BASIC PATHOLOGY
AND
MORBID HISTOLOGY

BY

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PREFACE

THIS book is designed to help the student who has just begun the study of Pathology and finds the subject difficult. Experience in teaching Pathology suggests two main reasons for such difficulty. The student may have such limited knowledge of Clinical Medicine that Pathology becomes a dead science or he may find the microscopical appearances of diseased tissues so far removed from normal histology that a meaningless picture is presented. Baffled by these difficulties some are tempted to abandon the effort to master the subject.

This book is based upon the first-year course in Pathology and is designed to help the student through these initial difficulties, and strives to graft on to the student's knowledge of Physiology sufficient clinical information to make Pathology live.

I have found that photomicrographs are often more incomprehensible to the student than the slides which they are intended to interpret. I have therefore illustrated this book with camera lucida drawings in colour and in black and white. In many cases the drawings have been grouped together for ease of comparison and to facilitate correlation of clinical and pathological data. All drawings are annotated.

Diagrams have been introduced to shorten and simplify the text and to provide condensed information to which the student can refer when revising for the final examination.

A few references have been included; these are not intended to be a complete list. They fall into two categories: (*a*) References to early work, included because these are often difficult to find in the literature; (*b*) References to modern work which may be of particular interest to the student.

If any more senior readers should find the analogies used in the text a little elementary, I trust that they will realize that the book was written for students and not for professors! The occasional lighter touch has been introduced deliberately because experience has taught that it helps the student to remember.

Acknowledgements: My friends and colleagues of the Department of Pathology at Cambridge have given me much assistance in the preparation of this book. My special thanks are due to Dr. A. M. Barrett, who not only read the whole text but also helped select suitable material for a number of the illustrations. I am also deeply indebted to Professor H. R. Dean, Dr. G. P. McCullagh, Dr. R. I. N. Greaves, Dr. G. Fulton Roberts, and Dr. K. C. Dixon for valuable help and suggestions. Dr. M. Hynes helped with the chapters on blood diseases. Mrs. A. Snow and Dr. G. E. Grove helped me with the manuscript. *Figs.* 24, 97–100, 106, 107, 168, 220–225, and 232–236 were drawn by Mr. Tudor Hart. My wife helped me with several of the illustrations, and Mr. G. C. Spurgeon gave valuable assistance with the diagrams.

D. B. C.

June, 1953.

CORRIGENDA

p. 84 *for* Mari *read* Marie
p. 141 *for* Antibuse *read* antabuse
p. 161 *for* Heuper *read* Hueper
p. 214 *for acidophils read eosinophils*
p. 273 *for* Guttman *read* Gutman

CONTENTS

PART I

THE REACTION OF THE BODY TO INFECTION

CHAPTER		PAGE
I.	Introduction	3
II.	The Battle of the Cells	5
III.	The Mobilization of Defence: The Inflammatory Reaction	12
IV.	Phagocytosis	19
V.	Spread of Bacteria in the Body	26
VI.	Resolution and Repair	38
VII.	Further Examples of Acute Inflammation	44
VIII.	Typhoid Fever	57
IX.	Tuberculosis	63
X.	Syphilis	84

PART II

DISEASES DUE TO BREAKDOWN OF PHYSIOLOGICAL MECHANISMS

XI.	Thrombosis, Embolism, and Infarction	101
XII.	Gangrene and Ulceration	118
XIII.	Trauma and Shock	128
XIV.	Degeneration and Necrosis of Specialized Cells	136
XV.	Atheroma	155
XVI.	Hypertension and Renal Disease	163
XVII.	Heart Failure	183
XVIII.	The Anæmias	203
XIX.	Leukæmias and Associated Conditions	214

PART III

TUMOURS

XX.	Introduction—Some General Aspects of Growth	227
XXI.	Tumours arising from Mesenchyme	230
XXII.	Tumours arising in Cartilage and Bone	238
XXIII.	Tumours of the Skin	244
XXIV.	Carcinoma of the Stomach and Large Intestine	252
XXV.	Tumours of the Breast	259
XXVI.	Cancerous and Precancerous Lesions of the Uterus and Placenta	266
XXVII.	Further Examples of Tumours which manufacture Hormones or are under Hormonic Control	270
XXVIII.	Teratoma, Hamartoma, and Mixed Tumours	275
XXIX.	Certain Important Tumours and their Mode of Spread—Carcinomata of the Bronchus and Kidney, Papillomata of the Bladder	283
XXX.	Intracranial and Allied Tumours	289
XXXI.	Experimental Methods in the Study of Tumours	298
XXXII.	The Role of Biological Principles in the Aetiology of Cancer	311
	Index	321

PART I

THE REACTION OF THE BODY TO INFECTION

BASIC PATHOLOGY AND MORBID HISTOLOGY

CHAPTER I

INTRODUCTION

OUR minds can only understand new ideas in terms of what is already clearly grasped. A new subject can therefore only be understood in the light of knowledge with which the student is already familiar. Pathology must therefore be grafted upon a vigorous stock of physiology and histology, and, in addition, certain fundamental principles must be explained in terms of analogies which are intelligible to all.

There are two ways of presenting a new subject. One is exposition by a classification of the facts : this method is neat and orderly but is apt to get hidebound in logic. A second method is to retrace the steps of the pioneers ; and this is usually the most interesting and fruitful approach, since they pitted their science and skill against the most obvious and important problems.

We could classify diseases into those caused by faulty heredity, developmental errors, abnormal physiology of hormones and glands, faulty nutrition ; those caused by failure of the blood-supply to the tissues, injury by physical or chemical agents, infections by bacteria or protozoan and metazoan parasites ; and, finally, the great enigma of cancer. We could set out these main aetiological factors of disease and study them one by one, but there are disadvantages in such a treatment. In the first place, you have already been introduced to some of these diseases when you studied biology, anatomy, and physiology. No attempt will be made in this introduction to pathology to review the ground already covered, and there are only brief references to congenital abnormalities, nutritional diseases, metabolic diseases, and parasitic infestations. In the second place, the cause of disease is only half the story ; the reaction of the body to the disease is the other, and equally important, half of pathology.

At the heart of pathology there lies a battle—a battle waged between man and his unfavourable environment. This is clearly seen if we study the struggle between a patient and an invading host of streptococci. It is equally true when we study the effects of injury, although here the unfavourable environment might consist of the wheel of a motor car or an incendiary bomb. Just as a student of history must study the tactics of each side engaged in a battle, so a student of pathology must consider both the aggressor and the defences of the victim of aggression : each is of equal importance ; each must engage his attention.

This analogy helps us to understand two other important facts about pathology. A battle is full of stirring action and dramatic incident. Pathology is just as dynamic. An intense drama is being enacted, which in man may be suddenly stopped, either by removal of the affected part by operation or by the death of the patient. How different from this is the impression gained by many a student that pathology is a science of dead things—a static subject; a science whose high altar is the marble slab of the post-mortem room; a science whose devotees haunt dusty museums, gazing at bottled specimens, or who peer endlessly into microscopes at *dead* fixed tissues. Pathology can be dry as dust if taken that way; or it can be the subject which floods light and understanding upon clinical medicine and surgery. It can become the saga of a battle waged by living organisms for survival, if you will take the trouble to reconstruct the story from the available evidence. In some cases it is rather like reconstructing a drama of the stage or screen from a series of still pictures of important scenes. It is always important to realize, when examining pathological tissues, that you are looking at a dynamic process which has suddenly been arrested.

Then, too, a battle is full of surprises: both sides are able to alter tactics. The aggressor, held on one front, may suddenly start a new and unforeseen offensive—which may, in its turn, be countered by fresh methods of defence. This is equally true of modern warfare and of the age-long conflict between bacteria and man. Both the invading bacteria and man, being living organisms, are adaptable; and the battle between them is as fascinating an interplay of attack and counter-attack as any modern campaign. Discover a new aid to man's defence like penicillin, and you start to breed a race of penicillin-insensitive staphylococci—and so it goes on. The fortunes of war are unpredictable!

To sum up: we will begin our study of pathology where the early pathologists began it, with a study of the effects of disease and injury upon man. When we study pathology, it is as if we are watching the film of a great battle, but cannot grasp every aspect of the conflict unless the film is halted. Experimental disease in animals can be stopped at suitable intervals in order to see the way in which the disease develops. In human pathology the morbid anatomy can only be studied when operation or death interrupts the unfolding drama of disease. This book is full of still pictures of what is a truly dynamic process. The student must realize, at the outset, that his task in medicine is to gain a vivid picture of the *natural history of the disease*. This includes the clinical history, clinical signs, the pathological findings (both naked-eye and microscopical), an understanding of the physiological disturbances which have occurred, and a knowledge of the agent which has caused the disease. These must all be integrated into one vital whole—the *clinico-pathological picture*.

CHAPTER II

THE BATTLE OF THE CELLS

In Chapter I the struggle between an invading organism and its victim—man—was likened to a battle. In any severe infection it would be nearer the truth to call it, not a battle, but total warfare.

In the wars of the past there have been many different types of invasion—by land, sea, and air. The human body can likewise be invaded by organisms using different, and often characteristic, portals of entry. Some organisms usually enter by wounds (staphylococci, streptococci, *Clostridium welchii*, etc.); others tend to spread along mucous membranes, e.g., the virus of influenza spreading along the respiratory passages, or the gonococcus spreading along the epithelia of the genito-urinary system. There are organisms, such as *Salmonella typhi*, which gain access to the body via the intestines; while others like *Mycobacterium tuberculosis* or *Str. hæmolyticus* may enter in several different ways. This kind of information, however, belongs to the natural history of the disease, and will be described in detail later. For the moment, let us describe, in general terms, what happens if the body is invaded by staphylococci or streptococci through a wound. Let us study the general organization of the body for defence against such a wound infection.

Any modern state liable to be called upon to resist aggression will maintain a peace-time army. The body is no exception in this respect, for it maintains a normal peace-time army of some 7000 leucocytes per c.mm. of blood, of which some 3500 per c.mm. are polymorphonuclear leucocytes, which can be considered as the 'shock troops' of the war against bacteria. This peace-time army of leucocytes is produced in the red bone-marrow—a highly active tissue comparable in size with the liver. About three-quarters of it is normally producing leucocytes. The bone-marrow can therefore be considered the 'home base' for the recruiting and equipping of the army of leucocytes, which, when they leave the bone-marrow, will enter the blood-stream, where they can be considered 'troops in transit'. The life of the polymorph is a short, and presumably merry, one of from three to five days. Old, effete, or damaged polymorphs are destroyed by the macrophages of the recticulo-endothelial system—phagocytic cells in the spleen, lymph-nodes, liver, and bone-marrow.

The spleen can therefore be regarded as one of the main 'demobilization centres'. Nucleic acid and some of its breakdown products increase the number of polymorphs in the circulating blood, and cause enlargement or *hyperplasia* of the active bone-marrow producing these cells. This state of affairs suggests that nuclear breakdown products of polymorphs destroyed in

the recticulo-endothelial system may be returned to the bone-marrow, and there stimulate production of a new batch of cells—analogous to a return of equipment from a demobilization centre to the home base. *Figs.* 1 and 2

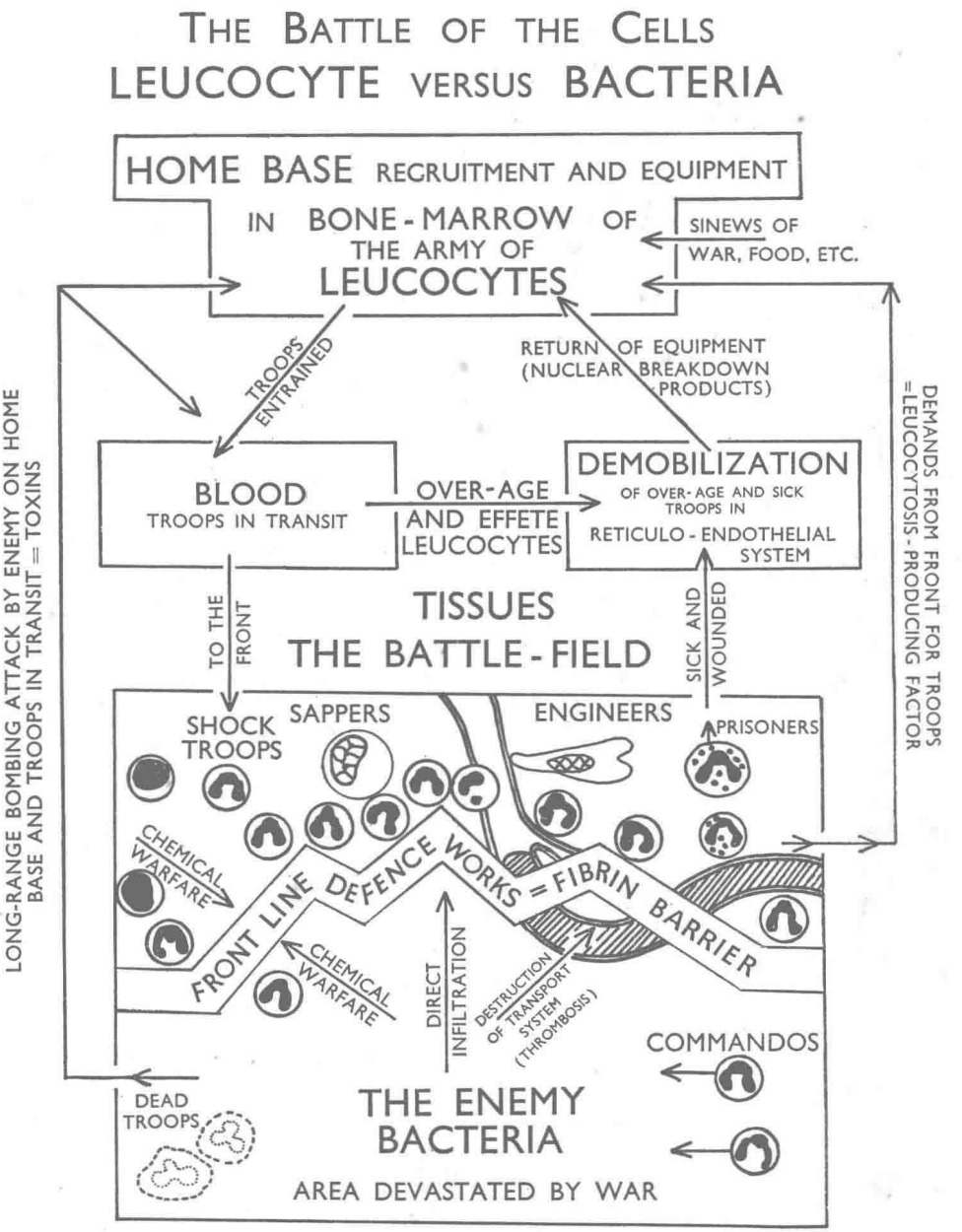

Fig. 1.

represent diagrammatically the general arrangement of the peace-time army of some twenty billion polymorphonuclear leucocytes and an equal number of other types of cells.

PRODUCTION AND DESTRUCTION OF LEUCOCYTES

MARROW INHIBITED BY :—

STARVATION and dietary deficiencies. Mitotic Poisons: Radium, X rays, benzol, nitrogen mustards, colchicine, carcinogenic hydrocarbons, urethane; also other drugs—organic arsenicals, thiouracil, and gold salts

MARROW STIMULATED BY :—

Products of nuclear breakdown (? normal physiological stimulus), small doses of inhibitory agents, leucocytosis-producing factor, and the unknown causes of leukæmias

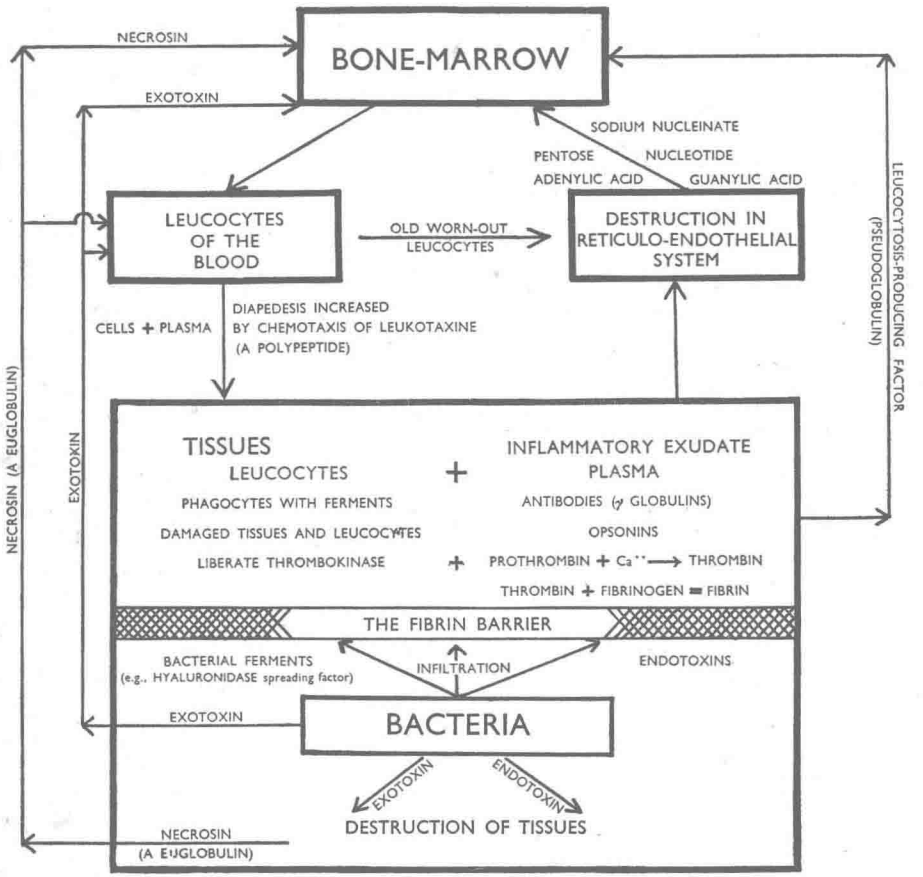

Fig. 2.

Now into the tissues let us introduce the invading bacteria in the shape of pathogenic *Staph. aureus*. These invaders, by their extremely rapid multiplication, build up their own army of aggression. Supposing East Anglia was suddenly invaded by a hostile force ; within a few hours, all the railways and roads leading to that part of England would be swarming with trains and lorrys taking troops and supplies towards the centre of the invasion. At first the traffic would move rapidly, but presently traffic congestion might slow the almost continuous columns of vehicles to walking pace. This mobilization of defence is entirely comparable with the inflammatory reaction which develops when infection enters the body. The local arterioles dilate, all capillaries open up, and the blood-stream moves more rapidly at first, and then slows down as the capillaries become lined with leucocytes, which proceed to migrate through the walls of capillaries and veins into the damaged tissues. The inflammatory reaction thus takes some of the army of leucocytes to the front. In addition, the dilated capillaries are more permeable than normal and leak plasma into the damaged area. This plasma will clot into a meshwork of fibrin. Such a ' fibrin barrier ' forms in the tissues in many infections, particularly those due to staphylococci, and, manned by the polymorphs, forms a first-line defence, which may be likened to a barbed-wire entanglement held by good shock troops.

Many of the polymorphs emulate Commandos and go into enemy territory, engulfing in their own bodies the staphylococci, taking prisoners, or (if you are more familiar with scientific language) destroying them by *phagocytosis*. Many of these polymorphs perish in ' No man's land ', liberating proteolytic enzymes. The mixture of bacteria, living and dead leucocytes, with liquefied products of destroyed tissues, constitutes pus. Other polymorphs, maybe with a load of prisoners, will be damaged, and both they and their prisoners will have to be dealt with by the reticulo-endothelial system. Thus it comes about that the local lymph-nodes enlarge, and, in more severe infections, the spleen as well.

We must now investigate the tactics of the enemy. What methods of aggression are used ? If the bacteria merely diverted to their own use the food supplies designed for the body, that would be bad enough, but in addition to ' living off the land ', the invading army has weapons which destroy the local tissues, and also has methods of spread into the surrounding healthy tissues. The local spread of infection is accomplished by three methods : by direct infiltration, by cutting lines of communication, and by chemical warfare. First, by direct infiltration through the fibrin barrier and wall of leucocytes. For this purpose the organism is armed with toxins and with enzymes. The staphylococcus has powerful toxins which not only hæmolyse red blood-cells and destroy local tissues, but kill leucocytes. These *hæmolysins* and *leucocidins* are definitely associated with its pathogenicity or *virulence*. In addition, the staphylococcus produces an enzyme, *coagulase*, which causes fibrin to clot (this may account for the fibrin barrier being such a prominent

feature of these infections). It also produces an enzyme, *hyaluronidase* (the spreading factor), which breaks down hyaluronic acid, the polymerized polysaccharide which forms the extracellular ground substance of developing connective tissue. The hæmolytic streptococcus, which is more invasive than the staphylococcus, not only forms toxins of the hæmolysin and leucocidin type, but also produces hyaluronidase and a powerful *fibrinolysin* which dissolves the fibrin barrier or prevents its formation. Thus the bacterial enemy is able to destroy the fibrin barrier and slay the polymorphs which defend it.

Perhaps the coagulase of the staphylococcus does not handicap it as much as would appear at first sight, because one important tactic in invasive warfare is to get across the defenders' lines of communication, and to cut off supplies to a zone of territory. This is a second method by which bacteria may enlarge their field of operation, for if a vessel runs through the infected area and becomes thrombosed, the area which it supplies will be invaded. Note the thrombosed vessel in *Fig.* 1. This could have been represented as a railway line entering the battlefield. Infective thrombosis is an important element in staphylococcal infections, as we shall see later.

Local spread is obviously of great importance, because eventually it may open the way for the bacteria into the main lines of communication—the lymphatics and the blood-stream—with serious or fatal consequences. But the invading organisms may win the war long before they have overrun their victim's territory. The poisonous substances, or toxins, which they produce are not only effective locally, but, diffusing into the blood- and lymph-streams, exert their effect widely. Thus leucocidins may damage or kill leucocytes before they reach the site of infection. Toxins may inhibit the power of the bone-marrow to produce fresh polymorphs. The function of the heart, circulation, and essential organs may also be impaired. It is rather like the shelling of troops in transit, and bombing of the home base and vital industries, which form such an important part of total warfare. Against these toxins, or this chemical warfare, the body may take some days to prepare an adequate defence. Given time, antibodies will be produced, possibly formed by the cells of the reticulo-endothelial system, and by the lymphocytes which will begin to accumulate around the local lesion. Both the cells of the reticulo-endothelial system and lymphocytes are now believed to make, and to shed off into the circulation, the globulins which are the active constituents of the antibodies or humoral defence mechanism of the body.

Turning from the weapons of the bacteria, we must consider in more detail the defences of the host, which we left at the stage of the first hurriedly constructed defence line—a fibrin barrier manned by polymorphs. Menkin, besides emphasizing the importance of the fibrin barrier, has recently isolated a crystalline diffusible *polypeptide* from inflammatory exudates. This he calls *leukotaxine*. It causes rapid dilatation of the capillaries and an outpouring of plasma and leucocytes. Menkin believes that *chemotaxis* by this substance is

responsible for the *emigration* of the leucocytes through the walls of the capillaries into an inflamed area. He has also isolated from inflammatory exudates (produced by injection of turpentine) a *pseudoglobulin*, which, injected intravenously, produces marked increase in the number of leucocytes in the blood (a *leucocytosis*). Whether this *leucocytosis-promoting factor*, or the increased destruction of white cells is responsible, there can be no doubt about the clinical fact that in many severe infections there is a marked leucocytosis. In pneumonia, for instance, counts of 30,000–50,000 may occur. Just as, in total warfare, urgent dispatches will come back from the front for reinforcements, and the army will be markedly increased in number, so in infection the number of polymorphs in the normal peace-time army may be increased as much as tenfold.

Menkin has also isolated a *euglobulin* from inflammatory exudates, which he calls *necrosin*. On injection this causes signs of acute inflammation and fever, together with a reduction of the number of white cells in the blood, or a *leucopenia*. As this substance is produced when normal tissues are damaged by chemical irritants, its effects, although similar, must be carefully distinguished from those of bacterial exotoxins. In war, destruction of part of the nation's territory and personnel causes a widespread disturbance of the national economy. Perhaps necrosin—a product of damaged tissues—might be likened to this economic aspect of total warfare. In other words during infection the body has not only to deal with bacterial toxins but also with poisonous products liberated from its own damaged cells. Leucopenia during acute infections is fortunately rare, but it sometimes occurs in fulminating infections, which overwhelm the defences of the body.

Fever frequently occurs as part of the reaction of the body to any severe infection. The rise of temperature increases the rate of metabolism and is believed to speed up the production of antibodies. It can be likened to the great increase of activity shown by a nation at war as it strives to produce arms and munitions for its defence against an aggressor. Do we not speak of the ' feverish activity ' to be seen upon such occasions ? The fact that the process may be costly, wasteful, somewhat disorderly, and very exhausting makes the analogy more apt.

To return once again to the first line of defence, the fibrin barrier manned by polymorphs. When the body gains the upper hand and the infection ceases to spread, the front becomes stabilized. A more permanent defence work is now constructed, walling off the area devastated by war. *Monocytes* or *macrophages* appear, which phagocytose dead cells, dead polymorphs, bacteria, and other debris. *Fibroblasts*—cells which produce fibrous tissue—invade the fibrin network, using it as a scaffold, and lay down a wall of fibrous tissue, or a scar. This process, which is called *organization*, will be studied in detail later. At the margin of a large abscess this fibrous-tissue wall may be of considerable thickness. The macrophages and fibroblasts are acting like the sappers and engineers in modern warfare, who replace the first thin