ANTISERA, TOXOIDS, VACCINES AND TUBERCULINS IN PROPHYLAXIS AND TREATMENT

BY

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THIRD EDITION

E. & S. LIVINGSTONE LTD.

EDINBURGH AND LONDON

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Published for
THE WELLCOME FOUNDATION LTD.
by
E. & S. LIVINGSTONE LTD.
EDINBURGH AND LONDON
1954

First Edition . . . 1948
Second Edition . . . 1951
Third Edition . . . 1954

Printed in Great Britain

ANTISERA, TOXOIDS VACCINES AND TUBERCULINS

To
A. T. G.

PREFACE TO THIRD EDITION

ALTHOUGH the first two editions of this book appeared as *Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment,* I have now decided to delete the first part of this title. My reason is that these four words, used by themselves, are no guide to the actual contents of the work, which are indicated quite accurately by the original sub-title.

It is gratifying that a new edition is again required after only three years. During this interval considerable progress has been made in immunology—a science which is now well-established—and in its clinical application. I have once more aimed at reviewing and, where necessary, simplifying essential information, while avoiding certain pitfalls consequent on the very rapid growth of the subject. Although serum therapy is " adjunct therapy," I have resisted the suggestion of some reviewers that I should describe the clinical features associated with different infections, and give the treatment other than sera appropriate for each. This monograph should be used to supplement, where necessary, text-books on infectious diseases and other general works.

In many fields, serological research continues to find abundant scope notwithstanding the advances in chemotherapy. The single or combined immunization of children against whooping cough, diphtheria and tetanus is a topical problem. Good vaccines are being prepared against whooping cough, now the most serious infectious disease in early life. Diphtheria, once the main concern of the immunologist, has recently become rare; but a warning is necessary that " if parents leave their children unprotected there may be a return of diphtheria outbreaks." There are now more deaths every year in England and Wales from tetanus than from diphtheria. Service experience has shown the value of active immunization with tetanus toxoid, which, if applied systematically, would obviate the risk of serum sickness and other disadvantages of the large-scale administration of horse serum. A mixture of tetanus toxoid and typhoid-paratyphoid vaccine is being used increasingly. Another prophylactic of importance to-day is B.C.G. which is playing an important rôle in national campaigns against tuberculosis.

Following the discovery of the common cold virus, interest has been renewed in the possibility of more effective control of colds and influenza. Specific measures for the prevention of poliomyelitis are also being studied, and prospects are encouraging. Smallpox vaccination has been somewhat neglected by an apathetic British public, but the numbers vaccinated are once again on the upgrade.

Although I have tried to check the inevitable expansion of this book so as not to alter its character, more space has been required for some sections, *e.g.*, those on serum reactions, combined immunization, B.C.G. and viruses. Much re-writing has been necessary throughout. Another change is that several references have been inserted in the text, in addition to a longer and more useful list at the end of the book.

I wish to thank colleagues and friends for many suggestions, especially Mr. A. T. Glenny, F.R.S., formerly Head of the Immunological Department of the Wellcome Research Laboratories, whose encouragement and help were invaluable throughout. Miss M. Barr, Dr. D. G. ff. Edward, Dr. A. E. Francis, Dr. J. M. Frisch, Dr. C. G. Pope, Dr. M. Sterne and Dr. A. C. White made useful contributions to certain sections of the text. My special gratitude is due to Dr. L. J. M. Laurent, Consultant Physician, Park Hospital, London, whose clinical knowledge of infectious diseases was placed freely at my disposal. Dr. D. G. Madigan, Consultant Chest Physician, Bromley, kindly read the chapters on Tuberculin Testing and B.C.G. I acknowledge my debt to Dr. Geoffrey Edsall, U.S.A., and Professor Payling Wright, Guy's Hospital, London, for numerous constructive comments.

The willing help of Mr. C. T. Healey, M.B.E., was indispensable in the compilation of the index, as was that of Mr. E. A. Jones in photographing suitable material. I wish also to record my appreciation of the co-operation of my secretaries, Mrs. M. Knight and Mrs. P. Mabbott. Finally, my publishers have continued to give me every possible assistance and courtesy.

H. J. P.

1954.

PREFACE TO FIRST EDITION

THIS little book has been written to present in convenient form the essential principles of immunology and their practical application in human medicine. There would appear to be a need for such a publication for the use of practitioners and senior students who have little time to abstract this information from larger works.

The text owes a great deal to the expert advice and constructive criticism of the Director and various members of the staff of The Wellcome Physiological Research Laboratories. I am specially grateful to Mr. A. T. Glenny, F.R.S., who has contributed so much to immunological science and has been my inspiring colleague and teacher for nearly twenty-five years.

I have also to acknowledge my indebtedness to Dr. R. Cranston Low and Mr. T. C. Dodds for kindly permitting the reproduction of six illustrations in colour from their *Atlas of Bacteriology*.

Lastly, my thanks are due to the publishers, Messrs. E. & S. Livingstone, for much patience and helpful guidance.

H. J. P.

1948.

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CONTENTS

I.—GENERAL

CHAPTER I

THE USES OF SEROLOGICAL PREPARATIONS

BIOLOGICAL products used in infectious diseases may be divided into three groups, *viz.*,

(1) sera of various types for prophylaxis and treatment by passive immunization,

(2) prophylactics, such as toxins, toxoids and vaccines (both bacterial and viral), for active immunization,

(3) diagnostic products, such as diluted toxins and tuberculins, used to detect the presence or absence of immunity. In this group are included certain sera, extracts and suspensions used in the laboratory for Wassermann and other complement-fixation, precipitin, or agglutinin reactions. Only a few diagnostic preparations, for use in man or in animals, come within the scope of this book.

Research is constantly in progress to make the means of defence against disease more effective. Advances have been made in the technique of production of sera and prophylactics, and the incidence and severity of undesirable reactions of one kind or another have been greatly reduced. Experimental work in the laboratory and in the clinic has led to further knowledge of the optimal interval between injections of prophylactics.

The historical aspects of immunology are summarized in the final chapter of this book (*p.* 196).

CHAPTER II

IMMUNITY

IMMUNITY (and immunization) is of two types, either passive or active.

1. PASSIVE IMMUNIZATION

When patients or susceptible contacts receive an immune serum or antiserum obtained from another human being or an animal, they are said to undergo *passive immunization*. In this type of immunization the extra antibodies are prepared in some other animal, and not in the patient's body itself, as in *active immunization*.

The antisera are produced mainly in the horse and in some instances in the rabbit, although human immune (mostly convalescent) sera have been employed in the attempted prophylaxis of a number of infectious diseases, including measles.

Passive immunity of *homologous* type is also transmitted from mother to offspring (*a*) in man, apes and rodents, predominantly via the placenta, and (*b*) in sheep, goats, cows, horses and pigs, via the colostrum, which may be rich in antibody and is absorbed rapidly by the new-born animal. On the other hand, serum of *heterologous* type, *e.g.* the diphtheria antitoxin (horse) in current use for the treatment of clinical diphtheria, does *not* pass by the placental route from the human mother to her baby. (For a fuller discussion of Inherited Immunity, including references, *see* Parish, *Brit. med. J.* 1951, **i**, 1164.)

2. ACTIVE IMMUNIZATION

Active immunization, resulting in immunity acquired by the body itself, may be (1) natural or spontaneous: (*a*) latent; (*b*) the result of an attack of a disease; or (2) artificial.

(1) Natural Immunization

(*a*) *Latent*

Active spontaneous immunization follows the entry into the body of virulent organisms in numbers too small to cause obvious

disease, *i.e.*, a latent infection. Small quantities of *antigens* (components of the organisms or products formed by their activity which may or may not be poisonous or toxic) pass into the blood, and as a result the body cells become trained to produce specific antidotes or *antibodies* (*e.g., antitoxin,* in the case of diphtheria, scarlet fever and certain other infections), which may be detected in the blood stream and measured. But even if antitoxin is *not* present, the patient may still be potentially immune. Should a serious infection develop, the body has an increased capacity to produce antitoxin rapidly so that the disease is overcome. (The organisms may survive and the healthy, immune individual, who thereby becomes a *carrier,* may infect non-immune contacts.)

(*b*) *After an attack of a disease*

In diphtheria and some other infections, an attack from which the patient recovers may confer a fairly solid immunity.

(2) **Artificial Immunization**

Artificial immunization aims at the production of antibody by safe means, *e.g.*,

(i) *in the case of diphtheria,* by injecting

(*a*) toxin weakened by the addition of antitoxin (so-called toxin-antitoxin mixtures were formerly in use), or

(*b*) toxin rendered harmless by formalin (toxoid), while retaining its antigenicity or capacity to produce antibody. Modern diphtheria prophylactics either consist of toxoid itself or have toxoid as their basis. These include adsorbed toxoids, where the toxoid is adsorbed on to a suspension of aluminium hydroxide, hydrated aluminium phosphate, or other suitable substance.

The active immunization of horses and occasionally other animals is necessary in preparing antitoxin for therapeutic purposes. The immunization process is continued for many weeks so that large quantities of antitoxin are produced (" hyperimmunization "). The procedure used for tetanus immunization, which is of topical interest, is very similar to that for diphtheria.

(ii) *In the case of the enteric fevers,* by injecting bacterial vaccines, which are suspensions of the killed bodies of the specific organisms.

(iii) *In the case of smallpox,* by injecting a viral vaccine, which is a suspension of living, modified virus.

The range of diseases, medical and veterinary, which can now be largely controlled by various kinds of prophylactics is increasing. Perhaps the greatest advances in recent years have been in our knowledge and understanding of virus diseases, against which attenuated or killed viruses are used as vaccines.

COMPARISON OF PASSIVE AND ACTIVE IMMUNITY

The essential points may be summarized as follows:

PASSIVE IMMUNITY

(1) **Is rapid in onset,** the rapidity depending upon the route of injection of the antibody.

Intravenous injection ensures the immediate presence of antibody in the blood stream; there is some delay after intramuscular injection and some hours may elapse before adequate amounts reach the circulation; there is still longer delay after subcutaneous injection. Whatever the route of administration, the amount in the circulation two or three days after injection is the same.

(2) **Is of short duration** (at the most, a few weeks) owing to the elimination of the foreign protein by the body. Passive immunization is thus an emergency measure to be used only for the immediate protection of contacts or the treatment of cases.

When homologous serum is used, as in the prevention of measles, the rate of elimination is much slower than in the case of horse serum. Homologous antitoxins, maternally conferred on young animals via the placenta (*e.g.* in man) or colostrum (*e.g.* in sheep) are also eliminated relatively slowly (*see* discussion of rate of loss of diphtheria antitoxin in young infants, *p.* 91).

ACTIVE IMMUNITY

(1) **Takes some time to develop** and is thus "a long-term policy" (Harries) against expected or potential risks. A single injection of an antigen such as diphtheria toxoid may give rise to only minimal or basal immunity (*primary response*) but in some way it educates the body so that a second inoculation, given

after a suitable interval, will produce large amounts of antitoxin rapidly (*secondary response*); this is the typical sequence. In practice, the response depends on the substance injected (antigen), the size, number and spacing of doses, and the educability of the body cells. (If one or both of the injections are inadequate, the resultant lies between the two standard responses and is termed an *intermediate response*.)

(2) Is lost even more slowly than it is acquired; potential immunity (the acquired power of rapid production of antitoxin or other protective antibody) almost always remains.

(3) Is capable of rapid restoration at least to its original level. Even if in individual cases the antibody is no longer detectable in the subject's serum, there remains with few exceptions a potential immunity throughout life, *i.e.*, the body cells possess the capacity to respond rapidly to stimuli so that adequate antitoxin or other antibody is produced when required.

The following notes and figures of **Circulating Antitoxin in Passive and Active Immunity** (for which I am indebted to Mr. Glenny) illustrate and amplify some of the points which have been made, with special reference to diphtheria (*see* Diphtheria Prophylactics, A.P.T. and T.A.F., *pp.* 86 *and* 89).

Passive Immunity

This is conferred when antitoxic serum is used for treating diphtheria or as a prophylactic measure for contacts.

Protection is obtained immediately after an intravenous injection of antitoxin. Antitoxin is rapidly lost, and little or none remains after a few weeks (**Fig. 1).**

Active Immunity

This results from some contact with the specific antigen, produced (1) during an attack of diphtheria, (2) from a latent infection, or (3) by the injection of prepared prophylactics.

The essential differences between actively immune and non-immune individuals are (1) the presence or absence of circulating antitoxin, and (2) the magnitude and speed of the response to the stimulus of an infection or an injection of prophylactic.

The first injection of an antigen into a non-immune subject acts as a *primary stimulus*. It is followed by a latent period of two or more weeks (**Fig. 2).**

When potent antigens such as A.P.T. are used, a further injection given four or more weeks later acts as a *secondary stimulus*. The cells have become trained, and antitoxin is formed much more rapidly. The peak of the curve is reached in about ten days, and represents a production of far more antitoxin than that produced by a single injection (**Fig. 3).**

Sometimes the responsive mechanism is not fully developed four weeks after the first injection, and the second injection acts as an *intermediate stimulus* resulting in a slower production of antitoxin **(Fig. 4).**