ANTISERA, TOXOIDS, VACCINES AND TUBERCULINS IN PROPHYLAXIS AND TREATMENT

BY

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FOURTH 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
1958

First Edition . . .	1948
Second Edition . . .	1951
Third Edition . . .	1954
Fourth Edition . . .	1958

Printed in Great Britain

ANTISERA, TOXOIDS VACCINES AND TUBERCULINS

To
A. T. G.

PREFACE TO FOURTH EDITION

THE aim of this book has been to encourage a better understanding and appreciation of a subject which is regarded as very difficult by both students and graduates. I hope this new edition will also continue to meet a need as a guide to essential information, and as a work of reference in its own restricted field.

More drastic revision than ever has been necessary throughout. Only two chapters, namely, those on "Antibacterial Sera" and "The Dick Test and Active Immunization against Scarlet Fever" have been shortened, whereas many others have been expanded, sometimes considerably, or rewritten. Instead of two chapters on "Active Immunization against Virus Diseases," there are now five, including one on "Poliomyelitis Vaccine." Although regrettable, the increase in the size and cost of this book has been unavoidable, being the result of important advances. The attempt to further the understanding of modern immunology would seem to be justified by the great benefits already accruing from the application of this science; the enormous saving of life, curtailment of illness, and consequent advantage to the national economy, make it one of the most rewarding branches of medicine.

I have drawn freely on the expert knowledge and advice of many colleagues and friends at the Wellcome Research Laboratories, whose help has been unstinted. As in the case of previous editions, I am specially grateful to Mr. A. T. Glenny, F.R.S. (Jenner Medallist of the Royal Society of Medicine, and retired Head of the Immunology Department, Wellcome Research Laboratories), who read the entire book carefully and critically at an early stage of the revision, and made many valuable suggestions. Dr. E. Ashworth Underwood, Director of the Wellcome Historical Medical Museum, discussed with me certain aspects of the historical chapter.

Dr. W. C. Cockburn and Dr. J. C. McDonald, Central Public Health Laboratory, Colindale, supplied much new information about gamma globulin, which I have incorporated in the chapter on "Antiviral Sera." Dr. D. G. Madigan, Consultant Chest Physician, Bromley, made useful comments on Tuberculin Testing and B.C.G. Dr. L. J. M. Laurent, Consultant Physician, Hither

Green Hospital, London, placed once more his wide clinical knowledge unreservedly at my disposal ; I have also quoted freely from our joint publications.

I wish also to record my appreciation of the help of Mrs. M. Knight in preparing the typescript, and of Miss V. Anderson, who scrutinized the final manuscript. My thanks are due to Mr. E. A. Jones, who photographed suitable material. Finally, I have much pleasure in thanking my publishers for their helpful collaboration and courtesy throughout the ten years of our association.

H. J. P.

1958.

EXTRACT FROM 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.

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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GENERAL

CHAPTER I

THE USES OF SEROLOGICAL PREPARATIONS

BIOLOGICAL products used in infectious diseases may be divided into three groups, namely:

(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 by the clinician to detect the presence or absence of immunity and also of allergy. Most of these materials come within the scope of this book. A much larger group of diagnostic preparations used in the laboratory is excluded, for example, certain sera, extracts and suspensions used for Wassermann and other complement-fixation, precipitin, or agglutinin reactions.

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.

Although many benefits have already been derived from the administration of sera and prophylactics, still greater benefits might result from a better understanding of the non-specific physiological factors which control the phenomena of parasitism. The biochemist has so far failed to explain the complex bodily mechanisms underlying "lowering of resistance," variations in the nature and course of certain infections in different animal species, and even the yearly and local variations in prevalence of the common cold or of poliomyelitis.

The historical aspects of immunology are summarized in the final chapter of this book (*p.* 216).

CHAPTER II

IMMUNITY

IMMUNITY is of two types, either passive or active.

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 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, such as 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.)

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 immunization follows the entry into the body of virulent organisms in numbers too small to cause obvious disease, that is, a latent infection. Small quantities of *antigens* (components of

the organisms or products formed by their activity which may or may not be 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, tetanus and certain other infections), which may be detected in the blood stream and measured. But even if specific antibody is *not* present, the patient may still be potentially immune. Should a serious infection develop, the body is able to produce antibody 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. But clinical tetanus is noteworthy as giving rise to only poor immunity for a short period, even when the illness has been severe.

(2) **Artificial Immunization**

Artificial immunization aims at the production of antibody by safe means, for example,

(i) *in the case of diphtheria,* in man, 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 stimulate the production of antibody. The expression " formol toxoid " is sometimes used instead of toxoid. 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. Aluminium compounds are an example of " adjuvants," which may be used to improve antigenic potency.

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 of horses is very similar to that for diphtheria.

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

(iii) *In the case of tuberculosis,* by injecting a living bacterial vaccine, namely, either B.C.G. or vole-bacillus vaccine.

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

(v) *In the case of poliomyelitis,* by injecting formaldehyde-killed viral vaccine.

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 and killed viruses are used as vaccines.

COMPARISON OF PASSIVE AND ACTIVE IMMUNITY

The essential points may be summarized as follows:

PASSIVE IMMUNITY

. . . 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.

. . . 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.* 100).

ACTIVE IMMUNITY

. . . 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 or tetanus 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 the initial injection is inadequate, the resultant lies between the two standard responses and is termed an *intermediate response.*)

. . . is lost even more slowly than it is acquired; potential immunity (the acquired power of rapid production of antitoxin or other protective antibody) may remain for many years.

. . . 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, that is, 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.

Passive Immunity

Fig. 1 shows the rate of loss of horse serum in other animals. In man there may be a steady logarithmic loss over many weeks of 50 per cent. or more each week. An accelerated loss may occur in sensitive persons (*see* Barr and Sachs, 1955; Army Pathology Advisory Committee Report on the Prevention of Tetanus in the British Army).

Active Immunity

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, and the highest titre is reached some weeks later **(Fig. 2).**

When potent antigens such as A.P.T. (*see p.* 95) are used, a further injection given four or more weeks later acts as a *secondary stimulus*. 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 and the second injection acts as an *intermediate stimulus* **(Fig. 4).**