diet containing 1,400–1,700 calories daily, and men one of 1,600–2,000 calories, together with a daily maintenance dose of 8–24 units of a long-acting insulin.

In the surviving cases the operation was followed by a fall in blood pressure and a decrease in heart volume. Where calcification of peripheral vessels existed before operation this was not affected, but no calcification occurred in other cases. Capillary fragility was normal. A definite decrease in albuminuria and in glomerular filtration rate was achieved, but the effective renal plasma flow remained unchanged. This can be considered to indicate a favourable effect on the renal circulation. No signs of progression of the renal disease were observed, though no conclusions are drawn as to improvement in the condition of the kidneys. The visual capacity improved in some cases, and the retinal changes did not progress further.

The limited period of observation and the small number of cases do not permit conclusions as to the therapeutic value of hypophysectomy for the vascular complications of diabetes, but results so far obtained are encouraging.

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REFERENCES

- Chabanier, H., Puech, P., Lobo-Onell, C., and Lelu, E. (1936). *Presse méd.*, 44, 986.
Luft, R., and Olivecrona, H. (1953). *J. Neurosurg.*, 10, 301.
— and Sjögren, B. (1952). *Nord. Med.*, 47, 351.
— (1955). *J. clin. Endocr.*, 15, 391.
— Ikko, D., and Ljunggren, H. (1954). *Ciba Foundation Colloquia on Endocrinology*, 8, 438.

PRESENT POSITION OF THE CHEMOTHERAPY OF BACTERIAL INFECTIONS*

BY

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No one will dispute that the "present position" of this subject is exceedingly complex. As the result of two major discoveries, the first of which—that of the sulphonamides—was made twenty years ago, an apparently unending series of potent new antibacterial drugs is being produced. If we look at the chronological sequence of these discoveries (Table I) it is seen that the two main trends overlap: further new sulphonamides and other synthetic compounds have been introduced since the beginning of the antibiotic era. It is scarcely surprising that some of these drugs should have been comparatively neglected, and there can be very few people with definite and well-supported views about the relative merits of the later sulphonamides. I was so impressed recently by the lack of information on this subject that I did a series of tests of the *in vitro* antibacterial activity of "gantrisin" and "elkosin" in comparison with sulphathiazole and sulphadimidine against four types of organism causing urinary infections. I found singularly little difference between them, and, although of

course they may differ in other desirable qualities, it seems that by this kind of test one good sulphonamide is very like another.

TABLE I.—Antibacterial Chemotherapy: Sequence of Discoveries 1935–55

	Synthetic Compounds	Antibiotics
1935	Prontosil	
1936	Sulphanilamide	
1938	Sulphapyridine	
1939	Sulphathiazole	
1940	Sulphadiazine	Penicillin
1942	Sulphadimidine	
1943	Sulphasomidine (elkosin)	
1944		Streptomycin
1945	p-Aminosalicylic acid	Bacitracin
1947	Sulphafurazole (gantrisin)	Polymyxin. Chloramphenicol
1948		Chlortetracycline
1949		Neomycin
1950		Oxytetracycline
1952		Erythromycin
1953	Isoniazid	Tetracycline

Among the antibiotics, on the other hand, no two are alike, apart from the close similarity between the tetracyclines. For each there is a whole series of different indications, which can only be expressed adequately by a detailed table of bacterial sensitivities. It is far too much to expect that the clinician should carry such a mass of information in his head, and the result of this is that a good deal of his use of antibiotics tends to be empirical. Not only may he be undecided in his choice of an antibiotic, but having chosen it he may still be uncertain in what form to use it.

The number of "dosage forms" of penicillin listed in a well-known American work is 46. It is true that some of them, such as toothpaste and suppositories, are trivial; others are mixtures with other antibiotics, with little merit except novelty; but for the single legitimate purpose of achieving a systemic effect the clinician has to choose between various forms of oral medication and the injection of preparations which in a given dose will exert an effect for either a few hours, one to two days, four to five days, or two to three weeks. The blood levels attained vary inversely with the duration of effect (Fig. 1).

There are special indications for soluble penicillin on the one hand, and for very long-acting preparations of it on the other, but for the treatment of everyday acute infections the relative merits of freely soluble and depot preparations are still arguable. I am inclined to subscribe to Eagle's doctrine (Eagle *et al.*, 1953), which, as I understand it, favours longer-acting preparations, but the late F. R. Selbie, shortly before his death last year, thought it necessary to re-explore the question experimentally, and reached a somewhat different conclusion (Selbie, 1954).

Indications for Different Antibiotics

I propose to consider only the use of antibiotics, and in the first place the indications for some of them. Apart from

FIG. 1.—Relationship between blood concentration and duration of effect following single doses of four forms of penicillin (schematic).

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the highly selective action of different antibiotics, their choice has been greatly complicated in recent times by the widespread development of bacterial resistance to some of them. Fortunately this change is by no means universal, and there remain some important indications which I have called

TABLE II.—*Immutable Indications for Antibiotics*

Penicillin.—Erysipelas, scarlet fever, or any other known infection by haemolytic streptococci. Lobar pneumonia. Gonorrhoea. Syphilis, yaws. Anthrax, actinomycosis.

Streptomycin.—Plague, tularaemia.

Chloramphenicol.—Typhoid fever.

Tetracyclines or Chloramphenicol.—Typhus (all forms). Undulant fever.

"immutable" in Table II. All these diseases have only a single microbic cause, and the first condition of successful antibiotic treatment, that the infecting species be known, is satisfied by merely making a clinical diagnosis. Further, these organisms are either incapable of developing resistance (as the haemolytic streptococcus is to penicillin) or derived from an animal reservoir (plague, anthrax, tularaemia, undulant fever) where they have had no chance of doing so.

Table III lists some conditions in which the effect of any given antibiotic is unpredictable for one of two reasons. In one category are infections by a single organism, *Staph. pyogenes*, in many of which the bacteriological diagnosis is

TABLE III.—*Conditions in Which the Effect of an Antibiotic is Unpredictable*

1. *Because Bacterial Sensitivity Varies*.—Boils, carbuncles, osteomyelitis, and other staphylococcal infections.
2. *Because Bacterial Cause Varies*.—Bronchopneumonia, bronchitis, pharyngitis, sinusitis. Endocarditis. Meningitis. Urinary tract infections. Wound sepsis. Puerperal fever.

self-evident—for example, carbuncle. The difficulty here is the increasing frequency of strains resistant not only to penicillin but to the tetracyclines as well. To judge by such findings as those of Needham and Nichols (1953) and of Kirby and Ahern (1953) this process has gone further on the American Continent than with us. It is still largely a hospital problem, the prevalence of resistant strains being much less in the general population. In hospitals it now overshadows all other kinds of cross-infection, and it is realized by those who have studied it in surgical and maternity units to be a serious threat, to which no answer has yet been found. According to Howe (1954), the frequency of sepsis, usually staphylococcal, in clean operation wounds in the Massachusetts Memorial Hospitals rose from 2% in 1949 to over 7% in 1953: it thus seems that the strains now prevalent, besides being penicillin-resistant, have a greater capacity for epidemic spread.

We still have one resource in dealing with staphylococci, even if resistant to all other major antibiotics: this is erythromycin. That this in its turn will fail us if misused can be seen from the therapeutic experiment of Lepper *et al.* (1953) at the Municipal Contagious Disease Hospital, Chicago: by extensive use of the drug they bred within a few months a staphylococcal population resistant to it. For serious infections due to such an organism there may be no remedy; deaths due to them are recorded from the Mayo Clinic (Martin *et al.*, 1954). We need to know more precisely under what conditions erythromycin resistance develops, so that we can avoid them without undue restrictions on the use of the drug.

The second category in Table III embraces infections of various body systems—cardiovascular, respiratory, nervous, and genito-urinary—which have no constant bacterial cause. Here treatment without laboratory aid is bound to be more or less empirical. Moreover, even when the cause is known, we again face the difficulty that the strain may be resistant to the antibiotic chosen. Not only staphylococci and some streptococci, but a great variety of Gram-negative bacilli—and these three groups of organisms cause the majority of such non-specific infections—nowadays sometimes prove resistant to an antibiotic to which they used formerly to

be sensitive. The antibiotic to which resistance is most common is streptomycin, and next come the tetracyclines; fortunately, abnormal resistance to penicillin is rarely seen in any organisms except staphylococci.

Of course it is possible to frame a logical plan for the blind treatment of some of these conditions which will often succeed: penicillin may be used first in bronchopneumonia and puerperal fever and a sulphonamide in urinary infection, followed by a change perhaps to one of the broad-spectrum antibiotics if the first remedy fails. But surely it is better that treatment should have a firm rational basis from the outset, and this the laboratory can provide.

Sensitivity tests are still being done by a variety of methods, some of which take two or even three days, a delay which the clinician cannot afford. Admittedly an accurate test by a tube-dilution method is necessary in, for instance,

FIG. 2.—Plate culture of *Staph. pyogenes* illustrating density of inoculum and uniformity of spreading desirable for both species identification and antibiotic sensitivity determination in primary culture. Cups were filled with: Top left, erythromycin 100 µg./ml. Top right, oxytetracycline 50 µg./ml. Bottom, penicillin 10 units/ml. The organism is fully sensitive to the two former but not to the latter.

bacterial endocarditis. But for most purposes the diffusion method, using disks or cups, applied in the primary culture, is perfectly satisfactory, and provides the answer overnight. In an emergency it can do so even more quickly: growth on a plate of a good culture medium begins to be visible within about five hours, and on several occasions in my laboratory we have reported the sensitivities of a staphylococcus within that time of receiving the specimen. To get dependable results from this method it is necessary to know how to spread a plate uniformly with an inoculum neither too heavy nor too light (Fig. 2), an art which in many laboratories seems not to have been acquired.

One of my two main conclusions, therefore, is that the treatment of non-specific infections should so far as possible be based on the bacteriologist's findings: if laboratory facilities have to be extended to provide for this there should be a good return on the outlay in improved therapeutic results and economy in drugs.

Drawbacks and Dangers of Antibiotic Treatment

I would venture, secondly, to suggest that there are many circumstances in which antibiotics are now often used when they should not be. The proportion misused in the United States has been put as high as 95% or even 99% (Jawetz, 1954). Much of this lavish consumption is on undiagnosed cases, insusceptible infections, especially virus diseases,

trivial conditions like simple catarrhs, and for purposes of prophylaxis, to which I shall refer later. The objection to such prescribing is not merely that it is wasteful, or that it hastens the widespread appearance of bacterial resistance: it is also that it can be positively and directly harmful.

The most dramatic and disastrous of these "side-effects" is the shock-like state, sometimes fatal within a few minutes, which can be produced by penicillin in sensitized patients. Precautions against this are possible, but the best safeguard for the future is to limit the use of penicillin to proper indications and thus reduce the frequency of sensitization. Streptomycin is toxic to the eighth nerve, and, although this risk is one which must be accepted in treating a serious disease like tuberculosis, perpetual vertigo or deafness is a heavy price to pay for the unnecessary use of this drug such as is being encouraged by the marketing of proprietary mixtures of penicillin and streptomycin. In patients with impaired renal function excessive blood concentrations are attained and damage can be done in a short time. Chloramphenicol can cause marrow aplasia, and estimates of the importance of this risk vary astonishingly: some physicians or hospitals have almost abandoned the drug, while others still use it freely. In my own hospital, where we have had three cases of marrow aplasia, two fatal, we now regard typhoid fever and *Haemophilus influenzae* meningitis as the only unequivocal indications for the use of this drug.

The tetracyclines are hepatotoxic, but only in excessive doses, and the chief drawback to these drugs is their tendency to cause nausea and diarrhoea: these symptoms may be accompanied by "superinfections" with resistant staphylococci or *Candida albicans*. The tetracyclines, more than any other antibiotic, cause replacement of the alimentary tract flora by undesirable species for two reasons: they are incompletely absorbed, particularly after large doses, and all five main classes of intestinal bacteria are susceptible to them (Table IV). What I have seen recently of diarrhoea

blame in a court of law for its omission if anything goes wrong and they are sued for damages. It is intolerable that therapeutic policy should be dictated by the fear of litigation.

TABLE V.—*Prophylaxis with Antibiotics***Legitimate Uses**

- Preparation for lobectomy, etc.
- " " operations on colon.
- Long-term prophylaxis of rheumatic fever.
- For dental extraction and tonsillectomy in rheumatic subjects.
- Labour with manual interference.
- Extensive and contaminated traumatic wounds.

Unnecessary Uses

- For any "clean" operation.
- For most operations on the mouth, throat, and stomach.
- In normal labour.
- For simple wounds.

When antibiotics are legitimately used to prevent dissemination of bacteria from a site of operation, timing is important. If administration is begun days beforehand, a resistant flora will be established, and the result may be disastrous. Thus the object of giving penicillin before dental extraction is not to sterilize the mouth, this being impossible, but to destroy bacteria entering the circulation at the time of operation: the first injection should therefore immediately precede this. That pre-treatment can result in an endocarditis due to a highly resistant streptococcus was illustrated by a case in my own hospital (Cates *et al.*, 1951).

Conclusions

The present position of the chemotherapy of bacterial infections may therefore be assessed as follows. It is almost a matter for regret that so many antibiotics have been discovered within a few years. Their number cannot be unlimited, and the extravagant use of those we now have may leave us in the position of a general who has expended all his ammunition before the battle is over. The choice is now so wide, and the indications are so complex, that few clinicians can keep fully abreast of knowledge about them.

While the number of antibiotics multiplies, the usefulness of each tends to diminish, owing to the development of bacterial resistance. Fortunately this change affects penicillin—still much the most valuable of them—only in connexion with one organism, the staphylococcus.

The situation is one which calls for more discriminating use. In the treatment of many non-specific infections this can only satisfactorily be based on laboratory findings.

REFERENCES

- Cates, J. E., Christie, R. V., and Garrod, L. P. (1951). *British Medical Journal*, 1, 653.
- Eagle, H., Fleischman, R., and Levy, Mina (1953). *New Engl. J. Med.*, 248, 481.
- Frei, E., Auner, C. R., Van Metre, T. E., jun., and Zubrod, C. G. (1955). *Ibid.*, 252, 173.
- Howe, C. W. (1954). *Ibid.*, 251, 411.
- Jawetz, E. (1954). *Ann. Rev. Med.*, 5, 1.
- Kirby, W. M. M., and Aizer, J. J. (1953). *Antibiot. and Chemother.*, 3, 831.
- Lepper, M. H., Moulton, Barbara, Dowling, H. F., Jackson, G. G., and Kofman, S. (1953). *Antibiotics Annual, 1953-54*, p. 308. Medical Encyclopedia Inc., New York.
- Martin, W. J., Nichols, D. R., Wellman, W. E., and Geraci, J. E. (1954). *Proc. Mayo Clin.*, 29, 379.
- Needham, G. M., and Nichols, D. R. (1953). *J. Lab. clin. Med.*, 41, 150.
- Selbie, F. R. (1954). *British Medical Journal*, 1, 1350.

TABLE IV.—*Degrees of Sensitivity to Five Main Classes of Intestinal Bacteria to Antibiotics*

	<i>Bact. coli</i>	Streptococci	Clostridia	Lactobacilli	Bacteroides
Penicillin ..	—	++	+++	+++	+
Streptomycin ..	++	+	—	+++	+
Chloramphenicol ..	+++	++	+	++	+++
Oxytetracycline ..	+++	+++	+++	+++	+++
Erythromycin ..	—	+++	+++	++	+
Polymyxin ..	+++	—	—	+	+
Bacitracin ..	—	+++	++	++	+

following antibiotic therapy, sometimes staphylococcal and sometimes without a positive ascertainable cause, has given me an altogether new respect for the normal intestinal flora: we should not interfere with it lightly. Tetracycline is said to be kinder to the bowel than its two cousins, but the experience of Frei *et al.* (1955) shows it to be far from blameless.

Prophylactic Use

No one can dispute that the use of antibiotics for trivial or insusceptible conditions is wrong, but there is room for argument about their use as preventives of infection, and very large quantities are used in this way. A doctor of my acquaintance was even offered a shot of penicillin by his dentist as "cover" for scaling his teeth!

A personal judgment on this subject is put forward in Table V. In the legitimate uses specified these antibiotics have been invaluable, but these uses are specialized and relatively uncommon. Far greater amounts are used in connexion with clean operations, to prevent either sepsis, which should not in any case occur, or chest complications. The latter, of course, still sometimes develop, and are then always resistant to the antibiotic used, and often more severe as well as more difficult to treat. Some surgeons in England now use antibiotics in this way, not altogether because they believe in it, but because it is now so usual that they fear

The Scottish National Institute for the War-Blinded is installing a new plastic plant in their workshop at Linburn. The hand-operated bench injection moulding machine is suitable for those with a double disability—i.e., total blindness plus an arm amputation or deafness. Since the Institution purchased the estate in 1944, the men there have been keeping poultry and working in light metals, leather, wood, and wire.