REFRESHER COURSE FOR GENERAL PRACTITIONERS

CHEMOTHERAPY*—II. INDICATIONS FOR THE USE OF PENICILLIN

BY

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The indication for using penicillin is not a disease, such as pneumonia or meningitis, but infection, wherever situated, by a sensitive micro-organism. This is now almost a truism, and since the advent of this and other forms of chemotherapy the profession as a whole has learned to think bacteriologically as it never did before. The laboratories are kept busy in providing the information on which rational treatment can be based. For this, it may be mentioned, they prefer a specimen obtained before treatment is begun; a short period of chemotherapy, even if not fully successful, can hopelessly obscure the picture. Naturally there are conditions, such as gonorrhoea and carbuncle, in which the bacteriological as well as the clinical diagnosis is self-evident, but even in some of these—and carbuncle is an example—it may be as well to confirm that the organism is normally penicillin-sensitive: staphylococci sometimes are not.

Sensitivity of Different Bacterial Species

In the past bacteria have been classed as either sensitive or resistant to penicillin. In fact, there is no such thing as complete resistance, but only a wide range of variation in sensitivity, the total compass of which is about 100,000-fold, and in the top ranges of this the bacteria and other organisms concerned are for practical purposes resistant, since the concentrations necessary to inhibit their growth cannot be attained anywhere in the body. At the other extreme are highly sensitive organisms, affected by concentrations easily attained throughout the body by giving moderate doses. Between these extremes there is a ladder of diminishing susceptibility with a species on almost every rung of it, and whether treatment will be of any value depends on how high a concentration can be attained at the site of infection. To maintain high concentrations throughout the body is difficult, arduous for the patient, and expensive; but to maintain them locally may be very much easier. In the central nervous system, and notably in the urinary tract, organisms which are outside the range of susceptibility for systemic effect may be successfully attacked.

If we retain the terms "sensitive" and "resistant" and make two categories of each according to their degree, some of the principal species can be classified as follows:

Fully sensitive (inhibited by 0.005–0.05 unit per ml.).—*Gonococcus*; *Meningococcus*; *Str. pyogenes*; *Str. viridans*†; *Pneumococcus*†; *Staph. aureus*†; *B. anthracis*; *Actinomyces israeli*†; *Treponema pallidum*; Vincent's organisms; *Erysipelothrix rhusiopathiae*.

Less sensitive (inhibited by 0.1–0.5 unit per ml.).—*Clostridia*; *C. diphtheriae*; *L. icterohaemorrhagiae*.

Moderately resistant (inhibited by 1–10 units per ml.).—*H. influenzae*; *Str. faecalis*; *Proteus vulgaris*; *Salm. typhi*.

Highly resistant (inhibited only by >50 units per ml.).—*Myco. tuberculosis*; *Shig. dysenteriae*; *Ps. pyocyanea*; *Bact. friedländeri*; most other Gram-negative bacilli; yeast-like and some other fungi; most viruses.

This list is far from complete, but the first category embraces the vast majority of infections for which penicillin is ordinarily used. It is noteworthy that four species in it have to be classed as variable, and in dealing with them it may be necessary to have a laboratory estimation made of the degree of sensitivity of the patient's own strain.

It is impossible within the compass of a short article to give an account, however brief, of all the possible uses of penicillin in different conditions. Many of these, however, if classified according to their causes, fall into only a few categories, in which the principles of treatment, if not its detail, are the same.

Haemolytic Streptococcal Infections

Streptococcus pyogenes of Lancefield's Group A is remarkably constant in its high degree of sensitivity to penicillin, which cannot be altered to any material degree by habituation either in the body or in the test-tube. Penicillin is therefore a dependable remedy for all infections caused by this organism, and the only serious question affecting its use concerns the merits of the sulphonamides as an alternative. Most strains are also fully sulphonamide-sensitive, and until the advent of penicillin we were perfectly satisfied with these drugs; indeed, they had brought about the greatest therapeutic revolution of modern times, and completely transformed the outlook in conditions which formerly had a high mortality. They are also cheap, easily administered, and reasonably free from risk, except in sensitized patients or those given very large doses.

Wound sepsis, acute throat infections, and puerperal fever, the three principal classes of infection which may be caused by haemolytic streptococci, can or could still be treated with sulphonamides with almost uniform success, although the response may initially be not quite so rapid as that to penicillin. Whether they should be is a matter of opinion, and involves considerations extraneous to the merits of the treatment, such as those of convenience and economy. It is perhaps reasonable to suggest that early and uncomplicated cases, at least of the first two of these classes, especially if undergoing treatment in their own homes, might be treated with sulphonamides only. Penicillin is always there in reserve should it prove to be needed. On the other hand, penicillin should be given from the first in severe wound infections, middle-ear disease, and puerperal fever, since here the inherent dangers are more immediate and less predictable, and a more rapidly acting and slightly more certain remedy is evidently called for.

Owing to its bactericidal action (that of the sulphonamides being merely bacteriostatic) penicillin is more capable of actually eliminating the organism as well as curing the disease. This is one reason for using it in scarlet fever, since it greatly shortens the period of infectivity: to ensure this effect treatment must be continued for seven days. It should not be forgotten that haemolytic streptococcal infection commonly complicates several other specific fevers, including severe diphtheria (for which large doses of penicillin are beneficial in any case) and smallpox.

*Part I appeared in the *Journal* of August 19, p. 453.

†Some strains may be less, or much less, sensitive.

Pneumococcal Infections

Pneumococci are usually fully sensitive to penicillin, but this species can acquire a moderate degree of resistance to the drug, and such strains are sometimes encountered. The same is true of their reaction to the sulphonamides. In general they are fully sensitive to the newer members of this series, but difficulties with resistant strains began to be encountered in the latter part of what may be called the sulphonamide era (1935-45); how often they occur now is unknown. There is this difference, that whereas the dose of penicillin can be multiplied twentyfold if necessary to meet this difficulty, that of a sulphonamide cannot.

The choice between the old and new treatments for the principal disease concerned here, pneumonia, must again remain a matter of opinion. It may perhaps be made on similar lines; that is to say, a mild case with otherwise favourable features may justifiably be given a sulphonamide only, whereas the patient whose condition justifies any serious anxiety should be given penicillin or both. Whenever possible the sputum should be examined, since in bronchopneumonia (and even in rare cases of lobar pneumonia) the infection may not be pneumococcal, and one of the newer antibiotics may be the only useful specific—e.g., streptomycin for *H. influenzae* or *Bact. friedländeri*. There is only one drug effective in all forms of pneumonia, virus as well as bacterial, and unfortunately we cannot afford in this country to give it to every case: this is "aureomycin."

Staphylococcal Infections

The position here is different in two ways: sulphonamides are relatively ineffective, and yet by a strange misfortune this is the one common sensitive species which sometimes possesses a high degree of resistance to penicillin. Staphylococci can in fact be rendered enormously resistant in the test-tube, but this change has nothing to do with the natural resistance which is now presenting a serious therapeutic problem: this has a different mechanism, and there is almost no doubt that selection and not habituation is the cause of its increasing prevalence. The general use of penicillin is steadily eliminating staphylococci sensitive to its action, while those naturally resistant to it survive and spread. At present the proportion of all staphylococcal infections which are due to these resistant strains appears to be only about 5% in the general population, but it often exceeds 50% in institutions such as hospitals and maternity homes: here cross-infection and the nasal carrier-state in nurses enable a resistant strain to become endemic.

There is ample proof that the degree of this natural resistance varies widely in different strains, and unfortunately its degree cannot easily be estimated. There is no general agreement on whether it can be overcome by greatly increased dosage; the truth almost certainly is that it sometimes can and sometimes cannot, depending on the degree of resistance. When it cannot, the best alternative is again aureomycin.

But for this qualification, which recent developments have made necessary, it could well be said that penicillin is more of a godsend for staphylococcal infections than for any other. It is invaluable in osteomyelitis, although here, as in any other lesion causing necrosis or suppuration, it does not remove the need for surgery. It is required for carbuncle, and may be used also in severe furunculosis and in staphylococcal infections of wounds, of the air passages, and of the urinary tract. Either applied locally or, if necessary, given parenterally, it is useful for all skin conditions of which staphylococci are the cause (sycosis, pem-

phigus, impetigo, blepharitis), and to some extent for any in which these organisms are important secondary invaders.

It is now advisable to consider infection in a few special situations, for which the method of treatment may be different.

The Circulatory System

Endocarditis.—It need scarcely be said that septicaemia of whatever origin, due to any sensitive organism, is the strongest possible indication for penicillin treatment. Equally so is endocarditis, whether acute or in the sub-acute form also known as endocarditis lenta. The treatment of endocarditis, particularly of the latter type, calls for more vigorous and sustained efforts with penicillin than any other disease. The latest conclusion reached from its study in this country is that a daily dose of two million units is advisable, and that treatment should be continued for at least six weeks. This dose should be so subdivided as to maintain a continuous effect. Among factors affecting the prognosis are the stage of the disease at which treatment is begun. Early recognition is thus vital, with repeated blood cultures for confirmation. Another is the degree of sensitivity of the organism. This is variable in *Str. viridans* and uniformly low in *Str. faecalis* and *Haemophilus parainfluenzae*, which are less common causes of the infection. Some cases will therefore require either very large doses of penicillin, perhaps reinforced with caronamide, or another antibiotic or combination of two, such as penicillin with streptomycin.

The Central Nervous System

Meningitis.—The only form of purulent meningitis which it is still advisable to treat with sulphonamides alone is meningococcal. When streptococci, pneumococci, or staphylococci are concerned penicillin must be used, and because comparatively little reaches the cerebrospinal fluid from the blood, intrathecal injection is necessary. The concentrations which can so be maintained in the cerebrospinal fluid are such that even less sensitive organisms can be attacked in this situation. These include *H. influenzae*, although streptomycin is to be preferred for this infection. Penicillin should be given intramuscularly as well as intrathecally, and when the organism concerned is also sulphonamide-sensitive one of the more potent sulphonamides which attains a good concentration in the cerebrospinal fluid—sulphadiazine being probably the best—should be given in addition.

Urinary-tract Infections

When penicillin is administered by injection some is destroyed in the body, but almost the whole of the remainder, amounting to 60% or more, is excreted in the urine. Thus if a patient is given 250,000 units a day and his urinary output is 1,500 ml., its penicillin content will be 100 units per ml., a far higher concentration than that attained in the blood or tissues. This means that infections of the urinary tract caused even by bacteria in what has been termed earlier the "moderately resistant" class may be successfully treated. The principal species, with the concentrations usually required to inhibit their growth, are:

<i>Staphylococcus aureus</i> and <i>albus</i>	...	0.02	unit per ml.
<i>Streptococcus faecalis</i>	...	2	units per ml.
<i>Proteus vulgaris</i>	...	8	units per ml.

Even some strains of *Bact. coli* are sensitive to about 25 units, although others are more resistant. *Bact. aerogenes*, *Ps. pyocyanea*, and various paracolon bacilli are

highly resistant, and penicillin is useless for them. Penicillin can thus be used for some urinary-tract infections, but only with any expectation of success if the nature of the infection is known and comes within no more unfavourable category than the "moderately resistant." Large doses are not necessary, but they should be given at least four times a day unless in a slowly absorbed form. No attempt need be made to alter the reaction of the urine, but output may with advantage be diminished by restricting fluid intake.

Prophylactic Use

The use of penicillin to prevent infection in very varied circumstances has become common, and a few personal opinions on some of these types of use may perhaps be expressed.

At least three seem fully justified. One is the prevention of infection in extensive and grossly contaminated recent wounds. The effect of the intramuscular penicillin given to casualties with the more dangerous types of wound during the attack on Normandy in 1944 astonished and delighted everyone who saw these men, and there is no doubt that this example should be copied in dealing with all wounds involving serious danger from sepsis generally and gas gangrene in particular. Another imperative indication is dental extraction or tonsillectomy in a rheumatic subject, or indeed in anyone in whom the temporary bacteraemia now known to be produced by these operations is likely to have any consequences. A third is prolonged labour with much manual interference, or any other circumstances particularly tending to infection of the placental site.

It is more doubtful whether penicillin should be used as a preventive of infection during the course of what should be a clean operation, or of post-operative chest complications. This sort of use is often unnecessary, wasteful, and not always successful, since infections, particularly of the chest, do occur in spite of it, and are then usually due to penicillin-resistant bacteria. It can be said even more emphatically that penicillin given alone is not a reliable preventive of infection in connexion with operations on the urinary tract. The majority of the Gram-negative bacilli apt to cause this are not merely resistant to penicillin: they appear to thrive on it. This is not simply a figure of speech: there are good reasons for believing that *Ps. pyocyanea*, for instance, is actually stimulated by penicillin, and it is not very uncommon for a urinary-tract infection to be produced by this organism *de novo* in a patient having a long course of penicillin treatment, for no other apparent reason than that the drug is being given. If penicillin is considered necessary to prevent tissue sepsis due to cocci, then a sulphonamide should be added to give wider cover for the urinary tract itself.

Reference to the list of the principal sensitive bacteria will serve as a reminder that penicillin can be used in a number of other diseases, for which there is no space for further discussion. On the other hand, it is without action in many other infections, and some of these are susceptible to the newer antibiotics, which are the subject of two articles to follow.

Impact, a quarterly bulletin issued by Unesco, gives reports of addresses and notes on books mainly on the theme of the impact of science on society. The first issue, which is dated April-June, 1950, includes a short introduction on the main theme, to which is attached a bibliography with notes on the books listed. The bulletin is obtainable for 3s. a year from the Unesco Sales Service, Unesco House, 19, Avenue Kléber, Paris, 16^e.

CREMATION

COMMITTEE AND CRANK

Disposal of the dead by cremation has become increasingly popular in the last thirty years. According to a recent report of the Cremation Committee¹ there were 1,796 cremations in 1920 and 79,607 in 1949. The following graph shows the number of cremations per 100 deaths in England, Wales, and Scotland in certain years from 1920 to 1949.

The committee was appointed in 1947 to review the regulations made under the Cremation Act of 1902, and to make recommendations. Its members were: Mr. H. A. Strutt (chairman) and Mr. R. S. Wells, of the Home Office, Mr. R. Howat, of the Department of Health for Scotland, Mr. J. M. Ross, of the General Register Office, and Mr. H. F. Summers, of the Ministry of Health.

Medical Certification

The regulations were framed primarily to prevent cremation being used to destroy evidence of crime. The normal medical attendant of the deceased gives a detailed certificate leading up to the opinion that there is no reason to suspect that death was due to other than natural causes (Form B); and an independent medical practitioner gives a shorter confirmatory certificate (Form C). Alternatively, a medical certificate (Form D) may be given by a pathologist who has conducted a necropsy on the case, or by the coroner (Form E). Authority to cremate is given by the medical referee (Form F).

The committee's main recommendations on medical certification are as follows:

The certificate in Form B should require further and more explicit details: (a) Where the medical attendant has consulted the coroner, the fact and the result should be stated on the form. (b) It should be stated whether or not a post-mortem examination has been made, and, if so, by whom it was made, and the result. (c) Particulars should be given of the date of any operation during the final illness or within a year before death. (d) The present question No. 13 should make it clear that the reference here is to private nursing. (e) The medical attendant giving the certificate should furnish his

¹ Report of the Interdepartmental Committee Appointed by the Secretary of State for the Home Department, 1950. (H.M.S.O., 9d.)

² *British Medical Journal*, 1880, 2, 461.

³ *Ibid.*, p. 794.

⁴ *Ibid.*, 1884, 1, 123.

⁵ *Ibid.*, p. 515.

⁶ *Ibid.*, p. 624.