HANDBOOK OF
ANTIBIOTICS

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PREFACE

For some time, the author has felt keenly the need for a compilation of information on the subject of antibiotics. Through the past few years, a veritable flood of technical communications has been pouring forth on this subject, and at this moment the signs point to an increase rather than a diminution in the number of contributions. As a result, the author's experience has been that any attempt to look up any aspect of antibiotics, either from the point of view of determining the overall status of a particular antibiotic or a comparatively minor problem such as the confirmation of a melting point, almost invariably became a major library project. Consequently, in self-defense, and before the amount of material accumulated in the literature became completely overwhelming, the author undertook the task of writing a comprehensive, yet concise, compilation in the form of a handbook or manual of antibiotics.

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The library of the N. Y. Academy of Medicine; the Chemists' Club Library; the N. Y. Public Library; the Columbia University Library; and the N. Y. Botanical Gardens Library and their staffs, without whose cooperation, the writing of this book would have been well-nigh impossible.

The N. Y. Academy of Sciences for graciously permitting the use of their literature prior to its publication.

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Synonyms, discarded names and components of multiple antibiotics are not included in the above antibiotics listing. These may be found in the alphabetical order of the ensuing text.

INTRODUCTION

The purpose for which this book was written is the accumulation of published information on antibiotics, not as a miscellaneous collection of facts, as for example by simple abstracts, but organized into a form suitable for ready reference. In keeping with this purpose, all the information in these pages are factual and appear wherever possible in "telegraphic" style, tabulations and statistical summaries. Speculation and theoretical discussions in the literature cited are either held to a minimum or entirely omitted. Needless to say, the author has incorporated no opinions of his own, due not to an exaggerated modesty but to a deliberate desire to produce a work based on facts and data alone, as far as is humanly possible. Parenthetically it may be added that there is nothing more embarrassingly awkward than an outmoded hypothesis or a discarded theory amid an otherwise prosaic factual compilation. To a limited extent, it was found necessary to recalculate or rearrange data, in a very few instances to convert bacterial nomenclature to conform with Bergey, in order to avoid confusion; but as a general rule, the data were compiled in the form appearing in the literature. Where contradiction of fact occurs, both sides are presented.

An earnest attempt was made to avoid the imbalance which frequently results when an author is more interested in some particular phases of his subject and tends to emphasize his special knowledge at the expense of other phases. This tendency was consciously held in check as the material was being compiled and as a result, the author feels that all facets of antibiotics have been covered impartially.

With regard to the type of data compiled, these may be described as primarily "basic" information, *i.e.*, relating more or less directly to the subject of antibiotics themselves rather than their application in applied and theoretical fields. Information which leads too far afield is largely excluded from the text, but is acknowledged by reference to the bibliography. For example, under "Production," the essential steps of the procedure are briefly described, but no attempt is made to enter into the details of equipment, yields, control, etc. This is particularly true of the clinical aspects of the section on "Spectrum in vivo." As compiled in these pages, this consists of tabular data and general conclusions derived directly from the literature. Obviously, a thorough treatment of this material can best be handled by a competent physician, and the reader is referred to the indicated literature on therapy, where such is available.

Primarily, the chief concern of this book is the antibiotic itself as the major source of interest, *i.e.*, its properties, its activity, etc. Of less concern are the associated properties of antibiotics: general problems of antagonism, of therapy, of toxicity, etc. The author will freely admit that he feels as great an interest in a antibiotic which is apparently valueless because of excessive toxicity or other undesirable therapeutic property, as in those which have great potentialities or have actually proved their value in practical application. In some instances, an apparently useless antibiotic is considered of even greater interest because of unusual chemical or biological properties. However, although the author must to some extent plead guilty to a purely academic interest in antibiotics, it should be emphasized that some of the obscure antibiotics mentioned in this volume or others as yet unknown, may suddenly emerge as a valuable product with important practical applications, although not necessarily in the field of therapeutics. Discouraging aspects like high toxicity, etc., may disappear under certain conditions (purification, counter-toxic agents, derivatives, etc.). Thus a serious consideration of all antibiotics without prejudice may prevent the loss of a potentially valuable product. Furthermore, it is conceivable that a particular antibiotic, useless now and in the future from the viewpoint of therapeutic application, may nevertheless be instrumental in clarifying problems of mode of action, of relation between chemical structure and bioactivity and other fundamental problems of antibiotic activity, as well as in nontherapeutic fields, *e.g.*, in industry and agriculture as bactericides and fungicides. In summary, the author wishes to state that he is interested in antibiotics — all of them — regardless of their value at the present moment, or for that matter of their potential value in the future as seen in the present.

Scope and Limitations. The information appearing in these pages covers the scientific literature about two-thirds of the way through 1949, although in a few instances it has been possible to include some antibiotics appearing in print up through the early part of 1950. Apart from the exceptions noted immediately below, all the antibiotics have been covered completely with respect to text and bibliography as regards the original literature. Review and discussion papers are largely omitted. (In one or two instances, the original communication was not available but the title of the reference or its source is included, nevertheless.) Any omissions other than those noted are to be considered as oversights, of which the author would like to be informed and for which he offers his apologies and the promise that they will be included in a subsequent edition.

The following substances, some of which may be regarded as antibiotics, were omitted from the text for the reasons mentioned:

(1) *Unnamed antibiotics.* These are omitted from purely practical considerations. At first thought, this may appear to be an apparently arbi-

trary decision, but careful consideration will make it clear that no other recourse is possible. In the first place, there have been described in the literature a large number of "active" extracts which vary in purity from crude extracts to pure crystalline products. Obviously, it would be confusing to include all these on an equal basis; yet it would be impossible to draw the line without actually becoming arbitrary. Secondly, these are identified only by the taxonomic designation of the producing organism, *i.e.*, as "Factor from," "Active principle from," etc. To include terminology of this type among the relatively precise procedure of simple names is not only awkward, to begin with, but will become overwhelmingly complicated in the future as additional information appears in the literature. This may be illustrated by imagining the resultant confusion in nomenclature should, for example, "Factor from *A. niger*" be reported also to be derived from *P. notatum;* or if *A. niger* be found to produce two or more separate factors! Obviously, this situation would be saved if arbitrary names were assigned. The identity of two or more differently named antibiotics creates much less confusion than would be imagined. When this occurs, the prior name, by date, is given preference, and the others merely listed as synonyms, remaining as points of reference.

(This criterion is one that applies only for the purposes of this type of compilation, and should not be interpreted as a criticism of the excellent studies which have been carried out in methodically going through a series of genera and species for indication of antibiotic production. As a matter of fact, the author has a very high opinion of these inclusive studies, particularly as source material in the search for new antibiotics, and has seriously considered the possibility of assembling this type of information, either in a separate volume or as a part of a future edition of this book. On the other hand, the author does not wish to be interpreted as lending support to the indiscriminate naming of "new" antibiotics without regard to their possible identity with those already isolated. It should be taken for granted that any announcement of a "new" antibiotic has been preceded by sufficiently exhaustive biological and chemical tests to insure that it is indeed "new.")

(2) *Substances primarily lytic in properties, e.g.*, enzymatic or surface-active, and have been studied primarily from the viewpoint of the lysis of dead bacteria. Where some activity against living bacteria has been indicated, they are included and described briefly.

(3) *Antibiotics which are ill-defined, questionable or have obviously exaggerated properties.*

(4) *Antibiotics having obviously feeble antibiotic properties.* In borderline cases, however, these are given the benefit of the doubt and are included.

(5) *Lysozymes, antibodies, and certain well-known metabolities.*

Penicillin and Streptomycin. Although all other antibiotics are described completely, it was found necessary for the purposes of this book to cover these two antibiotics in an extremely abbreviated form, without references other than those books which have large sections on penicillin and on streptomycin. An exhaustive treatment would completely unbalance this book by virtue of the bulk added and devoted to penicillin and streptomycin. (The complete bibliography of these, if included, would require more than the number of pages in this entire volume, exclusive of the space required for the text.) As a result, the newer and lesser-known antibiotics would be overshadowed by the mass of material devoted to two well-known antibiotics, and the use of the book for general reference to antibiotics would become more difficult. A compromise solution to this problem was given momentary consideration, *i.e.*, a "selected" bibliography and a curtailed version in place of a complete text on penicillin and streptomycin, suited in bulk to the complete coverage of the other antibiotics. This compromise solution was never given serious thought, however. The author felt at the time, and still feels, that if the coverage could not be complete, it had better not be included at all — that an incomplete bibliography and text is neither fish nor fowl. An additional factor in confirming this viewpoint has been the appearance of several excellent books on penicillin and streptomycin. No useful purpose would be served by rehashing material which has been covered in these texts. As a result of all these considerations, penicillin and streptomycin were written in extremely summary form, with facts and conclusions boiled down to the least common denominator and a bibliography consisting only of the aforementioned books. This summary coverage is primarily for the purpose of "rounding-out" the antibiotic listing and to avoid the obvious gap that would exist if these two were omitted entirely. Serious thought has been given to working up a companion volume to the present one, to include only penicillin and streptomycin.

DEFINITION OF AN ANTIBIOTIC

In the most parsimonious sense, an antibiotic is merely a member of the group of substances generally referred to as antiseptics, disinfectants, bactericides, fungicides, etc. There is little or no relation, chemically, biologically or otherwise, between all the various antibiotics, other than their ability to affect adversely the life processes of certain selected microorganisms. Despite the absurdly simple character of antibiotics there is a tendency on the part of a few observers in this field to assign them exaggerated attributes, which add nothing to their definition and to some extent even border on the mystic. Needless to say, this type of thinking will be ignored in this work. With regard to the function of antibiotics in contributing to the survival value of the antibiotic-producers, little or no evidence in favor

of this viewpoint has been uncovered, and in any case it is outside the province of a book of this type.

As defined by Waksman [*Science*, **110**, 27 (1949)], "An antibiotic or an antibiotic substance is a substance produced by microorganisms, which has the capacity of inhibiting the growth and even of destroying other microorganisms." This definition states that an antibiotic must be a product exclusively of microorganisms, from which it may be inferred that antibiotic-like substances produced by macroorganisms are not to be considered antibiotics but must be given other designations. On the other hand Benedict and Langlyke [*Ann. Rev. Microbiol.*, **193** (1947)] define an antibiotic as ". . . a chemical compound derived from or produced by living organisms, which is capable, in small concentration, of inhibiting the life processes of microorganisms." It will be noted in this definition that the qualification requiring that the antibiotic be produced by microorganisms only, is omitted and another qualification added, to wit, small effective concentration. The author is inclined to concur with the definition of Benedict and Langlyke. (However, it should be pointed out that these two authors disqualify penatin as an antibiotic, despite the fact that it fits all the conditions of their definition, on the grounds that penatin acts by producing hydrogen peroxide through enzyme action, and that it is the hydrogen peroxide which is the bactericidal agent. This conclusion implies that an enzyme cannot be an antibiotic, and may mean, with regard to the mechanism of action of antibiotics, that once the mechanism of action of an antibiotic is completely explained, it will cease to be regarded as an antibiotic. To this, the author cannot agree.)

The adequacies and inadequacies of the above definitions and of many others which have appeared in the literature are source material for endless discussion. However, as far as the purposes of this book are concerned, the author has cut the Gordian knot by proposing no new definition at all. Instead, an antibiotic is considered as such if it satisfies, more or less, all of the following conditions:

(1) It is a product of metabolism (although it may be duplicated or even have been anticipitated by chemical synthesis).

(2) It antagonises the growth and/or survival of one or more species of microorganisms.

(3) It is effective in low concentration.

A concomitant low toxicity to higher plants and animals at therapeutic levels is a desirable feature, but not a prerequisite.

It may be emphasized that the above criteria are not to be interpreted rigidly and are used only for convenience to fit the chemically and biologically miscellaneous compounds covered in these pages. In practice, an antibiotic will be accepted as such when so considered by reliable observers and in cases of reasonable doubt.

The author feels strongly that any distinction between antibiotics on the basis of their derivation from micro- or macroorganisms is artificial and may lead to confusion in the future as newer antibiotics increase in number. To restrict the term *antibiotic* to metabolic products of microorganisms alone would be undesirable for the following reasons:

(a) By inference, it excludes potentially the valuable antibiotic substances of higher plants and animals from future investigation.

(b) By inference, it arbitrarily assigns unique and unusual qualities to the metabolism of all microorganisms as contrasted to all macroorganisms. Apart from other considerations, actually there are no chemical or biological criteria for differentiating the antibiotics from microorganisms from those of macroorganisms.

(c) It needlessly brings up the necessity for coining new names for the antibiotic products of macroorganisms.

(d) It will introduce unnecessary confusion when specific antibiotics are found to be produced by both micro- and macroorganisms. Thus, citrinin, an antibiotic derived from *Penicillium citrinum* and lower fungi, has been reported as occurring in large quantities in the leaves of *Crotolaria crispata*, a flowering plant of tropical North Australia. Obviously it would be illogical to classify citrinin from *Penicillium citrinum* as an antibiotic, and the chemically identical substance from *Crotolaria crispata* as a nonantibiotic. Similarly, it seems unreasonable to accept phthiocol, derived from *Mycobacterium tuberculosis*, as an antibiotic and yet to reject plumbagin, derived from the higher plant *Plumbago europaea*, when their chemical structure indicates that one is an isomer of the other.

Consequently, with the above justification, the substances covered in the ensuing pages are considered antibiotics on an equal basis, regardless of the genus and species of the producing organism.

CERTIFICATION OF ANTIBIOTICS

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No other class of drugs has had a more profound effect on public health than the antibiotics. These products of the metabolism of microorganisms have provided medical science with extremely effective weapons for combating a long list of serious and crippling diseases including those of bacterial, virus, and rickettsial origin. Because of their continuing importance and widening use by the medical profession, more of each is manufactured and used every month. Only eight years ago, in 1942, we had insufficient penicillin to treat a single case; by 1944 we were supplying not only our own armed forces but those of our allies as well; and by January, 1949, over eight trillion units of penicillin were being produced monthly. One year later, in January, 1950, production had again doubled to the enormous figure of sixteen trillion units per month. Because of the "know-how" gained with penicillin, production of streptomycin increased in a similar rapid manner, and in January, 1950, six American manufacturers were producing this drug at the rate of eight million grams per month. The quantities of aureomycin, chloramphenicol, and bacitracin produced are also increasing at a tremendous rate. Since these drugs are produced by individual manufacturers, actual production figures are not available, but it can be said that the quantities manufactured of each are increasing rapidly. This is worthy of note when one considers that all of these drugs are similar in their effects on certain diseases.

Penicillin was a war drug, and its development came in a period of history when there was a great demand for drugs useful for treatment of war casualties. Although it was discovered by Fleming in 1929, nothing was done with penicillin until 1938 to 1941, when the Floreys, Raistrick, and others became interested in its possibilities as a means of combating infections in the war-wounded. The drug was extremely unstable, and it was through the early work of these English investigators that this problem was partially answered. Since England was unable to establish manufacturing facilities for penicillin because of the war, Florey came to this country to stimulate the interest of the United States pharmaceutical industry. Through the cooperation of the National Research Council, the medical profession, the War Production Board, the Food and Drug Administration, and industry, specifications were set up for penicillin, and funds were made

available where necessary by the Government to initiate production of the drug. During the early developmental stages there were many uncertainties in the production of this fermentation product and rigid control was a necessity. Within the plants, production control was difficult to establish and maintain; stability was a major problem, and the insurance of sterility and freedom from pyrogens and toxic substances required special attention. In addition, relatively early in the history of the drug it was recognized that there were several "penicillins" with different potencies, which complicated the picture that much more. Because of the need, the armed services obtained practically all the penicillin in the first three years of production. Recognizing the difficulties of production and assay of this important drug, the armed services requested the Food and Drug Administration to set up specifications for penicillin and to check each batch manufactured against those specifications. The Food and Drug Administration established laboratories for this purpose during 1942 and 1943, and these were the forerunners of the present pretesting program for antibiotics.

By early 1945 it was obvious that supplies of penicillin would soon suffice for civilian as well as military demands. This raised anew the question of appropriate control measures, since the procedures applying to control of penicillin for the armed services would not apply to penicillin intended for civilian use. Following a series of conferences between Government and industry, it was agreed that a system of predistribution testing of each batch by the Food and Drug Administration would be in the public interest. The Food, Drug, and Cosmetic Act of 1938 contained no provision which would cover such predistribution testing, and it was therefore necessary to request Congress to amend the existing law to provide for a system of certification for penicillin. The amendment was passed on July 6, 1945. It directed the Administrator of the Federal Security Agency to provide for the certification of drugs composed wholly or partly of any kind of penicillin. It authorized him to set up such standards of identity, strength, quality, and purity as he found necessary to adequately insure safety and efficacy of use. It banned interstate traffic in any penicillin-containing drug unless it was from a batch that had been certified.

Certification of penicillin, which in effect means examination by the United States Food and Drug Administration of each batch of the drug produced for identity, strength, quality, and purity before it is shipped in interstate commerce, was not initiated with the antibiotics, but originated over forty years ago with the voluntary certification of coal-tar food colors. Certification of these coal-tar colors became mandatory in 1938, and this was followed in 1941 by the certification of insulin. The certification of penicillin established a precedent as far as the antibiotics were concerned, and no opposition was offered by industry to the inclusion of streptomycin under a certification system by an amendment made March 10, 1947. Two

years later on July 13, 1949, the law was again amended to include the antibiotics aureomycin, bacitracin, and chloramphenicol.

The actual scope of antibiotics certification is one that deserves special consideration. Certification is neither necessary nor practicable for drugs generally. But the important antibiotics possess peculiar and unusual characteristics that make certification a useful and valuable procedure in safeguarding the public health.

These characteristics which are found in one or more of the antibiotics are:

A. Demonstrated therapeutic value in one or more disease conditions which constitute a major public health problem;
B. Probability of contamination with undesirable materials unless manufactured under the most careful controls;
C. Inherent instability, sometimes resulting in decomposition products which may cause untoward reaction;
D. Marked variation in therapeutic response with changes in vehicles or routes of administration;
E. Necessity for evaluation by biological or other methods lacking in precision.

The primary criteria for applying the certification procedure are the importance of the drug in combating serious and crippling diseases and the difficulty in evaluating the final commercial material. Certification does not relieve the producer of his responsibilities, but forcefully emphasizes the vagaries of the drug and the need for a stringent internal control system.

The establishment of regulations under the antibiotics amendment follows, at the present time, a fairly well-established pattern. Monographs are prepared establishing standards of identity, strength, quality, and purity for each dosage form, and a companion monograph is included to cover the tests and methods applied to determine conformance with the standards. When a new product containing a certifiable antibiotic is developed, the producer requests certification of the new pharmaceutical and furnishes the Commissioner of Food and Drugs with a statement of the conditions for which the drug is to be used; a full report of the investigations conducted to show the drug is safe and efficacious for such conditions; a full list of the articles used as components of the drug and the quantity of each; a description of the methods he proposes to use in the manufacture, processing, packaging, and control of the drug; a description of methods that can be used in testing the new product; samples of the drug and its components, and specimens of the contemplated labeling. If the information submitted is satisfactory to the Commissioner he then recommends to the Administrator of the Federal Security Agency that regulations be issued by publication in the Federal Register to provide for the certification of the proposed drug.

Once a monograph has been established, the manufacturer, or any other who has the legal right and meets the requirements of the regulations, may submit batches of the drug for certification. When samples have been received they are subjected to the tests described in the Official Tests and Methods, and if they meet the requirements, the batch is certified for distribution. If the batch does not comply with the standards, certification is refused and the batch must either be reworked or destroyed. It cannot be distributed.

The tests performed on samples of penicillin, streptomycin, dihydrostreptomycin, aureomycin, bacitracin, and chloramphenicol are completed and the results reported to the manufacturer within a four to five day period. By arrangement with the Administration many manufacturers obtain certificate numbers by phone or wire on the day the tests are completed. In any case, each manufacturer receives a formal document of certification on each batch of drug tested if it meets the standards of identity, strength, quality, and purity set up by the regulations. At the present time there are thirteen basic manufacturers of penicillin, seven of streptomycin or dihydrostreptomycin, one of aureomycin, one of bacitracin, and one of chloramphenicol.

Except for aureomycin and chloramphenicol, which are owned and produced by only one manufacturer each, a number of manufacturers purchase antibiotics for manufacture into a variety of preparations. These manufacturers usually purchase certified material for this purpose. However, a manufacturer may purchase uncertified material either for manufacturing use or for repacking. Material so purchased is subject to exemptions which allow the basic manufacturer of the drug to ship in interstate commerce without certification to repackers or to manufacturers of preparations. If a manufacturer of a preparation uses an antibiotic not previously tested by the Food and Drug Administration, he must submit for assay samples of the antibiotic used, as well as samples of the preparation. The preparation must be certified in any event, whether the antibiotic used in its manufacture was certified or not. This is true also of repacked antibiotics.

During the early days of penicillin production, very little of this drug was shipped in export. As time has gone on, however, there has been an increased amount exported. In the case of streptomycin, the reverse of this was true in that large quantities of streptomycin were exported during the early days of production, although the amount exported has been reduced to some extent during the past few years. Antibiotics that are shipped in export do not require certification unless the country to which the product is going requires it. Section 801(d) of the Federal Food, Drug, and Cosmetic Act provides an exemption if the drug is plainly marked for export if it meets the specifications of the foreign buyer and if it complies with the regulations of the country to which it is being shipped. Actually

most of the antibiotics shipped in export are certified or comply with the standards prescribed for certification.

Up to the present time, practically no antibiotics have been imported into the United States. With the increased production abroad, however, it is not unlikely that eventually penicillin and perhaps streptomycin may be imported. If they are, they must meet the same requirements as apply to the domestic products.

When the penicillin amendment was enacted it was recognized that this type of control should continue only so long as it was necessary to insure safety and efficacy of use. The law directed the Administrator, whenever in his judgment the certification requirements with respect to any drug are not necessary to insure safety and efficacy of use, to promulgate regulations exempting the drug from such requirements. It was under this provision that both crystalline sodium and crystalline potassium penicillin G were released from the certification requirements on April 1, 1950.