned briefly above, and of American reports; these both indicated that 1 g. daily was comparable in effectiveness to 2 g., and produced fewer and less severe toxic reactions.

So far as the clinical response was concerned, the effect of PAS alone could only be assessed by comparison with the untreated group in the original streptomycin trial. This procedure seemed justifiable since the cases were selected for the trial on the same criteria, and by a similar panel of physicians. Both this comparison with the untreated group of the first trial and the impressions of the physicians in charge of the patients confirmed that PAS has a beneficial effect in acute forms of pulmonary tuberculosis, though this is not as great, or as rapid, as is observed with streptomycin. The groups treated with streptomycin alone, and with streptomycin and PAS combined, both showed the same sort of favourable response as had been observed with streptomycin in the first trial. There was no statistically significant difference between the clinical or radiological results in these two groups, but there was a suggestion that the response to joint treatment was better than that to streptomycin alone. It should be noted that the treatment period was relatively short, being fixed at three months; this probably militated against PAS since the beneficial effects of PAS are generally agreed to be more slowly manifested than those of streptomycin. The most striking result of this trial, however, was the clear indication that 20 g. daily of PAS, given to patients receiving streptomycin, led to a dramatic diminution in the number in whom resistant strains of the tubercle bacillus emerged. Of the 49 patients receiving 1 g. streptomycin daily, without PAS, 33 (i.e. 67 per cent.) produced strains with a resistance ratio greater than 10. Of the 48 patients receiving both streptomycin and PAS, only 5 (i.e. 10 per cent.) produced such strains, and in these the resistance of the bacilli was, in general, at a rather lower level than in those receiving streptomycin alone. It is technically more difficult to estimate PAS than streptomycin resistance, and considerably less is known about it. Thirty-seven patients receiving PAS alone were investigated for the sensitivity of their organisms; at least one strain resistant to PAS was isolated from 12. Of the 30 patients receiving both drugs only two produced resistant strains. PAS resistance seems in general to be less permanent than streptomycin resistance.

The most obvious practical application of this knowledge was that PAS should always be given with streptomycin. The dose of PAS used in the trial, 20 g. daily, represents the reasonable limit of most patients' tolerance; for PAS is a nauseous drug to take, its disagreeable taste is well-nigh impossible to disguise, and even if it is given in cachets or specially coated granules it may still produce unpleasant gastric symptoms such as nausea, epigastric discomfort and anorexia. The only other toxic effects of PAS are rare and not serious; the chief ones are due to sensitization to the drug and consist of skin rashes, usually of an erythematous type, and drug fever. Both of these clear up rapidly on discontinuing the drug, and desensitization by the administration of gradually increased daily doses, starting with 0.1 g. or 1.0 g., depending on the degree of sensitization, is usually possible. The toxic effects of PAS are thus less serious than those of streptomycin. Nevertheless, the unpleasant gastric symptoms which so many patients experience while taking PAS in full doses made it desirable to find out whether a smaller dose than 20 g. a day might suffice to delay the emergence of streptomycin-resistant strains. A trial designed to answer this question is now nearing completion; preliminary results indicate that 5 g. is certainly, and 10 g. probably, less effective than 20 g. daily, and until further information is available it appears wise to prescribe PAS, 20 g. daily or, if this is not tolerated, up to the limits of the patient's tolerance whenever streptomycin is given.

**Modified Regimes of Streptomycin and PAS Dosage**

Some evidence has been advanced in the United States that a regime of continuous administration of PAS in the usual dose daily, together with streptomycin, 1 g. or 2 g. every third day, may be as effective as the continuous administration of both drugs, and that it is even less liable to give rise to the emergence of resistant strains of bacilli. Such regimes are clearly deserving of further study.

**Dihydrostreptomycin**

Dihydrostreptomycin, which is prepared by the hydrogenation of streptomycin, was introduced as a less toxic but equally effective variant of streptomycin. It now appears that although dihydrostreptomycin is less liable than streptomycin to give rise to vestibular dysfunction, it is more liable to give rise to deafness. Moreover, the latter, when it appears, is irreversible. Since the disturbance of vestibular function produced by streptomycin is rarely produced by the schemes of dosage at present used, and since, even when it does appear, compensation for it occurs in most cases in the course of time, it is evident that the
potential toxic effects of dihydrostreptomycin are more serious than those of streptomycin, and the latter is, therefore, the preferable drug.

Current Indications for Streptomycin-PAS Treatment

The knowledge that, if PAS is given concurrently, streptomycin-resistance might not be so serious a limiting factor has naturally led to a tendency to wider range in indications for streptomycin treatment in pulmonary tuberculosis. The practice of different physicians, and in different centres, however, still varies widely. It should be remembered that the danger of streptomycin resistance has not been removed entirely; it has simply been diminished by the addition of PAS. Moreover, in tuberculosis, the processes of healing and repair are much more complex, both immunologically and anatomically, than they are in acute infections; and in pulmonary tuberculosis especially, the mechanical factors provided by the presence of cavities and of obstructive lesions of the bronchi may not only call for treatment in addition to the use of effective antibacterial agents, but also interfere with the proper effect of such agents. A tentative list of indications for combined streptomycin and PAS treatment in pulmonary tuberculosis might now be made up as follows:

1. As Primary Treatment

   In acute tuberculous bronchopneumonia, especially if the condition is bilateral, antibacterial treatment is usually the only possible initial step; in many cases of this sort, however, even after a favourable response to such treatment, residual active lesions may require further treatment on accepted lines. Similarly, active tuberculous bronchitis requires initial treatment with streptomycin and PAS, even though further measures may be required later to deal with pulmonary lesions, depending upon the response to treatment and the presence or absence of bronchial stenosis (Figs. 10, 11 and 12). Pulmonary tuberculosis of diffuse miliary distribution is, of course, another indication for primary antibacterial treatment.

2. As Primary Treatment Combined with Collapse Therapy

   Certain acute predominantly or entirely unilateral forms of pulmonary tuberculosis respond extremely well to streptomycin and PAS, combined with early collapse therapy. If the latter takes the form of phrenic paralysis and pneumoperitoneum, it may be instituted without delay (Figs. 1, 2 and 3). If the distribution of the disease demands artificial pneumothorax (A.P.), it is best to wait for several weeks until the activity of the disease has been controlled; a normal temperature and a sedimentation rate of not above 20 mm. in the first hour are desirable before inducing A.P. Occasionally a patient with acute bilateral lesions may be made suitable for bilateral A.P. by streptomycin and PAS; and sometimes other combinations of collapse methods may be used, such as A.P. on one side, phrenic paralysis on the other, and pneumoperitoneum, or A.P. on one side and surgical methods on the other (Figs. 4 and 5).

3. To Prepare for later Collapse Therapy or Resection of Lung

   In some patients with extensive disease, fitness for surgical collapse therapy or resection may be attained only after a very prolonged course of antibacterial treatment. Among such patients are to be found some of the most gratifying results of modern treatment in pulmonary tuberculosis (Figs. 6 to 9).

4. To Deal with Acute Spreads of Disease in Patients already under Treatment

   Tuberculous disease may spread acutely in patients with older lesions which appear quiescent. This event is often a consequence of certain precipitating factors, such as intercurrent respiratory infections, operations under general anaesthesia and haemoptysis. Acute spreads may also occur in patients under treatment, especially by such forms of collapse therapy as thoracoplasty, or after lung resection. Whatever the cause, an acute spread of tuberculous disease must be regarded as an absolute indication for the use of streptomycin and PAS (Figs. 10, 11 and 12). All available evidence indicates that the sooner after its appearance an acute tuberculous process in the lung is treated, the more satisfactory will be the response. Patients with known pulmonary tuberculosis who develop haemoptysis should receive streptomycin and PAS prophylactically, until the haemoptysis has ceased, and it has been established by radiography that the disease has not spread.

5. To Treat Complications of Pulmonary Tuberculosis

   Tuberculous laryngitis generally responds well to streptomycin. In many cases it complicates active pulmonary disease of a type which in itself requires antibacterial treatment. However, it also often complicates the advanced stages of chronic fibro-cavernous pulmonary tuberculosis, in which very little improvement of the lung disease is to be expected from streptomycin treatment. The relief of the very troublesome symptoms of tuberculous laryngitis by streptomycin and PAS is usually so dramatic that they should often be used even in this group of cases. Other established
methods of treatment of the laryngitis should not, of course, be neglected.

Tuberculous enteritis is another complication of pulmonary tuberculosis which usually responds well to streptomycin and PAS. Similar considerations to those suggested for tuberculous laryngitis apply to the desirability sometimes of using antibacterial treatment more or less symptomatically in advanced cases of pulmonary tuberculosis complicated by enteritis.

6. In Association with the Surgical Treatment of Pulmonary Tuberculosis

Streptomycin and PAS will frequently have been used in the preparation of patients for surgical treatment, as suggested in paragraph 3 above. There is still no agreement about whether streptomycin and PAS should be used as a routine to 'cover' the stages of thoracoplasty operations. On the whole, the risk of spread after a properly planned thoracoplasty is so small, and the prospect of its successful treatment by streptomycin and PAS started as soon as there is clinical or radiological evidence of spread is so good, that many surgeons prefer not to use streptomycin and PAS as a routine during thoracoplasty operations.

Operations for resection of the lung in pulmonary tuberculosis present rather different problems. There is a special risk of infection of the pleura at the operation, and it will frequently

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FIG. 1.—Girl, aged 17 years. Consolidation of right lower lobe. T.B. in gastric contents. Temperature swinging up to 101.4°F. Streptomycin 1 g. and PAS 20 g. daily started April 12, 1951, and continued for three months. Temperature settled in seven days.

FIG. 2.—The same after two months of antibacterial treatment. Phrenic paralysis and pneumoperitoneum carried out within three weeks of starting treatment. Normal temperature, gain of 7 lb. in weight.

FIG. 3.—The same, one year after starting treatment. In excellent health. The tuberculous consolidation has resolved.
FIG. 4.—Woman, aged 21 years. Fairly acute tuberculous disease in the upper parts of both lungs, with cavitation. T.B. in sputum. Temperature swinging up to 100°F. E.S.R., 50 mm. Streptomycin 1 g. and PAS 20 g. daily started February 22, 1950, and continued for three months.


FIG. 6.—Woman, aged 29 years. Extensive tuberculous disease in both lungs, with cavitation in both upper lobes. Temperature swinging up to 99.4°F. E.S.R. 65 mm. Streptomycin, 1 g. daily, from June 2 to December 14, 1948.

FIG. 7.—The same after six months’ treatment. Much resolution of active disease. Tomogram showed persistent cavity at right apex. Both pleurae adherent.
happen that tuberculous lesions, unsuspected clinically, are present in the cut bronchus. For these reasons it is customary to administer streptomycin and PAS prophylactically before and after such operations.

Types of Disease in which further Investigation of the Indications for Streptomycin and PAS is Required

In some of the commonest types of pulmonary tuberculosis no satisfactory evidence is yet available whether or not streptomycin should be used. These include:

1. Minimal Pulmonary Tuberculosis without Symptoms

Patients with lesions of this sort are being discovered with increasing frequency, largely as a result of mass radiography. They will normally be investigated initially for evidence of activity. If such evidence is found the case may present some of the indications for antibacterial treatment outlined above. If, under observation, a symptomless minimal lesion shows no evidence of instability, it appears at least doubtful whether streptomycin is required. This is clearly a question which cannot be decided on a priori considerations. A controlled study of this important problem, though admittedly difficult to organise and likely
to produce results only after a very long period of observation, is urgently required.

2. Tuberculous Pleural Effusions
   Rather similar considerations apply to the common tuberculous pleural effusion without evidence of gross lung disease. Whether streptomycin has any place in the treatment of these is as yet uncertain. In individual cases, of course, indications for such treatment may arise, but no generally applicable rule can yet be made.

3. Primary Tuberculous Lesions
   Caseous lymphadenitis is known to respond poorly, if at all, to streptomycin, and since many of the pulmonary manifestations of primary tuberculosis are due directly or indirectly to enlarged and caseous hilar lymph nodes, they would not be expected to respond well to antibacterial treatment. Where, however, there is a frank tuberculous pneumonia, the ordinary response is to be expected. Since it is often impossible clinically to determine whether a pulmonary shadow associated with primary tuberculosis is due to frankly tuberculous changes in the lung, it is equally impossible to forecast the probable result of streptomycin treatment. In general, if a child with primary tuberculosis is febrile, or presents other evidence suggestive of activity of the infective process, streptomycin and PAS should be given a trial.

Contraindications to Streptomycin Treatment
   There are few cases in which streptomycin is absolutely contraindicated, but a very large number in which such treatment is so unlikely to produce favourable results that it is not worth attempting.

1. In chronic fibrotic disease the symptoms may be due not to activity of the tuberculous progress but to impairment of respiratory function by fibrosis and emphysema, to intercurrent bronchitis, or to secondary infection in the damaged broncho-pulmonary tree. In such cases not only is streptomycin unlikely to be effective, but the risk of the appearance of resistant strains of bacilli is certainly
greater than in cases with acuter and more responsive lesions.

Similarly, in cases with chronic fibrous-walled cavities not susceptible to any form of collapse treatment or resection, no favourable effect on the cavity is to be expected from streptomycin, and the risk of the appearance of resistant strains of bacilli is high. Of course, in such cases, the most determined efforts to find a possible means of combining streptomycin treatment with treatment directed towards closure of cavities must be made.

2. **Patients with streptomycin-resistant organisms.** At present these will nearly always be found to have received long courses of streptomycin in the past. As time goes on it is unfortunately to be expected that the number of unsuccessfully treated patients who are sources of infection with resistant organisms will increase, and hence the number of fresh infections with such organisms will probably also increase. Fortunately, at present this is a rather theoretical consideration.

3. **The age of the patient** must be taken into consideration in deciding whether streptomycin administration is advisable. The toxic effects upon vestibular function become much more frequent and severe in older age groups. Moreover, patients in these age groups often have predominantly fibrotic disease in which the response to streptomycin is unlikely to be dramatic. Of course, if a patient at any age is found to have an acute tuberculous broncho-pneumonia, streptomycin and PAS must be given. In older people some of the less urgent indications for streptomycin may be met by a long course of PAS alone, and regimes of continuous PAS with intermittent streptomycin dosage may be particularly useful in this age-group.

4. **In patients with poor renal function** caution is required in the administration of streptomycin. An important, though relatively small, group of such patients consists of those with amyloidosis affecting the kidneys; in such patients major surgical procedures may be under consideration for the eradication of a tuberculous focus. Streptomycin is excreted by the glomeruli of the kidney and thus, if glomerular function is impaired, delay in excretion may lead to very high levels of streptomycin in the blood and severe toxic symptoms after administration of normal doses. This does not constitute a contraindication to the use of streptomycin provided due care is taken. In patients whose renal function is impaired, the level of streptomycin in the blood 24 hours after the administration of a suitable dose intramuscularly should be estimated and the dose adjusted accordingly. It may be possible in patients with impaired renal function to maintain effective blood-levels of streptomycin by the administration of as little as 0.25 g. every other day.

**Other Anti-Tuberculous Agents**

The sulphones, while possessing some antibacterial activity, have proved to be so toxic clinically and to require such careful laboratory control for the avoidance of serious toxic effects, that they are unlikely again to enter into clinical practice in the treatment of pulmonary tuberculosis.

The thiosemicarbazones have a strong antibacterial effect both in vitro and in the experimental animal. Clinically, however, their activity appears to be approximately equivalent to that of PAS, and their toxic effects, notably haemolytic anaemia, are troublesome. Their activity as an adjuvant to streptomycin has not been completely investigated, but since it appears unlikely to be superior to that of PAS, it is very doubtful whether the latter drug will be displaced.

**Antibiotics.** Several new antibiotics have been shown to have a tuberculostatic effect, but few of them have been sufficiently non-toxic to be considered seriously for clinical use. Of these the most promising are neomycin and viomycin.

Neomycin was isolated in 1949 from *Streptomyces fradiae.* It is very active in vitro against the tubercle bacillus, including streptomycin-resistant strains. However, it has serious toxic effects, the principal of which are renal damage and deafness, which may be progressive even though administration of the drug is stopped. Unless it can be shown that these toxic effects are due to impurities which can be eliminated, it seems unlikely that this drug will enter into clinical practice.

Viomycin, derived from *Streptomyces florideus* or *punicus,* was isolated in two different centres in 1950. It has a strong action in vitro against the tubercle bacillus and relatively little against non-acid-fast organisms. In the experimental animal its anti-tuberculotic activity seems to be comparable with that of streptomycin, though slightly less. It is less toxic than any of the preparations of neomycin so far tested, but gives rise to renal damage manifested by albuminuria and casts, to vestibular disturbance and partial deafness and to electrolyte imbalance with a fall in potassium, calcium, phosphorus and chlorides, and increase in CO₂ combining power in the blood. Only preliminary information is as yet available on clinical trials of this drug. While it seems to have an anti-tuberculotic activity comparable with that of streptomycin, its toxic effects are more severe, and it is probable that if it finds a place in therapeutics this will only be in the treatment of streptomycin-resistant infections.

There is some evidence that terramycin, an
antibiotic whose range of antibacterial activity is in most respects similar to that of aureomycin, may have slight anti-tuberculous activity. This, however, is manifest, if at all, only with very large doses, and no results of clinical trials are yet available.

Summary

At present the administration of streptomycin intramuscularly concurrently with para-aminosalicylic acid by mouth is the standard method of antibacterial treatment in pulmonary tuberculosis.

The investigations which have led to the general adoption of this combined treatment are outlined and current indications for its use briefly discussed.

Though streptomycin has serious toxic effects and limitations imposed by the ability of tubercle bacilli to become resistant to its action, investigations of some newer antibiotics hold no promise that any so far discovered can replace it.

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Intermittent Streptomycin Regimes

Dihydrostreptomycin

Thiosemicarbazones

Neomycin

Viomycin

Terramycin

DEEP PELVIC RETRACTOR

Good retraction is an essential for deep dissection in the pelvis.

The retractor here illustrated, made for me by Messrs. John Bell & Croyden, has certain advantages.

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E. G. MUIR,
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J. G. Scadding

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