THE PHYSIOLOGY OF DISEASE

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PREFACE

THERE IS a growing tendency to introduce medical students to clinical work at an early stage in their course. This policy encourages the student to harness his vocational interest in medical matters to the acquisition of the necessary knowledge of the basic medical sciences. It also tends to blur the artificial distinction between preclinical and clinical training. The purpose of this book is to assist the student to integrate the preclinical and clinical subjects. Our aim has been to explain the physiology of disease in language and concepts that a junior student can redily understand, and thereby to ease the transition from preclinical to clinical work. We hope the book will be useful throughout the clinical years and help those people who are interested in improving their knowledge of physiological mechanisms in disease.

The book deals more with the events which occur when normal physiology breaks down than with the disease processes that cause the breakdown. Thus the student who is familiar with normal physiology should find it relatively easy to understand the material. The newcomer to clinical studies is sometimes overwhelmed and depressed by the great number and variety of diseases that can attack man. The transition is made easier if he realizes that damage to a body system usually leads to a logical and recognizable collection of effects which is relatively independent of the agent causing the damage. There are only a few *basic* clinical pictures associated with any system and this book attempts to describe and explain them.

The concepts upon which this book is based have developed as a result of our experience of teaching applied physiology to medical students in Belfast. We thank our student and professional colleagues for their helpful comments during the production of this book. We are also very grateful to the following clinical colleagues who looked at drafts of sections dealing with their own speciality and whose suggestions, which were most helpful, have been incorporated in the text: Drs. B. N. Barwin, J. S. Geddes, D. R. Hadden, Messrs. S. S. Johnston, A. G. Kerr, Drs. Jean H. M. Langlands, J. A. Lyttle, Professor A. H. G. Love, Drs. Elizabeth E. Mayne, J. McEvoy and T. A. McNeill.

We would still be struggling with our untidy preliminary drafts were it not for the skilful typing assistance of Miss Margaret Wilkinson and the draughtmanship of Messrs. C. Ferris, S. McGrann and H. Turtle. We would also like to thank Mr. Douglas Luke of Lloyd-Luke (Medical Books) Ltd. for his courtesy and helpfulness extended to us continuously throughout the preparation of this book.

Finally, we would appeal to our readers, especially students, to write to us about any parts of the book which seem inaccurate, incomplete, or difficult to follow.

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Belfast, *August 1974*

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Section I

INTRODUCTION

1. THE MISSING LINK

TOO OFTEN Physiology and the clinical subjects appear separate and clearly demarcated from one another so that the student leaves behind and forgets much of his physiological knowledge before he has the opportunity to relate it to his developing knowledge of Clinical Medicine. As the mechanisms of disease become more fully understood, applied Physiology is acquiring an increasing importance in clinical subjects. The aim of this book is to help the student to develop and maintain for himself the link between Physiology and Clinical Medicine. The book has been written primarily for the student who has completed a course in basic Physiology and is beginning his clinical studies. It is assumed that the reader has a general knowledge of normal human Physiology and its vocabulary, and an attempt is made to describe the effects and treatment of disease in the words and concepts of Physiology.

In this book we have concentrated on this relationship between Physiology and Medicine. Considerable space has been given to attempts to explain important concepts which students tend to find difficult to grasp. On the other hand, long and complete lists of the causes of disease have been largely omitted, as have descriptions of diseases and treatments whose explanation is as yet poorly understood. At the same time we have tried to maintain a sense of proportion by emphasizing items to some extent according to their clinical importance. We hope that a clinician reading this book will not find himself in a strange and rarified atmosphere of uncommon conditions and impracticable investigations.

Our plan of approach is to consider various disordered functions, for example, anaemia, heart failure, vomiting, renal failure, under the following headings:

1. **Definition:** Definition of condition in terms of physiological abnormality.
2. **Effects:** Description of effects in terms of disturbance of normal function.
3. **Causes:** Underlying causes of condition considered in physiological terms.
4. **Investigations:** Analysis of body fluids and other procedures which help to increase knowledge of abnormalities of function.
5. **Treatment:** Brief outline of treatment seen as an attempt to overcome or compensate for physiological abnormality.

When a student is interested in a specific clinical symptom or sign, such as cyanosis or dyspnoea, he should consult the index.

Many diseases, like many normal functions, cannot yet be explained satisfactorily in physiological terms. Students often waste time in a fruitless attempt to penetrate the screen of words that teachers use to mask their ignorance. We have tried as far as possible to distinguish clearly between what is known and what is not, between what is fact and what is speculation. This has been done in the hope that a student who has read a section will not feel inadequate because he has failed to comprehend what is in fact incomprehensible.

2. NORMAL VALUES

WE DO NOT generally refer to normal values for the various tests mentioned in this book because we are concerned mainly with the mechanisms of disease rather than precise criteria for diagnosis. Normal values are given in most textbooks of Medicine. In addition, the usual ranges of normal results are being increasingly often quoted with the patient's results on laboratory report forms. This is useful, because results for some tests vary from laboratory to laboratory and also it avoids the unnecessary task of trying to remember the ranges for all possible tests. There is by no means general agreement on the normal ranges for some tests as Table I shows with respect to the platelet count. In such cases, if one wishes to remember the normal range, it is reasonable to select one which is easy to remember, bearing in mind that all normal ranges are only approximate guides.

When interpreting the results of tests, it must be remembered that, due to normal variation, a few healthy people will have results outside the expected range. The upper and lower "limits of normality" are diffuse zones rather than linear boundaries. If the mean of a group of "normal" people $\pm$ 2 standard deviations is regarded as the "normal range" then 5 per cent of normal people must lie outside the normal range.

The more biochemical tests are carried out on an individual, the more chances the individual has of being classified as abnormal on at least one occasion. It is probably better to think of average values and standard deviations, rather than normality and abnormality.

A recent review article (*British Medical Journal* 1972, 1, 328) discusses the problem with respect to the white cell count. It quotes the case of an apparently healthy man whose white cell count over a period of seven years was usually above 25,000/mm^3—more than twice the generally accepted upper limit of

TABLE I

Quoted ranges for the normal platelet count in some textbooks of Physiology (P) and Medicine (M) as an example of the absence of general agreement on normal ranges. To be "normal" by all these standards, the platelet count would have to lie between 200,000 and 300,000. On the other hand, counts between 100,000 and 500,000 would fall within at least one of the normal ranges.

Textbook	*Platelet range/mm^3*
Bell, Davidson & Emslie-Smith (P) 1972	100,000-500,000
Best & Taylor (P) 1966	200,000-400,000
Cecil & Loeb (M) 1967	150,000-450,000
Davidson (M) 1971	150,000-400,000
Guyton (P) 1971	150,000-300,000
Harrison (M) 1970	140,000-440,000
Horrobin (P) 1968	150,000-500,000
Price (M) 1973	150,000-400,000
Samson Wright (P) 1971	150,000-350,000

normality. It is of significance that he was anxious about this abnormality. If it is necessary to carry out further investigations in such cases, considerable experience is required to know when investigations should cease; the patient must be reassured as far as possible. In some cases, it may be best to ignore a single abnormal result out of keeping with the patient's general condition.

For some tests, such as lung function tests, results depend so markedly on body size, age and sex, that expected results must be worked out for each individual. Blood indices, such as haemoglobin concentration, are higher in men than in women. Racial differences also occur. In addition to variations in the basic adult normal values, some tests have quite different results in children, and particularly in the newborn, as compared with adults. Some blood constituents, e.g. cortisol, fluctuate markedly throughout the day, and this regular diurnal variation means that sampling time must be known when the significance of the result is being considered. If there is doubt about the significance to be attached to the result of a particular test, it is often very helpful to consult the laboratory staff where the test was carried out.

3. RESERVE, COMPENSATION AND FAILURE

IN STUDYING the physiological consequences of breakdown of normal function in an organ, one may oversimplify by equating normal function with health and loss of function with illness. The body is a very durable machine with a formidable array of overlapping mechanisms for maintaining a state of normality. Thus when one mechanism breaks down, another usually takes over its function. This provides the body with defence in depth against injury. If this were not the case, man would be very vulnerable as there would not be any way of compensating for bodily damage.

This fact has considerable implications in understanding the effects of disease. Because the body can readily adapt to damage, damage or disease may be present without any obvious decrease in the ability of the body to carry out its normal activity. Damage usually has to be severe and widespread before signs of organ failure become manifest. When looking at the effect of disease processes on physiological functions, it is just as important to understand how the body compensates for loss of function as to understand how failure of that function affects the body as a whole.

Bearing this in mind, it is useful to consider the gradual erosion of function by disease as a process which occurs in stages. First there is the stage of falling reserve, then the stage of compensation and finally the stage of manifest failure. These stages will now be considered in some examples of disturbed function.

1. Loss of Renal Function

STAGE OF FALLING RESERVE

One of the functions of the kidneys is to excrete the urea produced by the deamination of amino-acids. Although urea is relatively harmless, its handling by the kidney provides a useful indication of the ability of the kidney to excrete more harmful but less easily measurable substances. On an average diet, a normal person would excrete about 20 g/day. If, as the result of disease or injury he lost one of his kidneys, he still would have no difficulty in excreting the normal daily output of urea. There would be no evidence from this function that he had lost half his renal tissue.

The reason for this is the enormous reserve of renal function; there is about 75 per cent more renal tissue than is needed to deal with the average day-to-day requirements for excreting urea. Because of this, widespread disease and destruction may be present in the kidneys without affecting urea excretion.

However the person with one kidney is a much less versatile and durable animal than the person with two. Firstly, with loss of reserve function, he has not the same ability to cope with extreme conditions, e.g. water, protein, or salt excess. Secondly, he is less able to cope with further renal damage than a normal person. By losing one kidney, he is made more vulnerable and his chances of survival are correspondingly decreased.

Stage of Compensation

When disease has eroded the reserves of function in an organ, function can still be maintained at an adequate level to support life by compensatory mechanisms. In the case of the kidneys and urea excretion, the normal output of about 20 g/day can be maintained by the employment of a variety of stratagems which increase the output of urine.

A rise in the blood urea level allows a higher concentration of urea to be presented to the nephrons which still function. The osmotic effect of this urea will result in an increase in urine output. A high level of urea in the plasma may compensate for a low urea clearance value; urea excretion = (plasma concentration) (clearance volume). In severe renal disease, limitation of renal blood flow may increase the release of renin and thus the arterial pressure. This tends to increase filtration at functional glomeruli and thus increase urinary output. Loss of renal function includes loss of the ability to concentrate urine. In these circumstances the reabsorption of urea by the renal tubules is decreased and the excretion in the urine correspondingly increased.

Stage of Manifest Failure

This can be considered a stage of *decompensation,* i.e. failure of function supervening when the compensatory mechanisms have been exhausted or overwhelmed. In the case of the kidneys and urea excretion, decompensation means that the normal daily production of urea cannot be excreted. The output falls below 20 g/day and urea steadily accumulates in the blood until death occurs.

It is at this stage that outside help is required if the patient is to survive, because the reserve and compensation mechanisms are exhausted. For example, he can be given a diet which is low in protein but sufficiently high in carbohydrate that he does not need to use his body protein to provide energy. These measures will reduce the rate of urea production in the body. His blood vessels may be connected to an "artificial kidney" so that his blood is dialysed outside the body. If a suitable donor is found, transplantation of a healthy kidney into the patient may permit renal function to rise again to a level which is compatible with life.

The stages described above are not always discrete and vary considerably from organ to organ. However, even if the stages overlap to some extent, it is useful to consider loss of function in terms of the stages. The concept can be applied to loss of function in nearly any system.

2. Loss of Muscle Joint Sense

Sensory information from receptors in muscles and joints about the position of the body are carried to the brain in the posterior columns of the spinal cord. This information is necessary for the execution of appropriate muscular movements in voluntary activity such as walking. Various diseases such as multiple sclerosis or sub-acute combined degeneration of the spinal cord cause progressive damage to these tracts. In the *stage of falling reserve,* the patient is able to walk normally without showing any sign of the spinal cord damage. However,