REFRESHER COURSE FOR GENERAL PRACTITIONERS

CHEMOTHERAPY—IV. THE NEWER ANTIBIOTICS

BY

LAWRENCE P. GARROD, M.D., F.R.C.P.

Bacteriologist, St. Bartholomew's Hospital; Professor of Bacteriology, University of London

A world-wide search for further antibiotics has now been in progress for nearly ten years. It has been far more extensive and systematic in the U.S.A. than anywhere else, and it is therefore not surprising that all its results of outstanding value are American monopolies. This survey has ranged over the whole plant kingdom, and interesting substances with antibacterial properties have been recovered from such things as algae, toadstools, bananas, and hops. They have also been found in many species of bacteria, some of them pathogenic. Despite this profusion and variety, properties such as to qualify antibiotics as chemotherapeutic agents are almost confined to those derived from the following three sources.

Higher Fungi.—*Penicillia* and *Aspergilli* in particular are frequent producers of antibiotics, but almost all of these other than penicillin itself are toxic, and no other is a suitable chemotherapeutic agent.

Actinomycetes.—These are the source of streptomycin, discovered in 1944, and of "aureomycin" and "chloromycetin," which have been known since 1948. These two are much the most important of the newer discoveries, and form the main subject of this article. Terramycin was first described only a few months ago, and its potentialities are still largely unexplored, but it is of similar nature to the two foregoing. Neomycin seems likely to prove too toxic for therapeutic use.

Bacilli.—This name is used in its generic sense, denoting Gram-positive sporogenous aerobes. These are the source of tyrothricin (originally "gramicidin"), now recognized as suitable only for local application, and of the polymyxins (including "aerosporin"), subtilin, bacitracin, ayfivin, licheniformin, and other substances which have been extensively studied and found to possess marked chemotherapeutic activity, susceptible organisms including many species of Gram-negative bacillus and in some cases the tubercle bacillus. Their disadvantage is a strong tendency to produce renal tubular degeneration, resulting in albuminuria and sometimes anuria. It is not yet certain how far this risk can be minimized or whether it may sometimes be justifiable to take it in order to deal with a serious and otherwise resistant infection.

Aureomycin and Chloromycetin

Except in a few research centres, these antibiotics are at present obtainable in this country only from Ministry of Health supply depots and are employed for the treatment of a few specified diseases in which their use is most strongly indicated. It is to be hoped that in time they will be more freely available; in the meantime this account of them may seem a little out of place in a "refresher course." However, it is written to complete a series and partly in anticipation of the future.

Aureomycin, derived from *Streptomyces aureofaciens*, so named from its golden yellow colour, is manufactured by Lederle & Co. The mould from which it is obtained is incidentally a valuable growth-stimulant for pigs and poultry. Chloromycetin (Parke, Davis & Co.) was origin-

ally obtained from *Streptomyces venezuelae*, but has now been synthesized. The synthetic product is that now marketed under the alternative name "chloramphenicol." These two antibiotics have many properties in common, notably their pharmacological behaviour, which differs from that of penicillin or streptomycin, with the result that they are administered in a different way.

Administration

It is fortunate that neither has to be administered by injection, since chloromycetin has much too low a solubility, and aureomycin hydrochloride, besides being none too soluble, forms a strongly acid solution which causes serious damage and severe pain when injected intramuscularly. (A form of aureomycin suitable for intravenous injection is available in the U.S.A. although not yet in England.) These difficulties are more or less unimportant, since both drugs exert their full effect when given by mouth, and the fact that the patient has merely to swallow capsules instead of submitting to injections is their most obvious advantage.

Capsules of either contain 250 mg., and two, three, or four may be given three or four times a day. Absorption is comparatively slow and incomplete, since both drugs have a marked effect on the intestinal flora. This is to a great extent suppressed, and the stools become almost odourless. Owing to slow absorption, the drug persists in the blood for as long as 12 hours or more after a single dose, and frequent administration is therefore unnecessary. Aureomycin also reaches the cerebrospinal fluid, and has been used successfully in meningitis. The intrathecal administration of either is out of the question. Both are excreted in the urine in fairly high concentration, though only a fraction of the dose administered can be thus accounted for.

Toxic Effects.—No serious toxic effects are known. Aureomycin has hitherto been apt to cause nausea, with or without vomiting, and diarrhoea in a minority of patients, but a more highly purified product now coming into use is said to obviate even this minor disadvantage. Chloromycetin is apt to cause only anorexia and dryness of the mouth.

Mode of Action.—Whereas penicillin and streptomycin are both bactericidal, aureomycin and chloromycetin are purely bacteriostatic in their action. The viable count of susceptible bacteria exposed to them *in vitro* under conditions favouring growth remains almost constant for many hours. Whatever the nature of this effect, it is apparently not one from which bacteria can learn to escape. A moderate and temporary increase in resistance to chloromycetin has occasionally been observed in some species, but even less evidence of any capacity on the part of bacteria to develop resistance has been observed in studies of aureomycin. It appears therefore that habituation, an ever-present threat to the usefulness of streptomycin, is not likely to impair that of either of these drugs, whether in the treatment of individual cases or by the general propagation of resistant strains.

General Indications.—These two antibiotics have a wide range of activity, overlapping that of penicillin and other chemotherapeutic agents to a considerable extent. It is by no means all-embracing: neither drug has any useful action on the tubercle bacillus, nor has chloromycetin on the spirochaete of syphilis or on the clostridia. Generally speaking, chloromycetin is the more effective against Gram-negative species, and aureomycin against Gram-positive. For the present, both drugs are likely to be used only in infections resistant to other forms of treatment, and the more important of these have now to be specified. Pride of place has to be given, not to any bacterial infection, but to rickettsial and certain virus diseases, the conquest of which is much the most notable achievement of these drugs.

Indications for Chloromycetin

Rickettsial Infections.—It is a staggering fact that all forms of typhus are now fully and easily amenable to chemotherapy. The story of the therapeutic trial of chloromycetin in scrub typhus in Malaya is now well known. Laboratory studies having shown that the drug possessed marked anti-rickettsial activity, a small supply was taken to Malaya and tried in cases of scrub typhus, with results so dramatic that from the first they left no room for doubt. A disease normally lasting a fortnight or more and having a far from negligible mortality could regularly be terminated in about 48 hours by administering only a few grammes of the drug. Small doses would also prevent the disease in subjects deliberately exposed to it. Similar curative effects are now known to be obtainable in epidemic typhus, murine typhus, and Rocky Mountain spotted fever. Aureomycin is also known to be effective in these three infections and in Q fever, the latter, incidentally, being the only rickettsial infection known to exist in the British Isles. Its recent recognition here suggests the possibility that more cases may come to light and provide a new though presumably restricted field of usefulness for this drug.

Typhoid Fever.—The action of chloromycetin in this disease is also unequivocal, if less dramatic, and the indication for it is imperative. There is a lag of about 48 hours before the treatment produces abatement of fever, and administration has to be continued for over a week if relapse is to be prevented. Bacteraemia is regularly abolished, but the organism is not eliminated from the intestine, and the persistence of a carrier state is unfortunately not prevented. Severe cases of paratyphoid should also be treated with chloromycetin, as may other varieties of salmonella infection, including the acute enteritis caused by members of the food-poisoning group. Aureomycin, although possessing an *in vitro* activity against *Salm. typhi* not far removed from that of chloromycetin, has a disappointing and inconstant effect on typhoid fever. In this it behaves like streptomycin, both illustrating the fact that *in vitro* is not an invariable guarantee of *in vivo* activity.

Undulant Fever.—Chloromycetin has not been as extensively used as aureomycin in this disease, but the evidence, so far as it goes, is that their effects are similar, if not indistinguishable. Fever is terminated within a few days, and provided dosage is adequate and treatment continued long enough—usually 10 to 14 days—cure may be permanent. Relapse, if it occurs, responds to further treatment.

Other Indications.—Chloromycetin has been used successfully as a urinary antiseptic, despite the fact that a large proportion of it is excreted in an inactive form. Most organisms found in the urine are fully susceptible to it. Notable exceptions are *Ps. pyocyanea*, which is usually very

resistant, and *Proteus vulgaris*, which is moderately so. It does not seem to be necessary to control the reaction of the urine in order to favour its effect. The drug will also cure gonorrhoea, with the advantage that, since it has little action on *Treponema pallidum*, there is no risk of masking syphilis. Other conditions in which its possible usefulness remains to be more fully explored are whooping-cough, cholera, and bacillary dysentery.

Indications for Aureomycin

As already stated, aureomycin is known to share the efficacy of chloromycetin in most rickettsial infections.

Virus Diseases.—There is unequivocal evidence of the efficacy of aureomycin in three virus diseases—primary atypical pneumonia, psittacosis, and lymphogranuloma venereum—and the drug is definitely indicated in these conditions. To what extent chloromycetin can replace it for these purposes is not yet known: primary atypical pneumonia is said to respond to both, though some evidence suggests that aureomycin is preferable. It is also claimed that aureomycin can cut short an attack of herpes zoster, but this remains to be proved by further experience. These are the only virus diseases, except perhaps trachoma, at present known to be influenced. There is certainly no action on poliomyelitis or on influenza or the common cold.

Undulant Fever.—As already stated, both antibiotics are effective remedies for this disease, and aureomycin has been used the more extensively, proving its worth in infections due to both *Br. abortus* and *Br. melitensis*.

Pneumonia.—It has repeatedly been emphasized by American authors that aureomycin is effective in all forms of pneumonia, whether due to pneumococci, streptococci, or staphylococci, to Gram-negative bacilli such as *H. influenzae* or *Bact. friedländeri*, or to the viruses of primary atypical pneumonia or psittacosis. The results in pneumococcal pneumonia have been found to equal those obtainable with penicillin. This all-embracing activity makes it possible to treat the disease successfully without even taking the trouble to discover its cause. When no facilities exist for doing so, this will of course be an inestimable advantage, and it seems likely that when aureomycin becomes freely available it will become standard treatment for pneumonia in general practice.

Staphylococcal Infections.—Aureomycin is the answer to the increasingly serious problem of penicillin-resistant staphylococcal infections. Some authorities in America take the view that aureomycin should be given from the first in staphylococcal septicaemia and other severe infections, pending an estimation of the sensitivity of the organism to penicillin. If this proves to be normal, then penicillin can be continued alone. The drug may now be obtained for such cases in this country if penicillin-resistance has been confirmed, provided that the patient is in hospital.

Venereal Diseases.—Aureomycin is unique in having a therapeutic effect in all common forms of venereal disease. It will cure gonorrhoea; it has a pronounced effect in syphilis, though its relative value in various forms of this disease remains to be determined; as already mentioned, it is effective in lymphogranuloma venereum; and, finally, it will cure non-specific urethritis.

Urinary-tract Infections.—On account of its wide range of activity, and the simplicity of its administration, aureomycin is probably the most commonly used urinary antiseptic in the U.S.A. at the present time. The drug is so

freely available that it can be used routinely without first trying older remedies. The only common infections resistant to it, as to chloromycetin, are those due to *Ps. pyocyanea* and, to a less extent, *Proteus vulgaris*. So long as scarcity persists with us, a sensible policy would be to treat any coccal infection, at least in the first place, with penicillin, and to reserve aureomycin for coliform infections (other than the two mentioned) which have proved resistant both to sulphonamides and to streptomycin. Aureomycin is excreted unchanged in the urine, which it renders acid, a condition favouring its activity. It is not clear how short a period of treatment will suffice, but four days at the rate of 3 g. daily is certainly enough in some cases. Nor is it yet clear how its merits for this purpose compare with those of chloromycetin. In my limited experience, one case of *Bact. aerogenes* infection was cured with aureomycin when chloromycetin had failed.

Miscellaneous Indications.—According to some American authorities, aureomycin is the most effective of the antibiotics in the treatment of general peritonitis. It is recommended that the initial doses be given intravenously. There is reason to believe that it will be effective in spirochaetal infections other than syphilis, such as relapsing fever and Weil's disease. Its effect in amoebic dysentery, accidentally observed when it was administered for another condition, has now been extensively confirmed, though it does not seem to have been shown to be actually superior to that of emetine. The claim that aureomycin acts in infectious mononucleosis remains to be substantiated.

Neither of the new antibiotics has much scope as a local application, but aureomycin borate has been successfully used in this way in various forms of conjunctivitis.

Conclusion

It will be evident from this account that aureomycin is the most widely useful of all the antibiotics, though chloromycetin is its equal in some conditions, and in one at least (typhoid fever) its superior. Chloromycetin is now being manufactured in this country, whereas for the present at least aureomycin and terramycin, for which there is likely also to be a large demand, have to be paid for in dollars. We are in a strange situation when international economic considerations have to be given weight in therapeutic policy, but it seems at present an inescapable duty to prefer chloromycetin to either of the others when it will serve equally, or even nearly, as well.

THE PROTECTION OF LABORATORY ANIMALS

[BY A SPECIAL CORRESPONDENT]

A document has been received from Major C. W. Hume, director of the Universities Federation for Animal Welfare, entitled "First Draft for a Model Act for the Protection of Laboratory Animals." The covering note explains that the ultimate purpose of this draft is to enable U.F.A.W. to help inquirers from abroad who desire to promote such legislation in their own countries. Those in favour of legislation regulating the use of animals for experiment—and few who have experience in this country of the Cruelty to Animals Act of 1876 can doubt its value—will applaud Major Hume's intention, however much they may be driven to deplore the form which it takes.

Seventy-four years' experience in this country of an Act which was introduced following a Royal Commission, and which has been the subject of a prolonged and critical study

by a second Royal Commission, has shown that the very delicate subject of animal experiments is capable of administrative control, provided the administration is wise, faithful, and not shackled by pettifogging statutory requirements. In so far as our present Act falls short of the ideal at which it aims, it is largely because its framers strove to crystallize in terms appropriate to 1876 ideas which were inevitably subject to change and development. For instance, the elaborate certificate system has proved a redundant safeguard of little value, the function for which it was designed having been usurped by the administration. The statute, however, requires that this machinery shall still operate, and the time of presidents and professors is taken up with scrutinizing and signing documents which are later checked at the Home Office; as often as not they are found wanting in some technical detail and have to be returned to the applicant to start their journey all over again.

The "Pain Condition"

The working of the present Act revolves round the so-called "pain condition," which accurately expresses the views of the second Royal Commission on Vivisection (1906-12) about the maximum amount of pain which in the pursuit of knowledge it was reasonable or justifiable to inflict on animals. It can be confidently asserted that this pain condition is rigidly observed. The obligation placed by it on the Home Office inspectors to order the destruction of animals which in their opinion are suffering unduly has not been called into action in recent years, and it must be emphatically stated that this, so far from being an indictment of inspectors, is a tribute to the conscientiousness of licensees and the sound sense of their colleagues.

In framing or administering an Act of this kind the guiding principle must be to relate the maximum amount of pain which it is permissible to inflict on animals for the acquisition of knowledge to that which public opinion tolerates in other pursuits. And since public opinion may vary from decade to decade allowance for this must be inherent in such an Act. Major Hume's draft is lengthy, specific to such a degree as to be unworkable, and inflexible, yet it still leaves unsolved many of the ambiguities of the Act of 1876. Moreover, the fact that many of his implications are scientifically unsound cannot be overlooked. To give but one example, he suggests that "the passage of a continuous electric current through the brain shall not be deemed to produce anaesthesia unless its path, amperage, and wave-form shall conform to requirements to be determined by the Minister in the light of experimental investigation." What can this mean if it does not imply that the Minister is to set up an advisory body to determine the path, amperage, and wave-form required to produce anaesthesia in all types of animal liable or likely to be the subject of experiment? One could add other examples, but to do so might suggest that this draft is capable of amendment and revision. This is not so. A wider knowledge of the administrative problems involved, of animals, and of scientists whose work demands the use of animals, is necessary to one who would tackle this problem usefully.

The draft suggests the setting up of a board of control to advise the Minister. This board "shall comprise persons who are competent to provide as wide an understanding as may be practicable of research in the sciences ancillary to medicine, persons with experience in veterinary practice, and persons who have been active in discouraging cruelty to animals." These three qualifications may presumably be mutually exclusive, so that we have the possibility of a board of control including persons who have been active in discouraging cruelty to animals but have no understanding of scientific matters—a dangerous situation.

What Is an Experiment?

Major Hume's Act proposes to regulate every "experiment" on a living animal, by which is meant "any test which is carried out on a living animal for a purpose other than veterinary diagnosis and is capable of causing suffering to, or interfering with, the normal health, comfort, or bodily or mental processes of the said animal, and includes *inter alia* any such test used for the purpose of biological assay." As an attempt at the