CLINICAL PATHOLOGY

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BLACKWELL
SCIENTIFIC PUBLICATIONS
OXFORD

FIRST PUBLISHED 1966

Printed in Great Britain in the City of Oxford by
THE ALDEN PRESS LIMITED
and bound by
THE KEMP HALL BINDERY

PREFACE

This book is intended to help students, housemen and general practitioners to make the best use of the Clinical Laboratory.

By applying basic biological principles to the problems presented in the diagnosis and treatment of the sick, we have attempted to bridge the gap between text-books of Clinical Medicine and manuals of Laboratory Technique. The book is divided into two parts. The first, on Clinical Microbiology, was written by one of us (J.D.A.G.) and the second, on The Processes of Disease, by the other (G.D.).

We are grateful to many who have helped us. The medical and technical staffs of our own department have given invaluable suggestions in showing how younger people react to what we have written. Drs E.S.Anderson, A.S.Beare, D.A.Cannon, W.J.Jopling, J.C.Kelsey, I.G.Murray, M.T.Parker; C.E.D.Taylor and Mr J.W.Barber-Lomax provided information in their own subjects for the section on Clinical Microbiology. Dr M.W.McNicol helped with the section on electrolytes and Dr T.L.Dormandy read the entire text of the second part of the book and made many useful suggestions.

We are also grateful to the medical artist, Mrs I.M.Prentice and to our secretaries Miss Margaret Cue and Mrs L.O'Callaghan. We acknowledge, too, the co-operation of the publishers and in particular Messrs Per Saugman and J.L.Robson.

We shall welcome constructive criticism which would help us to improve the book in a further printing.

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PART I

CLINICAL MICROBIOLOGY

I admonish all who have any knowledge in these matters that they write it down. Do it truly and plainly, not toilsomely and at great length, for the sake of those who seek and are glad to learn.

Albrecht Dürer
(1471–1528)

. . . except ye utter by the tongue words easy to be understood, how shall it be known what is spoken? For ye shall speak into the air.

I Corinthians, xiv, 9
(Authorized version)

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CHAPTER 1

THE MICROBIOLOGIST, THE CLINICIAN AND THE PATIENT

Pathology is no longer confined to recording the end-changes of disease as seen in post-mortem specimens. It now embraces a study of the living processes of the body and specially the disease processes so that any aberration may be recognized as soon as possible and any treatment appropriate for it may be initiated and controlled. This, then, is clinical pathology.

One of the functions of the clinical pathologist is the study of specimens taken from patients suspected of having some abnormality. For this, skilled laboratory techniques peculiar to microbiology, biochemistry, haematology and histology are required and much of this technical work can be and is legitimately carried out by the medical laboratory technicians. The most vital duty of the clinical pathologist, however, is to co-operate with the clinician in charge of the patient. The clinician and pathologist then pool the evidence which each has elicited from the patient so that with their past experience they may establish a true assessment of the patient's condition and, if possible, arrive at a diagnosis as a prerequisite for rational treatment. When the clinician asks the pathologist to carry out tests for him he should have a clear idea of the exact problem he wishes to have elucidated, but it is not part of his province to acquaint himself with the details of the laboratory techniques involved.

Towards the end of his undergraduate career the student prepares himself for his final examinations. He can, therefore, describe fully and accurately the symptoms and signs of a large number of clinical entities. When he becomes a houseman he finds, however, that the questions he has to answer are vastly different. He is usually the first to see the patient, from whom he elicits a history and symptoms and signs. From these he has to make his own diagnosis and initiate the treatment on his own responsibility, and in cases of difficulty he wonders whether the laboratory can help him, and if so, how. Which investigations will the seniors of his firm expect him to have asked for and which will the pathologist tell him are unnecessary? How, too, is he to interpret the pathologist's report and does it make necessary any immediate action?

We have written this book with these questions in mind. It is designed primarily for housemen and students on clinical firms. We hope that it will help them to use the facilities provided by the laboratory to the best advantage and to reduce the no-man's-land between them and the laboratory. We have tried to make the work as simple as possible so as to aid understanding, but without violating the facts. We hope, too, that our presentation of the principles underlying the tests used in the laboratories may be of use to postgraduate students who require this knowledge on which to base their clinical work.

The pathologist's role is not so simple as may at first sight appear to the clinician. Each of the specialist pathologists in a large hospital—bacteriologist, biochemist, haematologist and histologist—is faced with problems peculiar to his own subject.

For the bacteriologist the isolation and identification of any organism and the determination of its sensitivity to different antibiotics are all dependent on the collection of the right specimen at the right time, and before chemotherapy has begun, just as much as on the use of the correct methods of examination in the laboratory. Sometimes the selection of a particular portion of the material available is important and full clinical details should be furnished to guide the pathologist as to the exact methods he is to employ. Unfortunately it is usually the newest recruit to the staff of the ward who is given these responsible tasks and he may well not appreciate the importance of his duties and he may cause delay in transmitting the specimen to the laboratory, whereby it may be dried or chilled or otherwise rendered virtually useless.

The bacteriologist has perforce to depend largely on the results of growth in artificial media. Yet existence in a culture must be a poor exchange for life in an animal body where nutritional requirements are generously met and excreta are promptly removed. The cultural appearances give no indication of the variations which can occur in both the host and the parasite in natural infections. The environment provided by the medium determines the nutritional state of the organism it supports and may actually incite its variation. An organism grown in different media may show wide differences not only in the amount of its growth but in its virulence and even its antigenic structure. Many of these antigens play no part in either the pathogenicity of the organism or in the immunity of the host. Such antigenic changes are therefore not permanent and may confuse a taxonomist who depends solely on them. The bacteriologist therefore observes only the cruder morphological, cultural, biochemical and serological characters of the organisms he finds and attaches to them

taxonomic labels. Yet many of the phenomena he has observed have nothing to do with their parasitic life, and the deductions he may draw from their ability to infect laboratory animals are not necessarily applicable to the human subject. If the bacteriologist's work ends at this point, his reports may well be misleading and have disastrous consequences for the patient. These can be avoided by co-operation between the clinician and the bacteriologist and by correlating the clinical and laboratory findings. Further, the laboratory techniques are being constantly improved and the reports need no longer be so highly technical as to be unintelligible in the ward.

The bacteriologist may isolate and identify a known pathogen whose presence will fit in exactly with the patient's symptoms and signs. This will establish the diagnosis and possibly point to the appropriate treatment. Unfortunately the bacteriologist's work is rarely so dramatic and clear-cut. More frequently he finds difficulty in estimating what, if any, significance should be given to the presence of the organism he has found. It is not necessarily the cause of the patient's condition. The normal flora may have merely been altered or the organism found may be a harmless commensal and only a potential pathogen. Yet reputedly harmless organisms such as chromobacteria may occasionally be lethal. Even if the organism found is a known pathogen, its presence may not necessarily cause the patient's illness. Presence of a clostridium in a wound does not necessarily indicate an infection with it, and *Cl. welchii* in the vagina after a septic abortion may be harmless in one patient and quickly lethal in another. Coliform bacilli in a urine may be merely contaminants or indicate a cystitis. Staphylococci in a surgical wound may be mere accidental implants or the precursors of a fatal pyaemia in the patient and cross-infections in his contacts. Again, reinfection with tubercle bacilli after the acquisition of immunity is quite different from a primary infection. Typhoid bacilli isolated from a typhoid carrier may well deflect attention from an amoebic abscess in his liver. The all-important question to be answered is whether the organism is acting as a pathogen on the particular occasion on which it is found. Ideally the bacteriological and clinical findings should support each other. Clinical evidence will then make bacteriological findings significant, but when the latter are not so supported, they have to be interpreted with caution. The reverse is also true and repeatedly negative blood cultures may cast doubts on a diagnosis of subacute bacterial endocarditis.

The houseman should be warned against making unjustifiable deductions from the bacteriologist's reports. He may be tempted to select

from a mass of laboratory results only those which are in keeping with his clinical diagnosis and ignore all the other information. The presence of acid-fast bacilli does not *ipso facto* indicate tuberculosis, although it may well support such a diagnosis. When an organism cannot be revealed directly by isolation and identification, its presence may be deduced indirectly by the demonstration of antibodies specific to it. The tests for this are quantitative as well as qualitative and the results must be interpreted with caution. For instance, an antistreptolysin titre of 200 units per ml is only the upper limit of normal and must not be regarded as diagnostic of rheumatic fever. There are many pitfalls in the application of the results of serological tests to clinical work. In brucellosis proved by isolation of the organism, antibodies may never be demonstrable; their presence may be missed through the 'zone phenomenon' (page 317) or they may be merely the response to the injection of brucellin introduced intradermally as a test antigen. A positive Wassermann test is by no means synonymous with syphilis and may be merely a transient finding in pregnancy, primary atypical pneumonia, infectious mononucleosis and a wide variety of tropical diseases. It has also been occasionally noted after vaccination against smallpox or the injection of tetanus toxoid or foreign sera.

The work of the bacteriologist is subject to unavoidable delays which are not always appreciated by the clinician who, in his anxiety for his patient's welfare, is frequently in a hurry to collect all possible evidence to establish or confirm his diagnosis. The bacteriologist, on the other hand, has to wait for organisms to grow in his artificial media or for antibodies to develop in the patient. Appreciating his clinical colleagues' desire for quick results he may be tempted to report on specimens before sufficient time has elapsed for a complete investigation. The possibilities of misunderstanding are reduced if he makes it clear that his first report is merely an interim one and that a final report will follow. It is important, therefore, that the houseman should learn to appreciate the phrasing of the reports. Thus, a blood culture has to be kept incubated for at least a fortnight. It is inspected daily and as soon as a growth develops, it is reported. When, however, growth does not occur, an interim report is usually issued to the effect that no growth has occurred after 48 hours' incubation and a final report will follow. The use of highly selective media for the isolation of diphtheria and enteric bacilli delays the issue of a final report for at least 48 hours and may lead the clinician to think—quite unjustifiably—from the early reports that no pathogen was present.

All these difficulties stress the need for the closest possible co-operation between the clinical and laboratory staffs, and ideally the pathologist

should always be available for consultation at the bedside. Such an interchange of information can dispel some of the confusion which has arisen from the clinician and the pathologist each using a terminology appropriate to his own discipline but differing widely from that of the other. The surgeon and the pathologist may use the same word to express quite different meanings. The former may call the exudate of an acute peritonitis 'lymph', while 'lymph' to a pathologist means the fluid circulating within the lymphatic system. To a surgeon a haemolytic streptococcus is usually only the organism designated by the pathologist as a β haemolytic one, while the pathologist envisages by the same term the α haemolytic streptococci as well. Again, the clinician frequently uses terms such as nephrosis and goitre to indicate syndromes which have no exact pathological counterparts. Much of the medical terminology is confusing to the beginner. Lobular pneumonia is not lobar pneumonia but bronchopneumonia. Both are inflammations of the lung, but so also is pneumonitis, which may be either a virus pneumonia or a benign aspiration pneumonia. Enteric comprises typhoid and the paratyphoid fevers and they are all due to salmonellae, but salmonellae also cause food-poisoning: yet food-poisoning can be due to staphylococci, proteus or some of the clostridia.

It is the occurrence of unusual conditions which most frequently causes the clinician and the pathologist to consult each other. We have tried not to describe these rarities in detail out of proportion to the commoner conditions and we have tried to remember that 'rare conditions are rare' and that it is unjustifiable to make a really unusual diagnosis without full supporting evidence and unless no common diagnosis will fit the clinical picture presented by the patient. To make a rare diagnosis without these two conditions being fulfilled is a sign of lack of proportion rather than of an erudite knowledge of rare conditions. At the same time, the increased mobility of people and the immigration into the United Kingdom from tropical countries present many new problems in diagnosis. Leprosy is much commoner in the United Kingdom than it was twenty-five years ago and the early stages are easy to miss. Malaria is now seen comparatively frequently and leishmaniais has been found in a young woman after a fortnight's cycling holiday in France. The proper investigation of all such conditions needs collaboration with the laboratory. The epidemiology of a disease in one country is not necessarily the same in another and unless laboratory help is invoked, diseases which are due to different micro-organisms or different types of the same micro-organism may be erroneously regarded as epidemiological unities.

The results of research work are not always recorded in a form suitable for the routine investigations of patients. There is, therefore, a time lag before they are put to a practical use. This has the advantage that it may enable other workers to confirm them and assess their value before they are accepted. Gradually, however, the advances in knowledge, particularly in chemistry and virology, have increased both the number and the variety of methods available for the elucidation of disease and we have attempted to describe as concisely as we can the principles underlying these new tests. Sometimes a discovery acts as the opening of a door to an entirely new field and the workers in their eagerness to explore it leave behind the clinicians who have the responsibility for the care of patients. We have, therefore, tried to present in an assimilable form those parts of recent work which are of practical use in the elucidation of disease.

In addition to the pathologist's role in the diagnosis of the disease and the control of treatment an ever-increasing proportion of his time and energy has to be devoted to the prevention of disease and particularly the prevention of cross-infection within his hospital. The bacteriologist is now repeatedly asked for advice as to the need for disinfection of a ward or the method for sterilizing an instrument or the action required to prevent cross-infection, to identify and treat carriers and the methods of producing artificial immunity.

The part of this book dealing with microbiology begins with an account of definitive bacteriology, virology, protozoology and mycology. This has been limited to the organisms met with in clinical pathology. Descriptions of the criteria by which these organisms are recognized have been kept to a minimum consistent with affording the clinician an insight into the work done in the laboratory and an appreciation of the successes as well as the limitations of the methods employed. Technical methods have been deliberately omitted. The main part of the microbiological section has been arranged according to regional anatomy and descriptions have been given of the natural defence mechanisms and how they are overcome by the invaders; the resulting infections, infestations and hypersensitive states; their investigation; their treatment and their prevention by artificial means. Finally, preventive measures are described for the community, the hospital, the laboratory staff and the individual.

CHAPTER 2

INFECTION, INFLAMMATION, IMMUNITY, HYPERSENSITIVITY

Pathologia animata
Christian Lange (1619–62)

INFECTION

Infection is the invasion of the tissues by microbes, i.e. bacteria, viruses, rickettsias, protozoa or fungi.

The body is continuously in contact with microbes and is a potential host to many of them. It usually succeeds in preventing their invasion by means of its normal defence mechanisms. These are non-specific inasmuch as they are not directed against any particular microbe and they consist of:

1. The mechanical barrier presented by the skin and mucous membranes.
2. The antibiotic action of commensal organisms.
3. The antimicrobial action of the body fluids and cells.
4. The phagocytic powers of the body cells.
5. The general nutrition of the body.

1. *The Skin and Mucous Membranes*

These act as a mechanical barrier to organisms. Its strength varies with the different types of epithelium. The horny layers of stratified squamous epithelium present a stronger barrier than cuboidal or columnar epithelium, and both these are more effective than the epithelium of the conjunctiva.

Staphylococci and the spirochaete of syphilis can go through the unbroken skin, and if the skin has become sodden by prolonged immersion in water, *Leptospira icterohaemorrhagiae* can also penetrate it. Other organisms require a breach in the continuity of the surface for their entry, and this may be provided by wounds, burns and the bites of animals, including insects, ticks and mites. The mechanical defence of the skin is also broken down in exfoliative conditions and then the flakes of desquamated skin may bear enormous numbers of pathogens.

Deficiency of vitamin A produces changes in the skin, eyes and mucosae of the alimentary and respiratory tracts which markedly reduce their power to resist infection. This is common in Africa and China, and the

'toadskin' of Ceylon is an example. Many minor infections of the skin in infants in this country are helped by exhibiting vitamin A. Deficiency of vitamin B as seen in pellagra is also associated with skin infections, and deficiency of vitamin C is often a precursor of gingivitis.

The resistance of the skin is probably less effective against viruses than against bacteria and a herpetic whitlow is common in nurses working in neurosurgical units (page 134).

2. *The Antibiotic Action of Commensal Organisms*

The commensal organisms on the skin and in the respiratory and alimentary tracts are a powerful deterrent to potential intruders. The lactobacilli of the vagina produce acid which is inimical to β haemolytic streptococci. The streptococci of the mouth produce hydrogen peroxide which kills meningococci and diphtheria bacilli. When these useful commensals are inhibited or destroyed they may be replaced by highly pathogenic organisms. A broad-spectrum antibiotic may exterminate the coliform organisms in the bowel to allow a dangerous superinfection by organisms resistant to the antibiotic, such as staphylococci and monilias.

3. *The Antimicrobial Action of the Body Fluids and Cells*

Antibacterial substances are normally present in the mucous secretions, the red and white cells of the blood and tissue cells, the serum and the milk. The secretion of the healthy skin contains long-chain fatty acids (such as oleic acid). These are not strongly inimical to the commensals on the skin such as *Staphylococcus saprophyticus*, but they quickly reduce the number of haemolytic streptococci, diphtheria bacilli and other pathogens. The modern use of detergents, however, tends to remove these protective substances.

On the conjunctivae and mucosae there is a similar destruction of potentially pathogenic organisms. This leaves a flora which is more or less specific to the particular area and common to different individuals. Thus the lysozyme in tears (and in the nasal secretion) has a specific lytic action on some organisms. The mucus secreted by the mucous membranes confers a considerable degree of protection and many intruders are mechanically removed by the cilia of the bronchi and by the peristalsis and evacuation of the intestine. The saliva, too, though harmless to the organisms normally in the mouth, is inimical to meningococci. The gastric secretion with its free hydrochloric acid destroys many of the bacteria ingested other than tubercle bacilli.

Substances in blood cells and the body cells which are lethal to bacteria