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Abstract
From a dissertation read before the Royal Medical Society on Friday, 1st November, 1963.

Many attribute the earliest recognition of an antibiotic effect to Sir Alexander Fleming. However, in 1877, 50 years before Fleming's discovery, Pasteur and Joubert described the phenomenon of bacterial antagonism; the process whereby the growth of certain species is inhibited in the presence of others. In the particular case of the anthrax bacillus they found that growth was inhibited in cultures contaminated with 'common bacteria' (those types now known as the Enterobacteriaciae). Shortly afterwards the term "antibiosis" was introduced for such antagonism.

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The Status of Antibiotics

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History of anti-microbial therapy [1]

Many attribute the earliest recognition of an antibiotic effect to Sir Alexander Fleming. However, in 1877, 50 years before Fleming's discovery, Pasteur and Joubert described the phenomenon of bacterial antagonism; the process whereby the growth of certain species is inhibited in the presence of others. In the particular case of the anthrax bacillus they found that growth was inhibited in cultures contaminated with 'common bacteria' (those types now known as the Enterobacteriaciae). Shortly afterwards the term "antibiosis" was introduced for such antagonism.

The problem that faced these early workers was to discover substances with selective toxicity—substances which destroyed bacteria in concentrations having no effect on the cells of the body. Without this selective action, an anti-microbial substance is no more than an antiseptic. In medicine today it is important to remember this distinction. It is difficult to justify the use of antibiotic sprays to disinfect surgical wards, a use in which it cannot be said that selective toxicity is required.

In 1928, Sir Alexander Fleming recognised the effect on the growth of staphylococci of Penicillium notatum, a fungal contaminant. The mould had caused the lysis of the surrounding staphylococcal colonies. Ten years later Florey and his co-workers published the first paper on the clinical use of penicillin.

Since 1939, increased research into the development of antibiotics has resulted in over a dozen being available for clinical use. We must remember, however, that for each antibiotic that has found a place in therapeutics today, there are many hundreds that were isolated but which were subsequently found to be too toxic for clinical use.

Present clinical problems

When a clinician decides to treat an infection with antibiotics two problems face him; firstly drug resistance and secondly drug toxicity.

A. Drug Resistance

It is convenient to consider bacterial resistance to antibiotic action as being either congenital or acquired. We could regard those bacterial species outwith the spectra of individual antibiotics as being congenitally resistant to such drugs. Treatment of infections whose causative organisms show such resistance to the antibiotics in use, is doomed to fail.

More pressing at the present time is the acquired resistance of bacteria which were originally susceptible to given antibiotics. What is the nature of such resistance? What changes occur in bacterial structure to cause it? A rational approach to this problem would be to determine the precise modes of action of all antibiotics and to investigate the changes occurring as resistance develops. The table below summarises the likely modes of action of some antibiotics in common use.

ANTIBIOTIC	*MODE OF ACTION*	*TYPE OF ACTION*
PENICILLIN BACITRACIN	Inhibits cell wall synthesis	BACTERICIDAL
STREPTOMYCIN	Interferes with carbohydrate metabolism	BACTERICIDAL
CHLORAMPHENICOL	Interferes with protein synthesis	BACTERIOSTATIC
TETRACYCLINES NOVOBIOCIN ETC.	????	BACTERIOSTATIC

Since precise knowledge of the mechanism of antibiotic action is lacking, still less is known of the nature of the changes occurring to drug resistant types. Two opposing theories [2, 3] have been suggested. These have implications that are fundamental to the rational treatment of infection.

I. The Genetic Theory

This theory states that in bacterial populations, mutants which are less susceptible to the drug arise spontaneously, and that the production of these mutants is independent of exposure to the drug. Subsequently they thrive at the expense of the more sensitive strains if their environment contains quantities of the drug.

II. The Adaptive Theory

In this theory it is postulated that the drug is a direct stimulus to the development of resistance.

If we are thinking, as we should be, of the status of antibiotics in future years, it is the second theory that gives more cause for optimism. For if the use of antibiotics were restricted this would lessen the stimulus to the development of resistance. Conversely, if resistant strains arise despite restricted use of antibiotics, there is cause for concern.

The evidence for each theory cannot be included here, but most workers agree that the genetic hypothesisis is more able to explain certain accepted facts. In accepting this expert view, we should realise that the same mechanism need not operate in all cases. To support such a compromise, we need only think of the different patterns of developing resistance. For example with the tetracyclines, the first stage in the development of resistance forms strains that are resistant to only slightly increased concentrations of the drug. Subsequently resistance develops to higher and yet higher concentrations. By contrast, the resistance which develops to streptomycin may '*ab initio*' be of uniformly high level.[4] The pattern of developing resistance differs; it is likely that so too will the mechanisms of developing resistance.

Taking account of both theories, we can construct sensible rules for the antibiotic treatment of the individual patient. Moreover rational therapy benefits not only the individual but also the hospital community, for fewer drug resistant strains arise.

Guiding rules for antibiotic therapy

I.

To be most effective treatment must be started early in the course of the infection before many organisms and hence many resistant mutants have developed (genetic theory). Here a balance must be struck, for treatment must often be delayed until the sensitivity of the caustative organism is known. The following table shows a number of diseases caused by micro-organisms that have a consistent susceptibility to antibiotics. In such cases early treatment can be instituted on the strength of a clinical diagnosis (see table ii).

A corollary to this first clinical rule would be that in chronic infections of the lungs, the urinary tract, etc., little will be gained by hasty 'blunderbus' treatment. In such situations, two or three series of careful bacteriological investigations may be required before rational antibiotic therapy can begin.

II.

When the chosen treatment is started, there must be no delay in providing effective tissue levels of antibiotic. (Both theories.)

III.

Levels of antibiotic above the minimum inhibitory concentration (MIC.) of the infecting bacteria must be maintained long enough for all the causative organisms to be eradicated (adaptive theory).

If the drug concentration at any stage in treatment is below the MIC of the bacteria, not only is growth enabled to continue, but further, bacteriological evidence indicates that some stimulation of growth may occur. (See plate.)

IV.

Antibiotic must be eliminated from the body as rapidly as possible after successful treatment:

a) In order that the normal bacteriological environment is quickly restored.

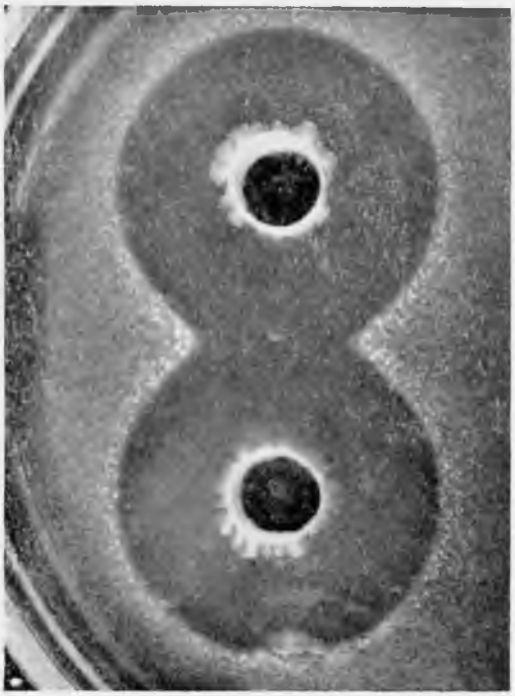
b) Lest the results of clearance tests are falsified.

e.g. After the oral treatment of dysentery, antibiotic levels that are significant may persist in the faeces for some time. In such cases, certain patients are declared free from infection although they still harbour the causative organism, temporarily masked by high residual levels of antibiotic.

CLINICAL DIAGNOSIS	*USUAL CAUSATIVE ORGANISM*	*APPROPRIATE ANTIBIOTIC*	*DURATION OF TREATMENT*
Lobar pneumonia Erysipelas Scarlet fever	Pneumococcus Haemolytic Streptococci	Benzyl penicillin 100,000 units/6 hours	5 days
Enteric fever	Salmonella (typhi and paratpyhi)	Chloramphenicol 250mg./6 hours or Ampicillin[6] 1 gm./6 hours	14 days 14-28 days
Typhus fever	Rickettsiae	Tetracyclines 250mg./6 hours	7 days
Brucellosis	Brucella	[illegible]	14 days
Meningitis	a) *Haemophilus influenzae	Chlorampyenicol 250mg./ 6 hours	5 days
	b) *Pneumococcus	Benzyl penicillin 20,000 units intrathecally +250,000 units intramusc	7 days
	c) *Meningococcus (dose for child of 1½ yrs.)	Sulphadiazine 500mg./6 hours Benzyl penicillin 250,000 units/6 hours	5-7 days

* Distinguished on the gram-stained film of the CSF.

Table ii



This photograph shows part of an agar plate on which staphylococci have been evenly distributed. Centrally two 8mm. cups have been punched out and in each a known amount of streptomycin has been placed. Diffusion of the drug through the medium has caused inhibition of the growth of the staphylococci inside large rings surrounding the cups. The rings of inhibition are sharply demarcated by zones of increased growth. At this point, the antibiotic concentration is just below that which causes inhibition of growth. If such sub-inhibitory concentrations of drug exist in the body, then similar increased growth may occur. The maintenance of adequate levels at the site of infection is of especial importance when using bacteriostatic antibiotics.

Having discussed the phenomenon of drug resistance and how it affects the treatment of individual cases, let us examine the 'natural history' of resistance in the community. The following table shows how the percentage of resistant strains of Shigella sonnei has changed in the last seven years. The figures quoted are the approximate values for the Edinburgh area.[9]

Therapeutic agent	Percentage resistant	
	1955	1962
Sulphonamides	97%	98%
Streptomycin	2%	27%
Tetracyclines	0%	3%
Chloramphenicol	0%	0%

It is readily seen that in the case of the first three substances there has been an increase of resistance. There has been no increase in resistance to chloramphenicol, for in this area the physicians, well aware of this drug's tragic side effects, do not use it in the treatment of dysentery. In the Glasgow area, where more chloramphenicol is used, the percentage of resistant strains is now about 2%. It is difficult to deny the obvious conclusion that with increasing use of antibiotics in a community, the proportion of resistant strains increases.

B. Antibiotic Toxicity

The vital property of anti-microbial agents for parenteral use is selective toxicity. No matter how great this is, it is certain that all antibiotics at present known will in some situations have toxic effects, the degree of severity of these being dependent on the level in the body. Although the many possible therapeutic disasters that could be caused by antibiotics cannot be elaborated here it must be emphasised that no antibiotic can be administered without the danger of ill effects. The deduction follows that a simple rule must be applied before ordering a course of antibiotic therapy:—

Antibiotics should only be used in severe or potentially severe diseases.

The use of highly toxic antibiotics can only be justified if such use is deemed to be life-saving, and if adequate facilities exist for the estimation of blood levels of the drug. It is depressing to think of the fatal marrow aplasias that have followed the empirical treatment of minor catarrhal conditions with chloramphenicol.

It has been suggested that the severe effects of the common cold can be forestalled by the prophylactic use of antibiotics, and that since this illness affects millions of people the result of such prophylaxis would be of great economic significance. However, as a result of the widespread use of antibiotics for this purpose, the secondarily invading bacteria would soon become resistant to the antibiotics employed. The economic benefit would be short-lived. Serious thought must be given to the question of treating such minor complaints.

SUMMARY

In this brief review the attempt has been made to pose certain questions regarding the policy for the use of antibiotics today and in future years. There was no space to consider still more controversial subjects such as the prophylactic use of antibiotics[5,7] or the value of antibiotic combinations.[8] The rational use of these drugs is not simple, and if further indiscriminate usage continues, the problems of the future will become still more alarming. Until now, the development of new antibiotics has kept pace with the steady increase in resistance to those used currently. It is foolish to suppose that the development of new drugs will continue. Our legacy, from the previous generation has been one of powerful drugs which can cure the most severe infections. If we misuse this, the legacy of future generations will be one of multiple drug resistance in infections more terrible than any we at present know.

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REFERENCES

1. Florey et al. 1949 Antibiotics vol. I. Oxford Univ. Press.
2. Drug resistance in micro-organisms. Ciba foundation Symposium 1957, London, Churchhill.
3. Lancet, 1962 1-845 Annotation.
4. Antibiotic and Chemotherapy , Barber & Garrod 1963. E. & S. Livingstone Ltd., Edin. & Lond.
5. Thalbourne & Young 1962 Lancet II p. 907.
6. Kennedy et al, 1963, Brit. Med. J. II 963.
7. Jawetz, 1963 Brit. Med. J. II 951.
8. Textbook of Med. Treatment. Dunlop. Davidson and Alstead, Ninth Edition 1964. E. & S. Livingstone.
9. Dr. R. R. Gillies, Dept. of Bact., Univ. of Ed. Personal Communication.