RECENT ADVANCES IN MEDICINE

CLINICAL LABORATORY THERAPEUTIC

BY

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PREFACE TO THE TWELFTH EDITION

In preparing this new edition we have taken the opportunity of thoroughly revising our book, and of adding about one hundred pages of new material. As the size of the book is little changed, it has been necessary to omit certain sections, including the chapters dealing with the kidneys and diphtheria. In Chapter I, now entitled Chemotherapy, the mode of action of the sulphonamide drugs has been rewritten, a note included on sulphamerazine, and a new section added on synthetic anti-malarial drugs. The penicillin Chapter is new, and in it penicillin is discussed both from the laboratory and the clinical aspects. This Chapter also contains an article on other antibiotic substances such as streptomycin, streptothricin and tyrothricin. Many alterations have been made in the Vitamin Chapter. The descriptions of the vitamin B complex and of vitamin K have been largely rewritten, and notes added on biotin, folic acid and dicoumarol.

New articles include those dealing with thiouracil, primary atypical pneumonia, infective heptatitis, homologous serum jaundice, bone marrow transfusion, and the use of thiocyanates in the treatment of high blood pressure. In the Sex Hormone Chapter the sections dealing with the urinary hormones for diagnostic purposes and the assay of the neutral 17 keto-steroids have been rewritten, and a fresh section prepared discussing the treatment of malignant disease by synthetic œstrogens. The last Chapter dealing with the methods has been rewritten and new descriptions added, which include such procedures as the estimation of the acid and alkaline phosphatase, the estimation of abnormal blood pigments, carboxyhæmoglobin, sulphæmoglobin and methæmoglobin, the estimation of thiocyanates in the blood and of the neutral 17 keto-steroids in the urine.

We wish to thank Messrs. Allen and Hanburys
to reproduce Fig. 38 showing the bone marrow tran
and Messrs. Adam Hilger Ltd. for Fig. 40 illustrat
electric Absorptionmeter.

We are grateful to Dr. A. E. Kellie for help in the biochemical sections.

Our publishers have kindly allowed us to make extensive changes in this new edition, and we are very grateful to them for their continued help.

G. E. B.
E. C. D.

LONDON.

PREFACE TO THE FIRST EDITION

DURING the last decade changes have taken place in medicine, especially in the routine methods adopted in the clinical and laboratory investigation of disease, and also in certain forms of treatment.

This book has been compiled with the following objects: to assist practitioners who have not had the opportunity of recent post-graduate study, to familiarise themselves with some of these advances; to provide a reference book for those who are working for the higher examinations in medicine; to give candidates studying for the primary examination for the Fellowship of the Royal College of Surgeons an account of the application of physiological and biochemical principles to medicine. It is also hoped that it will prove of assistance to the laboratory worker in that the recent chemical methods are dealt with in detail. It should also form a link between the wards of a hospital and the laboratories, giving fuller details of methods which are alluded to in medical textbooks, but often omitted from the handbooks on clinical methods. The recent work of American and Continental authorities has also been incorporated.

One of the chief difficulties has been to decide the actual scope of the contents, as they must of necessity encroach upon the domains of theoretical medicine, therapeutics, biochemistry and bacteriology. The guiding principle has been to confine the subject-matter to a description of such methods of diagnosis and treatment as are

used for medical patients in a general hospital, and which can be justly termed " recent advances in medicine."

Great care has been taken to give a workable description of each procedure, all techniques described have been performed personally by one or other of us, and the accounts are taken from our notebooks. Although these may differ slightly from the original descriptions, the methods described have been used by us as a routine for some time, and have given very satisfactory results. We have attempted to state the value of the results obtained by the various tests.

The authors wish to express their indebtedness to the numerous writers whose works have been consulted, and an endeavour has been made to acknowledge them by the list of references.

We have pleasure in thanking Sir Thomas Lewis for permission to reproduce the electrocardiograms taken from his book entitled " Clinical Electrocardiography." Dr. D. E. Bedford has supplied the polygraph tracings, and has also read through the proofs of the chapter dealing with the heart. We are grateful for his valuable suggestions and help. Further, we wish to express our thanks for the loan of certain blocks : to Messrs. Hawksley & Sons for the one illustrating the Jacquet polygraph ; to Messrs. Down Bros. for those illustrating the pneumothorax needles ; and to Professor Harris for the diagram of the electrocardiograph from Anrep and Harris' " Practical Physiology."

In conclusion we wish to acknowledge the unfailing help which we have received from the publishers of this volume.

G. E. BEAUMONT
E. C. DODDS

LONDON, 1924.

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RECENT ADVANCES IN MEDICINE

CHAPTER I

CHEMOTHERAPY

THE inception and development of chemotherapy belong exclusively to the twentieth century. Prior to 1900 very few purely synthetic compounds had been introduced into medicine, most of the remedies used being extracted from plant and animal sources. That purely synthetic compounds might be found which, whilst showing selective toxicity against the protoplasm of pathogenic organisms, would be tolerated by the tissues of the host organism was first conceived by Paul Ehrlich. There is little doubt that his faith in such a possibility carried him over the numerous setbacks which led to the final success of his classical work on synthetic arsenical drugs.

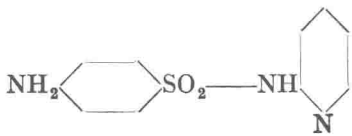
In this work Ehrlich knew something of the relentless search for high potency below the threshold of the minimum lethal dose. In almost fifty years of development others have shared in the vicissitudes of this struggle and, if the team is stronger, the difficulties are no less real. The introduction of the sulphonamides during the last decade has dwarfed previous discoveries in the field.

Sulphonamide Drugs

In 1935 Domagk (1) demonstrated that a new azo dyestuff, sulphonamidodiaminoazo-benzene (prontosil rubrum), was highly protective against experimental streptococcal infections in mice. The fundamental character of this observation was made clear shortly afterwards by Tréfouël et al. (2) when it was shown that sulphanilamide itself was even more effective than prontosil, and that the latter owed its activity to the fact that it was partially broken down in the body to sulphanilamide. In t
compounds more active than the parent substance
many thousands of sulphonamide derivatives have
in the last decade. In one important respect the o

work has been most clear—namely, that of all the modifications of the parent molecule which have been tried, only by substitution of the hydrogen atoms of the sulphonamide group, $-SO_2NH_2$, can the efficacy of the compound be increased. All other modifications lead to complete or partial loss of activity. In spite of this limitation, sulphonamide derivatives many times more active than the parent compound are in general clinical use.

Sulphapyridine (2-(*p*-aminobenzenesulphonamido)-pyridine). This synthetic compound, often known as M. and B. 693, has the formula :—



Whitby (3) has shown that this pyridine derivative is chemotherapeutically active in relatively small doses against pneumococci of Types I, II, III, V, VII, and VIII in experimental infections of mice. It is especially active against Types I, VII, and VIII, and appears to exert a definite action on the capsule of the pneumococcus. Further, it is as active as sulphanilamide against the hæmolytic streptococcus and meningococcus. It has a low toxicity and does not cause porphyrinuria in the animals tested. It is also efficacious in the treatment of gonorrhœa.

Clinical Applications. Evans and Gaisford (4) have published a series of 200 cases of lobar pneumonia, 100 of which were treated with M. and B. 693. The case mortality was 8%, as compared with 27% in the 100 control cases. Its use in the treatment of lobar pneumonia is now well established. Burford and Blades (5) conclude that the incidence of post-pneumonic empyema has been lowered by sulphonamide therapy. When an empyema occurs it is advisable to discontinue the drug as it masks the temperature, exerts a toxic effect on the patient, and does not affect the pocketed pus. Operation is necessary and pocket formation is liable to occur, with delayed expansion of the lung. Further, in our experience, in some cases although the initial response to treatment appears favourable and the temperature rapidly falls to normal, the pulse and respiration rates remain raised and resolution is delayed. Death may then occur. It has also special value in the treatment of pneumococcal meningitis,

and it is as effective as sulphanilamide in the treatment of streptococcal and meningococcal meningitis. It is occasionally successful in the treatment of staphylococcus aureus infections. The preparation is made up in 0·5 g. tablets, which are crushed and given in suspension in water or milk, or they are swallowed whole. At least 5 pints of fluid a day must be given by mouth to prevent urinary concentration and renal damage from crystallisation. If sufficient fluid is given, it is doubtful whether alkalis are also required. A soluble sodium solution is also put up for intramuscular injection, 3 ml. containing 1 g. This preparation may also be given intravenously, 3 ml. being diluted to 10 ml. with normal saline, the injections being given four-hourly. The intramuscular or intravenous injections are usually only given if the patient cannot tolerate the drug by mouth, but intramuscular injections are best avoided, owing to the risk of local muscle necrosis or of nerve damage.

Pneumonia. Streptococcal and Meningococcal Meningitis. The average adult dose is 4 tablets repeated in four hours, followed by 2 tablets every four hours for two-and-a-half days. Subsequently 1 tablet is given four-hourly for twenty-four hours, then 1 tablet eight-hourly for thirty-six hours, making a total of 23 g. in five days.

For children, gr. 1–1½ (0·06–0·1 g.) per lb. body weight should be given every twenty-four hours. Evans and Gaisford (4) recommend the following dosage :—

Age . .	1–3 months.	6–12 months.	2 years.	3 years.	5 years.
Dosage in Tablets (T.)	¼ T. 4-hourly.	½ T. 4-hourly.	⅔ T. 6-hourly.	1 T. 6-hourly.	1 T. 4-hourly.

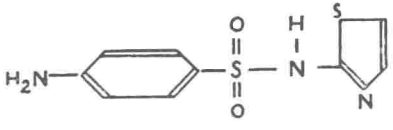
Pneumococcal Meningitis. Hodes, Gimbel and Burnett (6) emphasise the importance of a high initial dose and of subsequent doses sufficient to maintain a concentration of 10 to 15 mg. per 100 ml. in the cerebro-spinal fluid. Very young infants are given 1 to 3 g., and older children and adults 6 to 12 g. by mouth as an initial dose. This is followed by a quarter of the initial dose every six hours until the patient seems entirely well clinically, and several successive cultures of the cerebro-spinal fluid are sterile. This dose should not be reduced until the temperature has been

normal for a week, and half the amount is then given for several days. If the patient cannot swallow, the drug can be administered through a nasal tube. In all cases of pneumococcal meningitis an intravenous injection of a 5% solution of sodium sulphapyridine is also given every six hours, the first dose being on the basis of 0·1 g. per kg. body weight, and subsequent doses of 0·03 g. per kg. body weight until two successive cultures of the cerebro-spinal fluid are sterile. Coleman (7) reports that the case mortality has been lowered by the use of sulphapyridine from 100% to about 35%.

We have found sulphapyridine, given in doses of 1 g. t.i.d. for five days, very satisfactory in the treatment of acute gonorrhœal arthritis, the temperature falling in two days to normal, and the joint swellings and pains disappearing in five days. Sulphapyridine has also been used with beneficial results in the treatment of gonorrhœa, actinomycosis, anthrax, plague, and bacillary dysentery.

Toxic Effects. We have noted severe vomiting in some of our patients who have been treated with this drug. Drug rashes and drug fever are liable to develop if the treatment is continued too long and in some cases after only five days' treatment. Methæmoglobinæmia may occur as a complication, disappearing rapidly when the drug is discontinued. Hæmaturia has also been recorded, especially in warm countries or if insufficient fluid is taken. This may result in anuria and death.

Sulphathiazole (2-(*p*-aminobenzenesulphonamide)-thiazole). The success of sulphapyridine in the treatment of pneumonia encouraged the search for a specific against staphylococci, and sulphathiazole (M. and B. 760) has come into use. It has the formula :—



Sulphathiazole is rapidly absorbed from the intestine and quickly excreted. Reinhold et al. (8) have shown that the blood concentration varies on an average from 3 to 5 mg. per 100 ml. when 4 to 6 g. per day are taken. It is difficult to maintain a higher figure even when larger doses are given.

Clinical Applications. It has been used in streptococcal,