# THE CLINICAL APPLICATION OF ANTIBIOTICS

## PENICILLIN

BY

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OXFORD

*This volume, although a separate publication, is a continuation of the work described in* ANTIBIOTICS *Volumes I and II, and may be read in conjunction with it*

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# PREFACE

ORIGINALLY it was proposed in Oxford that a number of workers should produce a book on antibiotics covering all aspects of their discovery, isolation, and chemical, bacteriological, and pharmacological characters, as well as their clinical use where this had been found possible. The enormous growth in the literature of the subject that took place in the years after the book was begun made it impossible to realize this proposal. In 1949 two volumes[1] were published surveying the antibiotics then known, dealing mainly with their history and investigation in the laboratory. Although such laboratory researches form the basis of clinical application the space required made it impracticable to place the clinical work in its natural sequence in the same volumes. The book now published deals with the clinical application of penicillin and includes only a brief account of the most relevant laboratory work. It is hoped to produce later another, dealing with the clinical application of other antibiotics.

A volume is devoted to penicillin, not merely because this antibiotic has particular historical interest as the first to be shown to be a systemic chemotherapeutic agent, but because the lines on which its effects in man were explored have been a guide to the investigation of the antibiotics subsequently introduced into medicine. Moreover, if we consider toxic effects to be those produced consistently in tissue not previously exposed to the drug, penicillin has the distinction of having extremely little, if any, toxic effect in man. Thus, when it is being prescribed the question repeatedly arises whether enough of the drug has been ordered to ensure an optimum therapeutic effect. As no upper limit to the dose is imposed by toxicity this question is difficult to answer, and in the following pages much attention has been paid to the question of dosage. The actual doses that have been used are mentioned wherever known so that the reader may be reminded of the very small amounts of the drug that have controlled some serious diseases, and the relatively vast quantities that have been tried without ill effect.

An attempt has been made, where the available data allow, to compare the general picture and prognosis in any given disease before and after the introduction of penicillin. To avoid duplication comparisons of the effects of different chemotherapeutic drugs, or of combinations of drugs, are mentioned with the antibiotic most lately introduced into medicine. For example, the effects of penicillin and sulphonamides in pneumonia are compared in this book, while the comparison of penicillin and aureomycin in pneumonia will appear in the later volume; the combined use of penicillin and streptomycin in enterococcal endocarditis will be discussed more fully in the later volume under streptomycin.

The literature on antibiotics is now so great that no one person can hope to read it all critically, nor is it claimed that the references are fully comprehensive. Every effort has been made to include all the early work, and there are references to most publications on penicillin up to the end of 1949. Numbers of articles have been written since then, but of those appearing in 1950 it has only been possible to include, mainly in footnotes, those that

[1] *Antibiotics*: Florey, H. W., Chain, E., Heatly, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. P., and Florey, M. E. Oxford University Press, 1949.

manifestly threw fresh light on a subject. To make the book more readable the number of bibliographical references has been restricted in the text, others being placed at the end of each section. Care has been taken to mention in the text any paper in which a well-based conclusion has run counter to the findings of the majority of writers.

There has been difficulty in collecting articles from some countries during the post-war years, and in a few cases it has not been possible to obtain translations. In such cases published abstracts have been used. In doing so points of interest in the original papers may have been missed, for which apologies are tendered to the writers.

## ACKNOWLEDGEMENTS

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Although the present volume deals almost exclusively with penicillin a knowledge of the newer antibiotics has been essential to the writing of it. In this connexion I have received much help from Drs. W. McDermott, M. Finland, W. E. Herrell, W. H. Feldman, F. L. Meleney, W. S. Tillett, and Gladys L. Hobby. Many others freely gave me information, both during a visit to the United States of America and later, about the progress of research on the newer antibiotics.

The Sir William Dunn School of Pathology of Oxford University and Imperial Chemical Industries Ltd. provided penicillin for the earliest trials. Messrs. Chas. Pfizer and Company, Inc., Lederle Laboratories Division, Cyanamid Products Ltd., Messrs. Merck and Company, Inc., Messrs. E. R. Squibb and Sons, and Ben Venue Laboratories, Inc., of the United States, and United States Food and Drug Administration, and Messrs. Burroughs Wellcome and Company, Glaxo Laboratories Limited, and the Distillers Company Limited, of England, have supplied me with materials so that I might have first-hand knowledge of the advantages and difficulties encountered with each antibiotic before it appeared on the commercial market.

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Mr. L. T. Morton prepared the indexes, Miss D. M. Smith checked a large part of the bibliography, and Mr. J. Burtt also assisted me at one time.

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I am indebted to many publishers, authors, and firms for permission to reproduce illustrations, tables, and graphs—a list of these is appended.

Facilities for the treatment and observation of patients to whom antibiotics were administered have been made available to me at various times by the following hospitals: The Radcliffe Infirmary, Oxford; Oxford Eye Hospital: The Old Isolation Hospital, Oxford; The Wingfield-Morris Orthopaedic Hospital, Oxford: The 70th General Military Hospital; The Military Hospital for Head Injuries, Oxford; The American 2nd General Hospital; Birmingham Accident Hospital: Queen Elizabeth Hospital, Birmingham; Central Middlesex Hospital, London; Botleys Park War Hospital; The Radcliffe Penicillin Unit of the Medical Research Council; The Ministry of Pensions Hospital, Stoke Mandeville.

M. E. F.

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*American Journal of Medicine.*
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# GENERAL CONSIDERATIONS

## Chapter 1

# PROPERTIES OF CLINICAL IMPORTANCE AND GENERAL CONSIDERATION OF RESULTS

THE essential characteristics of penicillin, elucidated before any attempt was made to apply it to patients, still require careful consideration if the drug is to be used to the fullest advantage. A thorough knowledge and appreciation of its special features, and of the conditions favourable to its action in the human body, are as essential for its successful use in the clinic as is a knowledge of the degree of sensitivity of the pathogenic bacteria which are to be eradicated.

Some of the properties of penicillin make it an almost ideal chemotherapeutic agent. Apart from its capacity to kill or inhibit the growth of certain pathogenic organisms it is virtually non-toxic, it is soluble, diffusible, and readily absorbed, and it retains to a large extent its activity in the presence of normal and pathological body fluids. On the other hand, it has some inconvenient characteristics, for example, instability in solution under the conditions which usually prevail in the practice of medicine. In this chapter these properties, both desirable and undesirable, will be briefly discussed in their special relationship to clinical work. For a detailed account of the pharmacology of penicillin the reader is referred to Chapters 31 to 40 of Florey, Chain, Heatley, Jennings, Sanders, Abraham, and Florey (1949), where antibacterial action, toxicity, absorption, distribution in tissue fluids, and excretion are described.

### Properties

#### Antibacterial action

**Control of infection.** In Table 1 (abbreviated from Jennings, in Florey *et al.*, 1949, Chapter 31, p. 1064) can be seen the principal species of bacteria pathogenic to man which have been tested for their sensitivity to penicillin. It can be said that infections are amenable to treatment with penicillin as hitherto applied if the responsible organisms are inhibited by 10 u./ml. or less, provided a sufficiently high concentration of the drug can be maintained at the seat of infection and that the organisms do not produce penicillinase. The staphylococcus is probably the principal organism against which penicillin has been called upon to act, so that it is important to remember that strains isolated from lesions in man can be divided into two groups—those that are particularly sensitive to penicillin, that is to 0·15 u./ml. or less, and those that produce penicillinase which destroys penicillin (see Florey *et al.*, 1949, Chapter 33, p. 1092). The therapeutic response consequently might be expected to be either well marked or variable, and this has, in fact, been the case. With this exception the evidence summarized in the table shows that the most sensitive organisms *in vitro*, *Str. pneumoniae*, *Str. pyogenes* (group A streptococcus), and *N. gonorrhoeae*, cause the diseases that have responded

TABLE 1. SENSITIVITY TO PENICILLIN OF MICRO-ORGANISMS PATHOGENIC TO MAN.

(Adapted from Tables 159 and 167, from Jennings in Florey *et al.*, 1949, pp. 1008 and 1064.

| *Species* | *Disease with which organism commonly associated* | *No. of strains on which figures in col. 4 are based* | *Concentrations inhibiting growth, u./ml.* | *Other data* |
|---|---|---|---|---|
| *Actinomyces bovis* | actinomycosis | 57 | 0·005– > 1·5 | 35 strains inhibited by 0·08 u./ml. or less |
| ,, *muris* (*Streptobacillus moniliformis*) | .. | 10 | 0·001–0·6 | .. |
| *Actinomyces septicus* | .. | 1 | 0·01 | .. |
| *Bacillus anthracis* | anthrax | 9 | 0·02–5 | varies markedly with size of inoculum |
| ,, *cereus* | .. | 1 | 50–100 | .. |
| ,, *subtilis* | .. | 3 | 0·0085–12 | varies markedly with size of inoculum |
| Bacillus of Morax-Axenfeld* | conjunctivitis | .. | .. | perhaps moderately sensitive |
| ,, Petit* | ,, | .. | .. | ,, ,, |
| *Bacterium aerogenes* | .. | 62 | 30– > 100,000 | .. |
| ,, *coli* | .. | 80 | 15–5,000 | .. |
| ,, *friedländeri* | .. | 6 | 60–4,000 | .. |
| *Bartonella bacilliformis* | .. | .. | 0·01 | .. |
| *Brucella abortus* | brucellosis | 6 | 0·125–45 | .. |
| ,, *melitensis* | ,, | 6 | 0·25– > 16 | .. |
| ,, *suis* | ,, | 5 | 0·25– > 16 | .. |
| *Chromobacterium prodigiosum* | .. | 1 | 4,000 | .. |
| *Clostridium* (important pathogenic species) | gas gangrene, clostridial myositis, tetanus | more than 125 | 0·016–0·75 | .. |
| *Corynebacterium diphtheriae* | diphtheria | 375 | 0·004–640 | 364 strains inhibited by 1 u./ml. or less |
| ,, *equi* | .. | 11 | 8– > 10 | .. |
| ,, *pyogenes* | .. | .. | .. | 0·015–0·062 u./ml. for 4 strains titrated on solid medium |
| ,, *renale* | .. | 13 | 0·0001–0·1 | .. |
| Diphtheroid organisms (unidentified) | .. | 5 | 0·005–0·32 | .. |
| *Donovania granulomatis* | granuloma venereum or granuloma inguinale | .. | .. | moderately or highly resistant |
| *Erysipelothrix monocytogenes* (*Listerella monocytogenes*) | .. | 8 | 0·3–0·7 | .. |
| *Erysipelothrix rhusiopathiae* | erysipeloid of Rosenbach | 11 | 0·1–0·16 | .. |
| Fungi | .. | .. | > 10– > 1,000 | no end-point determined for any strain |
| *Fusiformis fusiformis* | Vincent's angina, tropical ulcer | 16 | 0·00125–2 | one report of greater resistance |
| ,, *necrophorus* (*B. funduliformis*) | .. | 3 | 0·0025–0·5 | .. |
| *Haemophilus ducreyi* | chancroid | 7 | 0·075–0·25 | .. |
| ,, '*haemolyticus*' | .. | 21 | 0·031–0·5 | .. |
| ,, *influenzae* Pittman types and related strains | respiratory tract infections, meningitis | 39 | 0·18–1·5 | .. |
| *Haemophilus influenzae* 'respiratory' strains | ,, | .. | .. | titrations on agar showed these to be slightly more resistant than type b strains |
| *Haemophilus parainfluenzae* | ,, | 2 | 0·37, 1·5 | .. |

* Organisms whose sensitivity could only be presumed from experiments in animals or by clinical trial.

TABLE 1 (*cont.*)

| *Species* | *Disease with which organism commonly associated* | *No. of strains on which figures in col. 4 are based* | *Concentrations inhibiting growth. u./ml.* | *Other data* |
|---|---|---|---|---|
| *Haemophilus pertussis* | whooping cough | 1 | 1 | .. |
| *Leptospira* | Weil's disease, &c. | 56 | 0·03–> 1 | 1 u./ml. partly or completely inhibited all strains tested |
| *Micrococcus tetragenus* | .. | 5 | < 0·5–> 200 | .. |
| ,, sp. | .. | 5 | 0·005–0·125 | .. |
| *Mycobacterium leprae** | leprosy | .. | .. | probably highly resistant |
| ,, *tuberculosis* | tuberculosis | .. | 1–1,000 | varies markedly with medium and size of inoculum |
| *Neisseria gonorrhoea* | gonorrhoea | 160 | 0·0018–0·3 | over 90% were inhibited by 0·03 u./ml. |
| ,, *meningitidis* | cerebrospinal fever | 55 | 0·016–0·5 | 96 other strains titrated on agar covered the same range |
| *Nocardia* sp. | actinomycosis-like lesions | 2 | 1, > 100 | .. |
| Paracolon bacillus | .. | 8 | 4–> 100 | .. |
| *Pfeifferella whitmori* | melioidosis | 2 | > 35 | .. |
| Pleuropneumonia group of organisms | .. | .. | > 50 | .. |
| *Proteus* | .. | 94 | 0·4–> 2,000 | .. |
| *Protozoa* | .. | .. | .. | effect sometimes shown by concentrations of the order of 1,000 u./ml.; partly due to impurities |
| *Pseudomonas pyocyanea* | .. | 19 | > 5–> 5,000 | no end-point determined for any strain |
| *Rickettsia mooseri** | murine typhus | .. | .. | some effect from large doses in animals |
| ,, *prowazeki** | typhus | .. | .. | ,, ,, |
| ,, *rickettsi** | Rocky Mountain spotted fever | .. | .. | no effect from moderate doses in animals. |
| *Salmonella* | .. | 163 | 1·5–> 50 | .. |
| *Sarcina* sp. | .. | 1 | < 0·5 | .. |
| *Shigella* | .. | 29 | 2–> 100 | .. |
| *Spirochaeta* (*Treponema*) *carateum** | pinta | .. | .. | highly sensitive |
| ,, *pallidum** | syphilis | .. | .. | ,, ,, |
| ,, *pertenue** | yaws | .. | .. | ,, ,, |
| ,, Reiter strain | .. | .. | 0·062 | with a small inoculum; higher concentrations were needed as size of inoculum was increased |
| ,, of Vincent's and allied infections* | Vincent's angina, tropical ulcer | .. | .. | probably moderately or highly sensitive |
| *Staphylococcus aureus* and *albus* | suppurative conditions | 976 | 0·002–1,000 | in the first years of penicillin therapy 0·05 u./ml. inhibited 50% or more in most series and 0·5 u./ml. inhibited 80% or more, but the more sensitive pathogenic strains tend to be eliminated in institutions where penicillin is in common use |
| *Streptococcus faecalis* and others in group D | urinary and mixed infections, endocarditis | 47 | 1·0–10 | some strains classified as *Str. faecalis* on biochemical grounds were reported more sensitive |
| ,, micro-aerophilic | ,, | 2 | 2, 5 | some strains may be more sensitive |
| ,, non-haemolytic (not grouped) | .. | 18 | 0·008–2·0 | .. |

* Organisms whose sensitivity could only be presumed from experiments in animals or by clinical trial.

TABLE 1 (*cont.*)

| *Species* | *Disease with which organism commonly associated* | *No. of strains on which figures in col. 4 are based* | *Concentrations inhibiting growth, u./ml.* | *Other data* |
|---|---|---|---|---|
| *Streptococcus pneumoniae* | pneumonia, meningitis | 125 | 0·0025–0·08 | 2 more resistant strains (1 avirulent) were reported |
| ,, *pyogenes* (group A) | suppurative conditions | 417 | 0·0012–0·17 | over 90% were inhibited by 0·08 u./ml. |
| ,, *viridans* | subacute bacterial endocarditis | 216 | 0·0025– > 8 | all except 4 strains were inhibited by 1 u./ml. or less |
| ,, others, various groups | .. | .. | 0·0025–0·313 | .. |
| *Veillonella* | endocarditis (1 case) | 2 | 1, 10 | .. |
| Viruses* | .. | .. | .. | evidence of some slight susceptibility in the psittacosis-lymphogranuloma venereum group; others highly resistant |

* Organisms whose sensitivity could only be presumed from experiments in animals or by clinical trial.

most rapidly and effectively to penicillin therapy. The species of spirochaete cultivable outside the animal body, as well as those tested by experiments *in vivo*, also have a high degree of sensitivity, and this has been borne out by the ready response of syphilis to attack by penicillin. Records of the results of treatment of other infections have shown a uniformity or variability of response to penicillin according to the range of sensitivity of the causal organisms. Only in diphtheria and tetanus has it been difficult to associate susceptibility of organism *in vitro* and therapeutic effect. Possibly this is associated with the important part played by extracellular toxins in these diseases.

**Effect on diagnosis.** During the last 8 years a bacteriological diagnosis has become an essential preliminary to the intelligent choice of treatment for bacterial diseases. Before the introduction of specific antibacterial chemotherapy it was legitimate to diagnose an inflammatory lesion in terms mainly of its anatomical site. Such anatomical diagnosis is now of secondary importance except in so far as the site may help to indicate the bacterial origin of the condition and determine the mode of therapy. The staphylococcus, streptococcus, and pneumococcus may invade any part of the body; the meningococcus, gonococcus, *C. diphtheriae*, and the spirochaetes and clostridia have certain sites of election in the initial stages of infection, while the anthrax bacillus and the actinomycetes occupy an intermediate position. Diagnosis in so far as it concerns the indications for penicillin therapy depends less on labelling infections by such names as meningitis, osteomyelitis, septicaemia, or dermatitis than on considering the micro-organisms which cause them. Since most pus-producing lesions of skin, bone, and muscle, and of synovial and serous membranes are caused by bacteria sensitive to the action of penicillin, they will be likely to benefit from its use; in syphilis or gonorrhoea the history and the site of the initial lesion will usually indicate the bacteriological diagnosis, but acute infections in the respiratory system present a more difficult problem. Here the infecting organism or organisms may be insusceptible to penicillin, and a bacteriological examination will be