REFRESHER COURSE FOR GENERAL PRACTITIONERS

CHEMOTHERAPY—III. STREPTOMYCIN

BY

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Streptomycin was the first successful product of the world-wide search for further antibiotics with chemotherapeutic powers following the demonstration of these properties in penicillin. It is formed by a soil fungus, *Streptomyces griseus*, and is of more complex chemical structure than penicillin. It is basic in nature, and the compounds which have been used in therapeutics are the hydrochloride, sulphate, and calcium chloride complex. More recently a slightly modified form, dihydrostreptomycin, has been introduced, for which it is claimed that toxic effects are less often produced when administration has to be prolonged.

Administration

When streptomycin is given by mouth its behaviour is entirely different from that of penicillin: it is not destroyed, but neither is it absorbed. Hence this route is indicated only in order to produce an effect in the intestinal tract itself. To obtain a systemic effect, streptomycin must be given, like penicillin, by intramuscular injection. Absorption after injection is somewhat slower, as also is excretion: following a single full dose—for example, of 1 g.—the drug can be detected in the blood for eight hours or more. It reaches all important areas in the body except the cerebrospinal fluid; like penicillin, it has to be injected intrathecally for the treatment of meningitis. It is excreted by the kidney, and thus attains a high concentration in the urine.

Dosage varies within much narrower limits than that of penicillin, because streptomycin is by no means free from toxicity. A daily dose of 4 g. has rarely been exceeded, and for long-continued treatment it is now more commonly 1 g. How many doses are given daily depends on the condition being treated. Tuberculosis is a special case, since a single daily dose (or injections at even longer intervals than one day) is used in treating this disease. On the other hand, the short-term treatment of an acute infection is usually accomplished by giving two, three, or four daily doses. It cannot be said that the best system for this kind of purpose has yet been defined by any deliberate comparison.

Mode of Action

Streptomycin is actively bactericidal. There is no optimum concentration for this effect, as with penicillin: the higher the concentration, the more rapidly are bacteria killed. The equivalent of that attainable in the urine will in a nutritive medium *in vitro* markedly reduce a susceptible bacterial population in a few minutes and extinguish it within an hour. The lower concentrations reached in the blood and tissues cannot act so rapidly, but there is no reason to assume any qualitative difference in the effects produced there.

If this were all that need be said about the action of streptomycin on bacteria, it would be a most remarkable drug and much more regularly successful than in fact it actually is. Its disadvantage is that bacteria can acquire a high degree of resistance to it with extraordinary rapidity. This is of such a degree that further treatment is futile, and it has often been observed within 24 hours of the beginning of treatment, though its appearance may be

delayed rather longer than this. The change is also permanent. It follows that in many cases only a single course of treatment can be given: either this succeeds, the infection being totally eradicated, or further treatment is precluded by acquired bacterial resistance. This is sometimes accompanied by "dependence"—the existence in the bacterial population of some cells which actually utilize streptomycin as a nutrient and cannot grow without it.

A sensible conclusion from these facts would seem to be that treatment should be brief and vigorous, allowing the least possible opportunity for bacterial recovery. This policy would require that the drug concentration in the blood and tissues be well maintained, and thus would call for frequent administration.

The time needed for tubercle bacilli to acquire resistance corresponds with their much slower growth, and is at least five weeks. Systems of dosage different from those applicable in other conditions have been found advisable for treating tuberculosis.

Toxic Effects

In patients with impaired renal function, streptomycin may accumulate in the body and has occasionally thus caused death. The only serious common toxic effect is on the eighth nerve, vestibular disturbances (vertigo and incoordination) being produced first, and deafness in more severe cases. Either effect may be permanent, but some degree of recovery occurs in more mildly affected patients.

These changes are never produced by any ordinary doses given only for a short period, such as a week. They are the product of long-term treatment, and their frequency and severity are then directly proportional to the dose: if this does not exceed 20 mg. per kg. daily no permanent damage will result. Intrathecal injections are particularly apt to have these effects. It is claimed for dihydrostreptomycin that it is much less apt to produce them, but this claim has not been fully borne out in recent experience.

Indications

Penicillin being the perfect chemotherapeutic agent, there is no need for any other except in infections insensitive to it. There are unfortunately many such, but each new discovery is effective against some of them. Streptomycin began this process by subtracting from the list infections due to the tubercle bacillus and to a number of Gram-negative bacilli. A satisfactory table of species classified according to their sensitivity to streptomycin cannot be prepared because strain variation in sensitivity is so marked. It must suffice to say that *Mycobacterium tuberculosis*, unless it has had previous contact with streptomycin, is uniformly and highly sensitive, being inhibited by not more than 0.2 µg. per ml.; that almost all species of Gram-negative bacilli are also sensitive, but to concentrations varying from as little as 0.1 to as much as 25 µg. per ml. or more; and that most penicillin-sensitive organisms, such as streptococci and staphylococci, are usually also sensitive to streptomycin, though to a less degree.

The main clinical indications for streptomycin are therefore tuberculosis, various infections due to Gram-negative

bacilli, and occasionally coccal infections if they are abnormally penicillin-resistant. The latter are usually much better controlled by "aureomycin," if this is obtainable.

Tuberculosis

This is no place to discuss in detail the indications for streptomycin in various forms of this disease or the systems of dosage advisable. At the risk of seeming to belittle the functions of general practice, it has to be said that the decision to undertake this treatment is one in which the expert should usually have a say, while the conduct of the treatment itself may be difficult outside a hospital or sanatorium.

Streptomycin is of course imperatively indicated in otherwise fatal forms of the disease—in miliary tuberculosis and meningitis. It has been strikingly successful in rapidly extending lung infections and in ulcerative tracheo-bronchitis. Its place in the treatment of more chronic disease, whether of the lung or elsewhere, is much more dependent on the features of the individual case and on the possibilities of combined surgical treatment.

Tubercle bacilli cannot be successfully attacked either in a cavity in the lung or in a large caseous focus in, for example, the kidney. There is thus no prospect of eliminating the infection in patients with such lesions. The only effect will be to limit extension while treatment continues, and to deal with bacilli in smaller and more accessible foci. This may be valuable if surgery is undertaken at the same time, and particularly if it is necessary in order to render surgery feasible. On the other hand, to rely solely on streptomycin in a case of chronic pulmonary tuberculosis with cavitation is expecting altogether too much of the drug, and will rarely produce any ultimate benefit.

Indiscriminate treatment may be positively harmful, not only to the patient but to others, because its effect is usually to make the bacillus resistant to the drug. This means that streptomycin will be useless in any subsequent acute exacerbation, and in treating the disease in anyone else who may acquire it from this patient. The danger of breeding and spreading streptomycin-resistant strains of tubercle bacilli is a very real one, and disastrous instances of its results have already been seen in the U.S.A. American studies have made it clear that cavitation is a major factor in promoting acquired bacillary resistance in treated patients. Fortunately combined treatment with *p*-aminosalicylic acid (given orally at the rate of 12 g. daily) diminishes the frequency of acquired resistance as well as reinforcing the action of streptomycin on the tubercle bacillus.

Plague and Tularaemia

It may be that in years to come these will be the only diseases for which streptomycin is used. Both are derived from wild-animal reservoirs in which the micro-organism has no chance of acquiring resistance to the drug, and in both it is strikingly successful. In pneumonic as well as bubonic plague streptomycin has been found curative, and in tularaemia, even in its more severe forms, all reports are agreed that the effect is immediate and invariable. These are in fact the two specific diseases in which the drug has had its greatest success, and we should not forget that there are some parts of the world in which to possess an effective treatment for plague constitutes a therapeutic advance of the first order.

Septicaemia

The forms of septicaemia in which streptomycin is principally indicated are those due to Gram-negative bacilli of

coliform type—usually *Bacterium coli* itself, *Proteus vulgaris*, or *Pseudomonas pyocyanea*—and seen as complications of severe urinary-tract infection, middle-ear disease, wound sepsis, and lesions of the intestinal tract. It is important to determine the sensitivity of the organism to the drug, since if this is subnormal another antibiotic such as "chloromycetin" may be indicated. Full and frequent doses (1 g. three or four times a day) are required until the generalized infection has been overcome.

Meningitis

There are several kinds of meningitis in which Gram-negative bacilli are concerned for which streptomycin is strongly indicated. One is the spontaneous form occurring in young infants and due to *Bact. coli* or sometimes to a species of *Salmonella*. In *Haemophilus influenzae* meningitis, usually seen at a later stage of infancy, streptomycin should also be used, but sulphadiazine and immune serum may be advisable in addition. Thirdly, *Ps. pyocyanea*, *Proteus vulgaris*, or other coliform bacilli may cause meningitis complicating trauma or otitis media, or resulting from contamination of materials used in operative procedures on the central nervous system; the meningitis which has unfortunately followed spinal anaesthesia or even simple lumbar puncture is an example.

Streptomycin should be given intrathecally as well as intramuscularly: the full daily dose by this route is 100 mg. for an adult. Here again not only the initial but subsequent tests of sensitivity (if cultures continue to yield growth) should be carried out, and one of the newer antibiotics substituted if resistance develops.

Urinary-tract Infections

Streptomycin is the most potent of all urinary antiseptics, with a wide range of activity. Properly used, it will often succeed, even in long-standing infections, when everything else has failed. There are three main conditions which must be satisfied in order to ensure a good prospect of success. First, any underlying predisposing cause must if possible be removed; in the presence of obstruction or calculi only temporary benefit, if any, can be expected.

Secondly, it must be determined by cultivation of a properly collected fresh specimen of urine and by sensitivity tests of the organisms found that streptomycin is the right drug to use. If a staphylococcus, a streptococcus, or even *Proteus vulgaris* is found, penicillin is likely to be preferable. On the other hand, *Bact. coli*, *Bact. aerogenes*, *Ps. pyocyanea*, and various paracolon bacilli, which should normally be more or less sensitive to streptomycin, are nowadays sometimes found to be completely resistant. This is often the consequence of previous treatment, but is now beginning to be seen in patients who have never had the drug, and must therefore be attributed to the dissemination of resistant strains from other treated persons, a development which has long been foreseen and which must tend steadily to restrict the field of usefulness of streptomycin.

When treatment has been decided on, the third condition to secure is alkalinity of the urine, since the drug possesses little activity in an acid medium. Unless the infection is due to a urea-fermenting organism, when of course the urine will be persistently alkaline owing to the formation of ammonia, it may be necessary to give 2 g. of sodium bicarbonate four times a day for one or two days before this condition is secured. The specimen tested should be that passed on waking in the morning, and not until this is at least neutral to litmus, if not frankly alkaline, should

streptomycin be given. The object is then to maintain a high concentration in the urine for the short period required to sterilize it, and theoretically three or more doses daily are advisable: two have been used with success, but one only is inadequate. A dose of 0.5 g. three times a day or of 1 g. twice a day will usually suffice, though more vigorous treatment is safer and can do no harm in the short period necessary.

Sterility in successful cases is achieved in less than 24 hours, and it is useless to continue for more than three days: to what extent the period of treatment can be shortened further without risk of failure is not yet known, but in my own experience patients have been cured of long-standing infections by only three and four 0.5-g. doses. If the organism persists it will usually be found to have acquired a high degree of resistance, precluding any further treatment with this drug.

Intestinal Infections

Streptomycin given by mouth—for example, in 1-g. doses four times a day—is of value in bacillary dysentery and in acute salmonella enteritis, although, unfortunately, it does not seem to diminish the liability to subsequent persistence of a carrier state. Its usefulness in infantile gastroenteritis is a subject of dispute, possibly because there are varieties of this condition, some of its imperfectly known causes being streptomycin-sensitive and others not. Despite its *in vitro* activity against *Salmonella typhi*, the drug is practically useless in enteric fever, for reasons which are still obscure. It may be used either alone or together with sulphasuxidine to disinfect the bowel preparatory to operations on the colon: administration should not be begun more than two days before operation, since otherwise resistance may have been acquired before this takes place.

It may be added here that streptomycin and other antibiotics have been successfully used in peritonitis. It is exceedingly difficult on the available evidence to decide what their effect is, and which is likely to be most useful in any given case, but owing to its wider range of activity, including many intestinal species (with the notable exception of the clostridia), streptomycin is at least theoretically preferable to penicillin.

Lung Infections

A strong indication for streptomycin has been pneumonia due to *Bact. friedländeri* or *H. influenzae*. How far it should be replaced by the newer antibiotics for this purpose is not yet clear. More chronic lung and bronchial infections due to these and similar organisms may also be treated, but the benefit is likely to be only temporary if there are underlying structural changes, as in bronchiectasis. The value of the drug in whooping-cough is doubtful.

Local Application

Like penicillin, streptomycin can also be applied locally in a number of ways. It has been administered by inhalation for infections of the bronchial tree. It can be employed in the same way as penicillin for infections of the conjunctiva, cornea, and the interior of the eye itself. The instillation of a solution is useful in the treatment of otitis externa and otitis media when Gram-negative bacilli such as *Proteus vulgaris* and *Ps. pyocyanea* are concerned. The same organisms can rapidly be eliminated from superficial wounds, burns, and such lesions as varicose ulcers by spraying a solution or the application of dressings wet with it, if these operations and the general aseptic management of the case are conducted with care and skill.

Only a short period of application should be necessary for such purposes. It has to be remembered that repeated contact with streptomycin over a period of some weeks leads to sensitization. This has been seen frequently in nurses handling the drug, who develop erythematous and oedematous lesions of the face and hands. It should be possible by careful technique to avoid such contact in making up and administering doses, but once the condition is established there is no remedy but avoidance of any further dealings with the drug.

INTERNATIONAL SOCIETY OF HAEMATOLOGY

MEETING IN CAMBRIDGE

The third congress of the International Society of Haematology was held in Cambridge under the presidency of Sir Lionel Whitby from August 21 to 26. Some 500 delegates attended from many parts of the world, and nearly 200 papers were read during the conference, grouped under the four headings, anaemia, leukaemia, problems of coagulation, and immuno-haematology.

The social events included a reception by the president on Monday, August 21, and the society's dinner on Wednesday, August 23, at which it was announced that Dr. A. Pavlovsky, of Argentina, would be president for the next congress. A reception was also held by the vice-chancellor in Pembroke College on Tuesday, August 22, and garden parties were given by Captain R. G. Briscoe, Lord Lieutenant of the county, at Longstowe Hall, and by Sir Lionel Whitby in the grounds of Downing College.

A number of delegates showed scientific exhibits, and several commercial firms displayed products of interest to haematologists. Films were shown and a demonstration of colour television microscopy was given by Messrs. W. G. Pye and Co., Ltd.

Anaemia

The first meeting on this subject was devoted to therapy, and Dr. E. LESTER SMITH (England) opened with a paper describing the isolation and properties of vitamin B₁₂. The effect of its oral administration in pernicious anaemia in the absence of known sources of intrinsic factor was then discussed by Dr. E. H. MORGAN *et al.* (U.S.A.), and Dr. GRACE GOLDSMITH (U.S.A.) described the effects of vitamin B₁₂ given orally and parenterally and of a concentrate of intrinsic factor in macrocytic anaemia. Other contributions concerned the therapeutic effect of vitamin B₁₂ obtained from a variety of new sources, the use of the vitamin in the treatment of tropical macrocytic anaemia, and the effect of cobalt therapy in various anaemias. A further session on pernicious anaemia and vitamin B₁₂ was opened by Dr. O. P. JONES (U.S.A.), who described the action of anti-anaemic substances on embryonic prehepatic erythropoiesis. Dr. G. LARSEN (Norway), describing the pathogenesis of the macrocyte, pointed out that even in adequately treated pernicious anaemia macrocytes occur in the peripheral blood. These cells have a normal mean corpuscular volume, but their thickness is about half normal. Their life-span is about 40 to 60 days, and they are more resistant than normal cells to hypotonic saline. Experiments were described which suggested that there may be alterations in the haemoglobin of these macrocytes, with a failure of normal haemoglobin maturation. Drs. J. MOSBECH and A. VIDEBAEK (Denmark) presented the results of an investigation, with adequate controls, into the prognosis in 301 cases of pernicious anaemia (see *Journal*, August 12, p. 390). Further papers and discussions centred on the question of whether vitamin B₁₂ alone was a fully adequate haemotherapeutic agent in pernicious anaemia. Experimental work on the megaloblast problem and the maturation of erythroblasts was discussed by Drs. G. ASTALDI (Italy), D. DANTCHEV (Bulgaria), and P. COLOMBO (Italy).