AUREOMYCIN

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Aureomycin was first described in July, 1948, by Duggar and his colleagues (1948). It is an antibiotic derived from a soil actinomycete, *Streptomyces aureofaciens*, and is effective against a wide range of bacteria and even against some viruses. There is already a large literature concerned with its clinical use, but few well-controlled trials have been carried out. Its value is definitely established only in those conditions which have responded most dramatically to its use and in which previous chemotherapeutic agents had had least effect.

Pharmacology

Aureomycin is a yellow crystalline powder containing carbon, hydrogen, nitrogen, oxygen and chlorine (Broschard *et al.*, 1949). It is usually issued for use as the hydrochloride, which is soluble in water only to the extent of 14 mgm./ml. giving a pH of 2.5 to 4.5, but is much more soluble in a carbonate buffer solution at pH 8.5. For intravenous use 0.5 gm. has been given in 500 to 1,000 ml. of 5 per cent. dextrose, or 0.1 gm. in 10 ml. of 0.75 per cent. sodium carbonate. It may be given intravenously in smaller volume at neutral pH by dissolving 0.1 mgm. of aureomycin in 5 ml. of a solution containing 131 mgm. of L-leucine. Intramuscular injection is very painful and is not recommended, but aureomycin is well absorbed from the intestine, and it is usually given by the mouth in capsules, each containing 0.25 gm. In powder form in sealed ampoules aureomycin will keep for many months, but it deteriorates rapidly on exposure to air. In concentrated solutions at pH 4 it is stable for several weeks at temperatures of 4 to 37°C., but quickly loses its activity in dilute solutions or at neutral or alkaline pH, though the activity of such solutions is maintained if they are kept frozen at -20°C. (Harned, *et al.*, 1948). After a single dose of 0.5 to 0.75 gm. by the mouth aureomycin appears in the urine within an hour, reaches a maximum concentration in 2 to 16 hours and continues to be excreted for 2 to 3 days. Only about 12 to 15 per cent. of the dose can be recovered from the urine (Collins, 1948), the rest being excreted as an

inactive compound. Maximal serum concentrations of 0.6 to 2.5 γ /ml. are attained in 2 to 4 hours after a single dose and levels of 5 to 20 γ /ml. are maintained with a dosage of 1 gm. 4- or 6-hourly (Brainerd, 1949). Opinions differ as to whether adequate levels are reached in the cerebrospinal fluid when aureomycin is given by the mouth; the evidence on the whole suggests that such levels are in fact attained (Harned, 1948, Kierland, 1950, Bryer, 1949). The same is probably true of other body fluids (Dowling, 1949, Herrell, 1949).

Dosage

Initially most of the cases were treated with 0.25 gm. 4- to 6-hourly. It is now customary to give larger doses such as 1 gm. initially followed by 0.5 gm. 6-hourly. For severely ill patients 1 gm. 6-hourly has been suggested (Rose, 1949), reducing to half the dose when the temperature reaches normal. For children, 50 to 100 mgm./kilo/24 hours may be given in 4- to 6-hourly doses. No careful studies on dosage have been made and the doses suggested are tentative only.

Toxicity

The only important toxic effects of aureomycin given by the mouth have been nausea and vomiting, sometimes accompanied by soft, bulky stools. Although this occurred in up to 50 per cent. of cases in early series, the incidence varied from batch to batch of the drug and there is much less trouble with recent and presumably purer samples. Occasionally black tongue, vaginitis (Rose, 1949) or irritation of the scrotum (Lennette, 1948) have been reported. Some cases are said to have had temporary euphoria (Long, 1949). No toxic effects on the kidney have been met with.

Bacteriology

Aureomycin is mainly bacteriostatic, being bacteriocidal only in very high concentration. Its mode of action is unknown. It is more active at acid than alkaline pH. It has a wide bacterial spectrum (Bryer, 1949, Paine, 1948, Alexander, 1949, Price, 1948). It is in general less active

than penicillin, weight for weight, against gram-positive cocci, though more active than chloramphenicol. Against gram-negative bacteria it is about as active as streptomycin, rather less so than chloramphenicol. With the wide range of action of aureomycin it is easier to state which bacteria are relatively resistant than to list the susceptible organisms. Most strains of *B. pyocyaneus* (*Pseudomonas aeruginosa*) and of *Proteus vulgaris* are insusceptible (Bryer, 1949, Paine, 1948), as are some strains of *Streptococcus faecalis* (Price, 1948) and of *Aerobacter aerogenes* (Collins, 1949). Tubercle bacilli are affected only by high concentrations of aureomycin and it has been found ineffective in experimental (Steenken, 1949) and in human tuberculosis (Steinbach, 1949). It is very active against certain viruses such as those of lymphogranuloma venereum and ornithosis (psittacosis), possibly against herpes zoster (Binder, 1949) and the supposed (but as yet unidentified) viruses responsible for some outbreaks of 'primary atypical pneumonia' (Kneeland, 1949, Schoenbach, 1949, Meiklejohn, 1949). The viruses of influenza, poliomyelitis, rabies, canine distemper, equine encephalomyelitis, mumps (Wong, 1948), vaccinia and herpes simplex (Rose, 1949) are unaffected in the laboratory. Aureomycin is said to have an amoebicidal effect *in vitro* (McVay, 1949).

Drug resistance

In contrast to streptomycin, bacterial strains resistant to aureomycin are only obtained with difficulty in the laboratory and so far such strains have not been a clinical problem. But bacteria showing a moderate increase in drug resistance have been isolated from a few cases during or after treatment (Harvey, 1949, Schwachman, 1949).

Clinical uses

Aureomycin has been tried out, on the whole rather unsystematically, in a large number of different infections. These may be grouped as follows:

Infections in which aureomycin has been outstandingly successful

In brucellosis the use of aureomycin is undoubtedly a major advance. Not only infections due to *Brucella abortus* (Knight 1949), already susceptible to combined streptomycin and sulphadiazine, but also those due to *B. melitensis* (Spink, 1948, Debono, 1949), and *B. suis* (Schoenbach, 1948) have responded dramatically. Relapses have occurred, but the incidence of these has been reduced by continuing a dose of 4 to 6 gm. a day for at least a fortnight. Herxheimer reactions have

been encountered at the beginning of treatment; to avoid these Spink and his colleagues (1948) recommend working up the dose gradually from 0.1 gm. a day. In lymphogranuloma venereum aureomycin is much the most effective drug yet tried (Wright, 1948). In cases of so-called 'primary atypical pneumonia' aureomycin has on the whole been very effective (Kneeland, 1949, Schoenbach, 1949, Meiklejohn, 1949), but in one series (Harvey, 1949) was no more successful than in controls treated with penicillin. Of course, it is probable that the term 'primary atypical pneumonia' includes conditions of varied aetiology. Although chloramphenicol has been more extensively used than aureomycin in the treatment of rickettsial diseases, it seems likely that aureomycin may prove just as effective. Murine typhus (Knight, 1949), Brills' disease (Schoenbach, 1949), Q fever (Lennette, 1948, Brainerd, 1949), Rocky Mountain spotted fever (Ross, 1948) and rickettsial pox (Rose, 1949) have responded well in most cases.

Infections in which aureomycin is effective but other effective drugs are available

In the treatment of most gram-positive coccal infections aureomycin is second only to penicillin. Pneumococcal pneumonias respond well (Woodward, 1949, Finland, 1949, Olshaker, 1949, Gocke, 1949), as do staphylococcal infections in the lung (Schwachman, 1949, Finland, 1949) and elsewhere (Logan, 1950, Spink, 1949). Penicillin-resistant staphylococci remain susceptible to aureomycin (Spink, 1949, Nichols, 1949). Pneumonias due to streptococci (Finland, 1949, Olshaker, 1949) and *Haemophilus influenzae* (Finland, 1949) have responded satisfactorily, but the results in infection with Friedlander's bacillus have been variable (Rose, 1949, Collins, 1949), perhaps because individual strains vary in aureomycin sensitivity (Price, 1948). Urinary tract infections due to susceptible organisms have on the whole responded well, often after failure of other antibiotics. But in the presence of anatomical abnormalities relapses may occur, the susceptible organism frequently being replaced by *Proteus*, *B. pyocyaneus* or *Aerobacter aerogenes* insusceptible to the drug (Rutenberg, 1949, Collins, 1949). Bacteraemia due to *B. coli* and to *aerobacter aerogenes* has been successfully treated (Spink, 1949). It seems possible that aureomycin may be better than penicillin in the treatment of leptospirosis (Brainerd, 1949) and may be even more effective than streptomycin in tularaemia (Woodward, 1949). Preliminary reports suggest that in primary and secondary syphilis (Kierland, 1950, Willcox, 1949) the initial response is as good

as that with penicillin; the longer-term results have yet to be assessed.

Infections in which aureomycin is probably inferior to other drugs

Although aureomycin is shown to have some suppressive effect in gonorrhoea it is inferior to penicillin. In typhoid, although possibly of some value, it is clearly inferior to chloramphenicol (Finland, 1948, Collins, 1948). Two cases of anthrax have responded satisfactorily, but, at least in vitro, the organism is more susceptible to penicillin or streptomycin (Annotation, 1949).

Infections in which the effect of aureomycin is still doubtful

There are many conditions in which the effect of aureomycin is still doubtful, either because of variable results of treatment or because insufficient cases have yet been treated. It is reasonable to point out once more that unless the response of an infection to a new drug is consistent and dramatic the only way to determine the drug's therapeutic value is by properly controlled trials. Response to aureomycin therapy in a limited number of cases has been claimed in psittacosis (Woodward, 1949, Brainerd, 1949), non-specific urethritis (Finland, 1948, Willcox and Findlay, 1949), lymphocytic choriomeningitis (Grater, 1949), Stevens-Johnson syndrome (Lynas, 1950, Church, 1950), tropical ulcer (Amפוfo, 1950) and yaws. Variable results have been reported from aureomycin treatment of glandular fever (Rose, 1949, Spink, 1949, Brainerd, Lennette *et al.*, 1949) herpes zoster (Rose, 1949, Binder, 1949, Brainerd, 1949), herpes simplex (Rose, 1949, Duke-Elder, 1950), pemphigus (Spink, 1949, Brainerd, 1949, Bettley, 1950, Whittle, 1950) and amoebiasis (McVay, 1949, Bordes, 1950). In one series of cases of bronchiolitis in infants the patients treated with aureomycin seemed to fare a little better

than control cases (Thompson, 1949).

Aureomycin greatly reduces the flora of the lower bowel (Dearing, 1950), at any rate temporarily, and successful results have been claimed in the treatment of peritonitis (Wright, 1949). Subjective and objective improvement has been reported in ulcerative colitis, possibly due to control of complicating bacterial infection (Marks, 1949). Some benefit has been claimed in uncontrolled trials of aureomycin in pertussis (Bell, 1949), but it seems likely that chloramphenicol will prove the drug of choice in this condition. In eye infections variable results have been obtained (Duke-Elder, 1950), but response to local treatment has been very promising in a few cases of trachoma.

Conditions in which aureomycin is probably ineffective

Unsuccessful treatment with aureomycin has been reported in salmonella infections, infective hepatitis, pulmonary tuberculosis, chicken-pox, mumps, rheumatoid arthritis, Hodgkins' disease, polyarteritis nodosa, lupus erythematosus disseminatus and the common cold.

Conclusions

At present aureomycin is the drug of choice in brucellosis, in pneumonia due to viruses other than influenza and in lymphogranuloma venereum, though in each of these conditions chloramphenicol, which is more easily manufactured, may prove an important competitor. Aureomycin may be found as good as chloramphenicol in the treatment of rickettsial diseases. It is of value in many infections due to penicillin-resistant staphylococci or to streptococcus faecalis. It is often successful in urinary and other infections due to aureomycin-sensitive bacteria when other drugs have failed. But the precise place of aureomycin in these and many other fields of therapy has yet to be accurately defined.

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PRIMARY OR ESSENTIAL HYPERIDROSIS

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Primary hyperidrosis may be defined as excessive sweating of unknown aetiology. It is a diagnosis of exclusion for although this condition has many characteristic features and can usually be diagnosed from the history alone, secondary and thermoregulatory sweating must first be eliminated. Thermoregulatory sweating occurs mainly on the body and is a physiological mechanism designed to maintain the body temperature within a narrow range. Its features are so distinctive that there are no difficulties in diagnosis. Secondary hyperidrosis is a symptom of a local or general cause. Thus it may follow, for example, central nervous system disease, an irritative peripheral nerve lesion, toxic states or even a glomus tumour. It is unusual for it to have the strictly symmetrical distribution of primary hyperidrosis, and the presence

of a causative lesion establishes the diagnosis (Wright, 1948).

The following is a typical case of primary hyperidrosis:

Patient A.H., male, aged 19 years. Occupation: Hotel trainee.

The patient developed normally until the age of eight when he began to sweat excessively on the palms and soles of the feet. The dorsum of the hands and feet, face and body continued to sweat normally. The axillae were affected by the hyperidrosis but to a much milder degree. The sweating was not affected by climatic conditions, and was as excessive in winter as in summer. The hyperidrosis was precipitated by varying stimuli, but particularly writing and driving a car. Embarrassment and strange company acted to a less