CHEMO-
THERAPY
OF
INFECTIONS

Collier

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CHEMOTHERAPY OF INFECTIONS

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FOREWORD

We have seen more advances in the chemotherapy of infections in the last twenty years than in all the preceding centuries. Until the middle 'thirties there was only one type of bacterial disease which was susceptible to efficient chemotherapy. In 1909 Ehrlich revolutionized the treatment of syphilis by the introduction of Salvarsan and allied compounds, but their value was limited to a few spirochaetal infections and we had no chemicals which would effectively destroy the ordinary septic infections from which we suffer.

For many years we had " antiseptic " substances which were used (and still are) for local application to infected areas, but all the antiseptics in common use twenty years ago were more poisonous to the blood cells than they were to the infecting bacteria. This toxicity of antiseptics to human cells made them unsuitable for introduction into the body although when applied to an infected surface they could kill the bacteria that they were able to reach.

In the middle 'thirties the sulphonamides arrived and showed us that chemicals existed which could destroy the ordinary septic infections inside the body. First there was Prontosil which acted by virtue of the liberation of sulphanilamide. Sulphanilamide proved effective in streptococcal, gonococcal and meningococcal infections. This was soon followed by sulphapyridine which defeated the pneumococcus and later by sulphathiazole and others which were powerful enough to have some action on the staphylococcus. These were enormous advances but sulphonamide treatment had certain disadvantages.

Then in 1941, penicillin, which I had described in 1929, was concentrated and its chemotherapeutic properties were demonstrated by Florey and his associates at Oxford.

Penicillin was a much more powerful antibacterial agent than the best of the sulphonamides and at the same time it had practically no toxicity for the human body. It only affected certain microbes but for infections due to sensitive bacteria it quickly established itself as the drug of choice. The story has often been told of the value of penicillin to the armed forces during the war, especially in the treatment of septic wounds and venereal disease.

The success of penicillin was followed by a search for other antibiotics and in the last decade a number of new ones have appeared

which have greatly widened the scope of antibiotic therapy. Doubtless there will be many further advances.

In this volume Dr. Collier has described the general aspects of chemotherapy and the different chemotherapeutic agents. There are chapters on how some of the drugs work, on the development of resistant forms of bacteria, on the problem of getting the chemical to the microbes and on many other subjects which are of the greatest interest.

It is not for me in the foreword to praise or criticize the contents of this volume—that is the duty of the reviewer. There is no doubt, however, that Dr. Collier has taken an immense amount of trouble to produce a book which will be a welcome addition to the literature on chemotherapy.

ALEXANDER FLEMING.

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I have to acknowledge with thanks permission to use many of the illustrations. The source of each is indicated in the caption.

H. O. J. C.

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INTRODUCTION

THE PROBLEM OF "LEVEL"

Every reader brings to the understanding of a book his own experience and point of view. Since the trainings, experiences and viewpoints of his readers may vary greatly, an author has the problem of finding a "level" to suit most of them. At what technical level should he write? What assumptions should he make about his readers' technical knowledge?

One answer to such questions is to choose a certain level and keep to it; but it is not the only answer. Some authors, such as Euclid, have begun very simply and become more difficult. The present book is planned so that the level rises as the reader proceeds. The Introduction outlines the ways in which the material will be handled, the early chapters discuss as simply as possible the general principles of chemotherapy and the later consider in some detail particular drugs and diseases.

LIMITS OF THE SUBJECT MATTER

The term *chemotherapy* applies to the chemical treatment of diseases caused by parasites or by the multiplication of malignant cells.[1] The present book discusses the chemotherapy of parasitic infections, a branch of science that has grown very fast in recent years. In describing the features and conditions of its growth, examples are taken from diseases caused by protozoa, by bacteria (Fig. 1a) and by rickettsias, but not by parasitic worms or by viruses (Fig. 1b). All the organisms discussed are therefore microbes, in the sense that we can see them with the help of a laboratory microscope, but not without it. In addition to the treatment of microbial infections already established in the body, their prevention by means of drugs (*chemoprophylaxis*) is also discussed.

The substances used in chemotherapy include those synthesised by chemists, such as sulphanilamide, and those made by other living organisms, such as quinine by a tree and penicillin by a mould. Both these types of chemicals are called *drugs*, a term that does not cover those substances the body makes in response to infection, which help to protect it against microbial attack. While substances of this latter

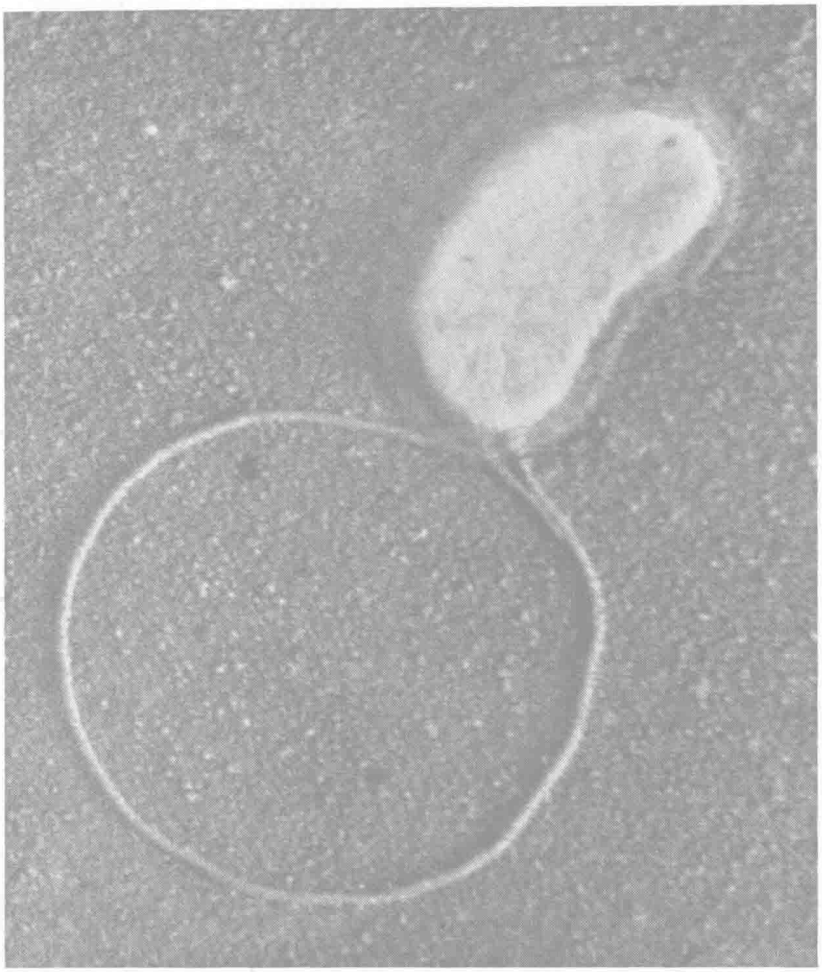

Fig. 1(*a*)—Electron micrograph of a bacterium, *Vibrio metchnikovii*, magnified by 40,000, Note the distinct envelope and the flagellum arising from the inner zone.
(van Iterson, W. *Biochemica et Biophysica Acta*, 1948, 1, 527.)

type, of which *antitoxins* are an example, are successfully used in the treatment of some diseases, their use is not conveniently included in the term chemotherapy. Although in the writer's opinion these substances are part of our subject, they will be mentioned only briefly in the pages that follow.

Another restriction in the scope of the subject matter should be mentioned. Chemical substances may be used against microbes, either when these organisms are outside the body, in water, air, excreta etc., or, on the other hand, when the microbes are actually living in the

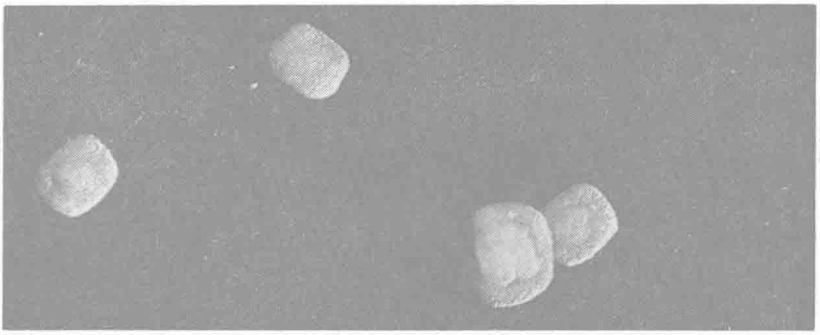

Fig. 1(*b*)—Electron micrograph of vaccinia virus, magnified by 40,000. Note (i) a slight difference between inner and outer zones, (ii) the granular appearance due to large protein molecules, and (iii) a chain of large protein molecules apparently stripped off one virus body.

(Dawson, I. M., and McFarlane, A. S., *Nature, Lond.*, 1948, 161, 464.)

tissues. Generally speaking, the exacting requirements which apply to substances used against microbes within the body do not apply where micro-organisms have to be destroyed outside the body in liquids or air. Consequently, the chemicals used are different, and this book deals only with chemical substances used against microbes infecting the body itself.

Even within the limits outlined above, this book omits many interesting substances and important infections. For example, mandelic acid, which can clear certain infecting bacteria from the urinary tract, is not mentioned, nor are the disease-causing fungi. An attempt has been made to include especially those subjects in which important results

have recently been achieved, those which illustrate the underlying principles of microbial chemotherapy, and finally, those which show the historical development of this branch of science.

SCIENTIFIC LITERATURE

The publication of the results of research is essential to scientific progress, for only published work can be properly confirmed, criticized and built upon. As science is now being pursued on a large scale, scientists have become seriously embarrassed, as can be seen from a leading article in *Nature*,[2] by the vast bulk of scientific writing which is published weekly. All the facts, experiments and views expressed in the numerous scientific papers printed in the many scientific periodicals form a stream out of which the individual scientist attempts to fish the facts and theories which are useful to him, and to which he attempts to contribute something which will be of use to others. The task of keeping up with the literature is made lighter by the classification and collection of abstracts of papers in bulletins, by the publication of articles which review recent additions to our knowedge and by the publication of frequent new editions of the popular text-books. In the present book, an attempt is made to refer to the literature along the following lines. Where possible, when original discoveries are discussed, the papers which announce them are referred to at the end of each chapter. In these references the titles of journals are shortened according to the *World List of Scientific Periodicals*.[3] To refer only to announcements of original discoveries however, would omit the conclusions gained by the contrasting experience of many workers on the same subject. Consequently articles, booklets and books which state the general conclusions arrived at by the work of many different scientists are also referred to at the end of each chapter. As a result, a short list of selected references is given from which, owing to the size and scope of the book, very many papers and articles that might be included are omitted.

THE NAMES OF BACTERIA

The names of genera and species of bacteria are very confused, because different workers use different names for the same species. Throughout these pages the names adopted in the third edition of Topley and Wilson's *Principles of Bacteriology and Immunity*[4] are used. In addition to the name based on genus and species a common name is

used for many bacteria important in disease. Thus the microbe *Streptococcus pneumoniæ* is more commonly and conveniently called the pneumococcus.

THE NAMES OF CHEMICALS

The names of chemical substances are no less and perhaps more confusing than those of microbial species. In the first place a substance may be known by its full chemical name. A simple example of such a name is "*para*-aminobenzoic acid", while a less simple example is provided by the chemical name for vitamin B_1, viz.: "3-(4'-amino-2'-methylpyrimidyl-5'-methyl)-4-methyl-5-β-hydroxyethyl-thiazolium chloride hydrochloride". If a substance is of biological importance, it should be given a short name, preferably related to its chemical constitution. Thus vitamin B_1 is called "aneurine" in this country (from its curative action on neuritis due to deficiency of the vitamin) and "thiamine" in the United States (from its salient chemical characteristics). Such short names as "aneurine" have the blessing of the *British Pharmacopœia*,[5] the official list of substances and preparations of established therapeutic merit.

In addition to its full chemical name and its official name in the *Pharmacopœia*, a commercially important substance may be christened with numerous trade names. For example *para*-aminobenzenesulphonamide, known in the British and United States *Pharmacopœias* as "sulphanilamide" and "sulfanilamide" respectively, was reported by the Medical Research Council[6] in 1946 to possess the following alternative names:

"Ambesid"
"Colsulanyde"
"Deseptyl"
"Lysococcine"
"P.A.B.S."
"Prontalbin"
"Prontosil album"
"Prontylin"
"Proseptine"
"Proseptol"
"Rubiazol-A"
"Stramide"
"Streptazol"
"Streptocide"
"Streptozone"
"Sulfamidyl"
"Sulphonamide P"

In the pages that follow, an attempt is made to use the official names wherever possible. Where a substance does not appear in the *Pharmacopœia* or other official volumes, the name given by the worker who

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