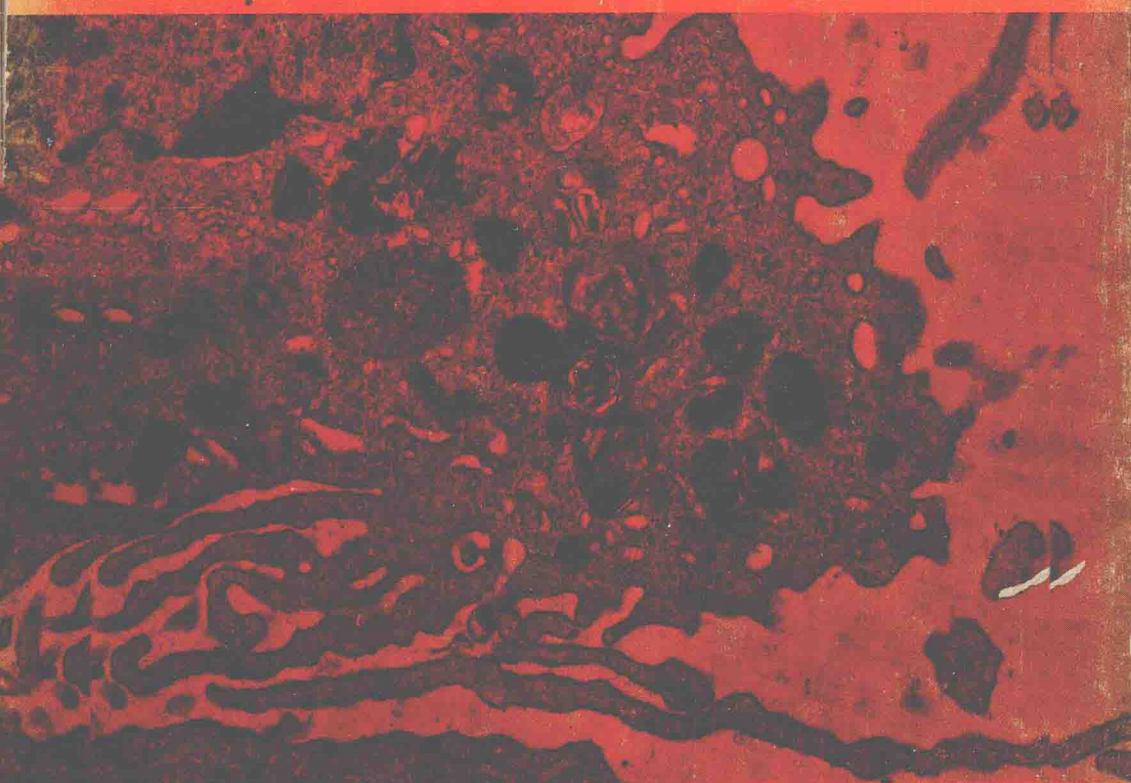
Biological Structure and Function 2

The Macrophage

B. VERNON-ROBERTS



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THE MACROPHAGE

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BIOLOGICAL STRUCTURE AND FUNCTION 2

THE MACROPHAGE

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To Jayne
to whose help and encouragement
this book owes its existence

PREFACE

The macrophages, which are widely distributed throughout the body tissues, have long been known to play a major role in host defence mechanisms and are the cells ultimately responsible for the disposal of most foreign materials and damaged host tissues. It is widely recognized that they participate in a variety of metabolic processes in both normal and pathological circumstances. In recent years, increasing attention has been paid to these cells as participants in cell-mediated immunological reactions and antibody production. The wide range of activities of macrophages has ensured that their study has continued to engage the interest of a wide range of scientific disciplines.

The purpose of this monograph is to provide an account of present knowledge regarding the life-history of the macrophage, and the evidence for its role in various physiological and pathological processes. I hope that a clear demarcation exists between the presentation of the findings and conclusions of other authors and my own speculations. Where controversial topics are presented, I have consciously endeavoured to limit my approach to the examination of the relevant evidence without bias.

I hope that the scope of this monograph and the approach which I have used will not only appeal to those who have a research interest in this field, but will also be of value to clinicians and pathologists seeking a deeper understanding of basic mechanisms underlying body defence mechanisms and certain disease processes.

I am indebted to Professor T. Nicol for introducing me to the ubiquitous macrophage, and to many other colleagues with whom I have had the pleasure of working or have discussed the many aspects of this cell. It gives me particular pleasure to record my gratitude to Professor I. Doniach for his constant interest and encouragement during the preparation of this monograph.

I thank all those colleagues who have generously allowed me to use illustrations from their published work, and I have pleasure in recording the contributions of Dr I. Carr; Professor B. N. Halpern, Dr G. Biozzi and Dr B. Benacerraf; Dr M. G. Hanna and Dr A. K. Szakel; Dr A. H. E. Marshall; Dr R. J. North; and Professor T. Nicol, Dr D. L. J. Bilbey, Dr J. L. Cordingley and Dr L. M. Charles. I thank the editors and publishers who granted me permission to use these illustrations, the sources of which are acknowledged in the legends for the relevant figures, and the original place of publication recorded in the references.

I am particularly indebted to Mrs Lynda Moore for the patience and care with which she typed out draft and final copies of the manuscript, to Mr R. M. Hammond and Mr G. Walter for preparation of most of the illustrations, and to Mr A. Gray for preparing the electron micrographs.

Grateful acknowledgements are due to the librarians of The London Hospital Medical College, The British Medical Association, The University of London Library at Senate House, and The National Lending Library.

Last, but not least, I record my gratitude to my wife. Not only has she relieved me of all domestic problems and spent many hours of solitude during the prolonged gestation of the manuscript, but she also assisted in checking the typescript and reading the proofs. Without her wholehearted and constant encouragement, the task of preparing this monograph would have been beyond my powers of endurance.

B. VERNON-ROBERTS

CONTENTS

INTRODUCTION

The presence of amoeboid mononuclear cells at inflammatory sites appears to have been first described by von Recklinghausen in 1863, after he had observed them in the inflamed cornea and omentum in various species of animals. He was able to distinguish these amoeboid cells from pus cells (polymorphonuclear leucocytes) and postulated that they may have been derived from fixed connective tissue cells. Some twenty years later, Metchnikoff drew attention to the fact that in addition to the free mononuclear phagocytic cells of the blood and lymph there were normally present in the connective tissues and certain organs fixed cells which were able to engulf small particles by throwing out amoeboid processes. In an outstanding series of publications, Metchnikoff went on to describe the distribution of these cells in the liver, spleen, lymph nodes and in the central nervous system in invertebrates and vertebrates, including man. He later grouped the free and fixed large mononuclear cells together as 'macrophages', and distinguished them from the leucocytes of the circulating blood which he called 'microphages' (Metchnikoff, 1905).

Although it had been recognized for many years prior to Metchnikoff's observations that micro-organisms were commonly found within white cells during inflammation, the opinion had been generally held that micro-organisms found the interior of leucocytes to be favourable to their survival, and it was generally believed that leucocytes played a role in disseminating micro-organisms throughout the body. However, the observation that leucocytes emigrated into the tissues during inflammation suggested to Metchnikoff that these cells must play a protective role in host defence. He set about proving his hypothesis by inserting rose prickles into the transparent bodies of the larvae of starfish, and observed the accumulation of amoeboid cells around the foreign body, noting the similarity to inflammation induced in the human. He extended his studies by introducing various kinds of bacteria into lower animals, and demonstrated that they were ingested by similar cells. By clearly demonstrating the defensive role of phagocytic cells, Metchnikoff established the cellular theory of body defence.

The study of macrophage morphology and distribution was much enhanced by the introduction of non-toxic vital dyes suitable for histological use. These dyes, such as trypan red and trypan blue, are preferentially ingested by macrophages. Using vital staining techniques it was subsequently shown by many workers that macrophages exist as 'free' cells

scattered extravascularly throughout the connective tissues and among the cells of the thymus, spleen and lymph nodes; and also as 'fixed' sessile cells lying along the walls of blood sinusoids in the liver (Kupffer cells), spleen, bone marrow and other sites, and along the walls of lymph sinuses in lymph nodes. Different investigators often gave special names to these cells to designate either their function or their presumed origin, and the macrophages have been synonymously called clasmatocytes, rhagiocrine cells, polyblasts, reticulum cells, reticular cells, polymorphous histogenic wandering cells, pyrrhol cells, resting wandering cells and histiocytes.

Aschoff was the first to recognize that the mononuclear phagocytes probably constituted a functionally unified system of cells, and later introduced the term 'reticulo-endothelial system' to cover the entire range of cells which possessed the capacity to take up vital dyes (Aschoff, 1924). The term 'reticulo-endothelial system' was derived from the fact that the cells forming the system were considered to be involved in the formation of the 'reticulum' (extrasinusoidal solid pulp) of the lymph nodes and spleen, or were those lining blood or lymph sinusoids. Aschoff divided all cells which have the capacity for ingesting vital dyes into four groups. Cells of groups I and II exhibited relatively little vital staining capacity and consisted of the endothelium of blood and lymphatic vessels and the fibroblasts of the connective tissues. Group III consisted of the 'reticulum' (pulp) cells of spleen or lymph nodes. Group IV comprised the sinusoidal lining cells of lymph node sinuses, and the sinusoids of the liver, spleen, bone marrow, adrenal cortex and pituitary. This latter group also included the histiocytes (free macrophages) of extravascular connective tissues. Cells of groups III and IV were considered by Aschoff to form the 'reticulo-endothelial system', while those of groups I and II were excluded.

About the same time that Aschoff was delineating his 'reticulo-endothelial system', Del Rio Hortega and dé Asua (1924) demonstrated the presence of the microglial cells in the central nervous system by impregnating them with silver carbonate. In cerebral inflammation and injury the microglial cells could be shown to become transformed into the characteristic mononuclear phagocytes of the central nervous system – the 'compound granular corpuscles'. Because of the resemblance between these phagocytes of the central nervous system and those elsewhere in the body, Hortega and dé Asua applied the silver carbonate technique to various tissues outside the central nervous system and showed that cells similar to the microglia were present in them, and that these cells had phagocytic properties.

Subsequent workers showed that silver impregnation not only demonstrated a system of cells which included the 'reticulo-endothelial system' as defined by Aschoff, but also included a related series of phagocytic

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cells which were not demonstrable by vital staining. The cytoplasm of all these cells had such an affinity for metal salts that they were called 'metalophil cells'. Marshall (1956) made a detailed and critical survey of the morphology and distribution of the metalophil cells and resolved a number of discrepancies in the results of vital staining and in terminology. He concluded that there is no exact parallelism between the metalophil cells and the 'reticulo-endothelial system' as defined by Aschoff, and that the metalophil cells are considerably more numerous. It thus appears that the 'reticulo-endothelial system' is not a distinct cytological entity but is a functional state of some of the metalophilic macrophages depending largely on local factors such as cell disposition and lymph and blood circulation. This is clearly exemplified by the blood monocytes which are metalophilic but do not take up vital dyes. Moreover, using a silver impregnation technique, Marshall was able to distinguish and describe the different morphology of the strongly metalophilic macrophages and reticulum cells and the primitive reticular cells which were not metalophil.

Although the mononuclear phagocytes of the body represent a large, widely distributed and morphologically somewhat heterogeneous group of cells, it is now evident that, as described in later chapters of this monograph, the macrophages have ultrastructural, metabolic and functional characteristics which may be used to distinguish them from other cells. It would appear that to avoid confusion the simplest and best appellation to include all the macrophages of the body seems to be 'the macrophage system'.

The most striking functional characteristic of macrophages is phagocytosis. At one time, the uptake of both solid particles and fluid droplets were considered to come under the heading of phagocytosis. However, Lewis (1931) introduced the term 'pinocytosis' (drinking by cells) to name the process by which macrophages take up fluid droplets. The electron microscope has revealed that a variety of cells other than macrophages can also take up submicroscopic particles and fluid droplets in vesicles formed by invagination of the cell membrane. It would appear that the mechanism of particle uptake (phagocytosis) and fluid uptake (pinocytosis) may in fact be identical and differ only in the content of vesicle formed, and the term 'endocytosis' is often used to encompass both processes.

Although the properties of phagocytosis and pinocytosis are not confined to macrophages, this does not invalidate the specificity of the macrophage as a cell which is able to recognize and ingest particles which may be relatively large and which also may be harmful to the organism (bacteria, fungi, yeasts, protozoa, effete erythrocytes, dead leucocytes, foreign bodies, etc.). It is now known that the macrophage system is also involved in immune processes, the inactivation of bacterial endotoxins,

resistance to traumatic and haemorrhagic shock, the prevention of irradiation sickness, haematoclasia and bile pigment formation, and the metabolism of lipids, steroids, cholesterol, iron and proteins. Moreover, macrophages have been implicated in the aetiology of atherosclerosis, hypercholesterolaemia, lipoidoses, haemolytic anaemias, amyloidosis and neoplasia.

The widespread distribution and the involvement of macrophages in a multiplicity of physiological and pathological processes ensures that the study of the macrophage system of cells is an exercise which can involve many scientific disciplines and can be approached at various levels of interest in all branches of science.

TABLE 1. *The distribution of macrophages in mammals*

Anatomical site	*Localization of cells*
Liver	Kupffer cells lining hepatic sinusoids; connective tissues of portal tracts
Spleen	Lining venous sinuses and enmeshed in Billroth cords of red pulp; scattered among lymphocytes of Malpighian follicles in white pulp; in marginal zones
Lymph nodes	Lining subcapsular and medullary sinuses; scattered in medullary pulp and in lymphoid follicles of cortex
Bone marrow	Lining venous sinuses of red marrow; scattered monocytes and macrophages in extrasinusoidal tissues
Thymus	Scattered throughout cortex and medulla; within Hassall's corpuscles in some species
Lung	Within interstitial tissue of alveolar wall; in alveolar spaces
Central nervous system	Microglia
Serous cavities	Peritoneal and pleural fluids; 'milk spots' of peritoneum and pleura
Adrenals	Lining sinusoids of cortex (particularly zona reticularis); scattered in medulla
Joints	Type A or M cells of synovial lining; within synovial fluid
Subcutaneous tissue, alimentary tract, pituitary, testis, ovary, endometrium, kidney	Connective tissues generally, lining vascular channels in pituitary, testis, ovary and decidua
Blood	Monocytes and some macrophages
All sites	Inflammatory exudates

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THE DISTRIBUTION AND MORPHOLOGY OF MACROPHAGES

ANATOMY OF THE MACROPHAGE SYSTEM

The widespread distribution of the component cells of the macrophage system results in certain morphological differences which are due to the structure, metabolism and blood supply of the organs of which these cells form a part, to their functional requirements, to their relation to tissue fluids, and to their relation to the specific parenchymatous cells of the organ concerned.

For descriptive and functional purposes it is still sometimes profitable broadly to follow Metchnikoff in considering that the macrophages of the body may be grouped as 'fixed' macrophages lying along the walls of blood and lymph channels in direct contact with circulating blood or lymph, and 'free' macrophages situated extravascularly in the connective tissues, in solid organs, and in the central nervous system. However, it is important to remember that both the 'fixed' and 'free' cells can be mobilized, and that these prefixes are used for descriptive convenience alone. Moreover, there are additional component cells of the system which are present in the circulating blood, and comprise the monocytes (immature macrophages) and mature macrophages.

Table 1 summarizes the anatomical distribution of the cells which are considered as members of the macrophage system in mammals.

MACROPHAGES IN SPECIAL SITES

LIVER

The liver contains more macrophages than any other single organ. Light microscopic studies after metallic impregnation, vital staining or intravenous injection of colloids reveal that the major portion of each liver sinusoid is lined by actively phagocytic branching stellate macrophages, the Kupffer cells, whereas the central and peripheral regions of each sinusoid are lined by less actively phagocytic endothelial-type cells. A considerable number of studies on liver ultrastructure have been carried

out, and there is general agreement that electron microscopy confirms the presence of two types of cell, the endothelial cell and the Kupffer cell, lining the sinusoids. However, there are conflicting reports regarding the absence or presence of a true basement membrane underlying the cells lining the sinusoids, and also with regard to the existence of gaps between adjacent cells; and from the available evidence, it appears that the structure of the liver sinusoid may vary from one species to another (Burkel and Low, 1965). In general, it seems that the endothelial lining of the peripheral part of the sinusoid is continuous and has an underlying basement membrane: the part of the sinusoid adjacent to the central vein also has a continuous endothelial lining with an underlying basement membrane; between the central and peripheral portions (comprising about 90 per cent of the length of the sinusoid) gaps are present between adjacent cells; Kupffer cells are present in this intermediate portion of the sinusoid and do not have an underlying basement membrane.

The endothelial cells and Kupffer cells are separated from the hepatocytes (liver parenchymal cells) by the space of Disse (Fig. 1). The absorptive surfaces of the hepatocytes are differentiated into short microvilli which occupy the space of Disse together with a network of delicate collagen fibrils. Cells described by some authors as pericytes may be present, but some undoubtedly have the fine structure of macrophages. Occasional cells rich in lipid inclusions, and undifferentiated mesenchymal cells known as 'Disse-space cells', are also occasionally observed within the space of Disse (the perisinusoidal space).

When normal untreated animals are sacrificed after the intravenous injection of a single dose of colloidal carbon, the liver exhibits phagocytosed carbon located within Kupffer cells located in the mid-zonal and peripheral portions of the liver lobules (Fig. 2). After repeated injections of carbon, or pre-treatment of the animals with oestrogen, it can be seen that all the cells lining the liver sinusoids take up carbon (Fig. 3). It would thus seem that the endothelial cells may be 'recruited' to act as phagocytes, since they are capable of displaying phagocytic activity before the proliferation of Kupffer cells or the influx of macrophages from elsewhere can occur. This suggests that the endothelial cells of the liver sinusoids differ from those lining vascular channels in most areas of the body, since the latter do not exhibit any marked degree of phagocytosis. It would seem reasonable, therefore, to regard the liver sinusoids as being lined by a mixed population of true mature macrophages (the Kupffer cells) and specialized 'endothelioid' or potential macrophages. In this connection, although the endothelial cells normally have markedly different ultrastructural appearances from Kupffer cells, they do not have all the features of true capillary endothelium. Thus, their fenestrations differ from those of true capillary endothelium by the absence of a

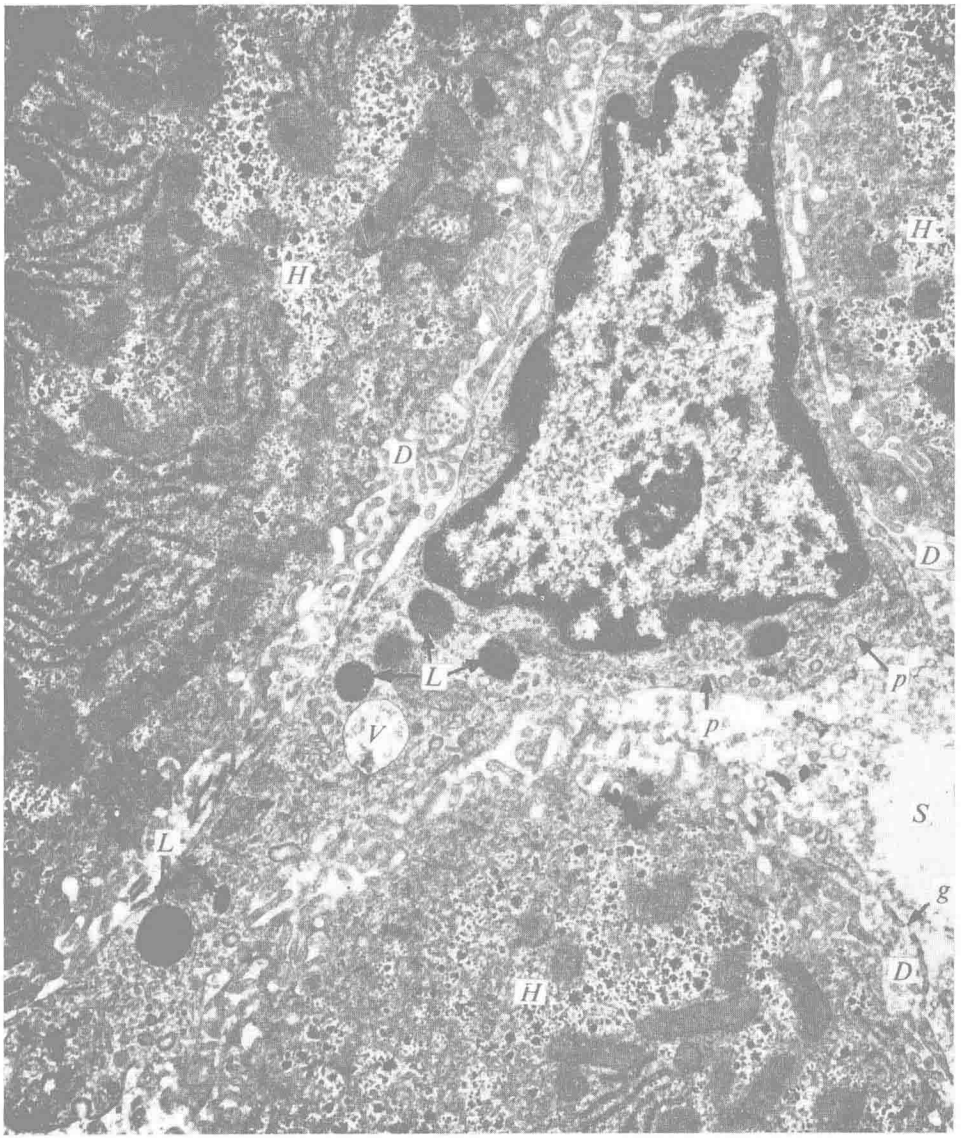

Fig. 1. Kupffer cell in guinea-pig. The macrophage contains several dense bodies (*L*) which are probably lysosomes, a vacuole (*V*) which is probably phagocytic in origin, and exhibits pinocytotic activity (*p*). It is separated from the hepatocytes (*H*) by the space of Disse (*D*) which contains the microvilli of the hepatocytes and communicates with the lumen of the sinusoid (*S*) via inter-cellular gaps (*g*). × 12,500.

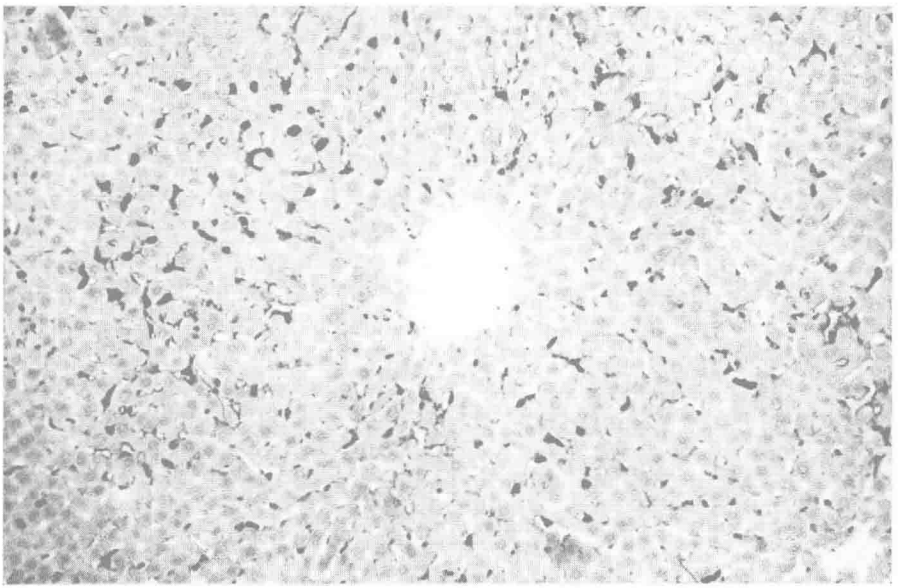

Fig. 2. Liver of untreated guinea-pig 10 minutes after intravenous injection of carbon. Shows carbon-containing Kupffer cells located in intermediate portion of liver sinusoids. Neutral red. × 120.

diaphragm within their fenestrations, and they do not consistently possess an underlying basement membrane (Wisse, 1970). The Kupffer cells do not possess fenestrations, and usually contain prominent lysosomes and occasional phagocytic vacuoles (Fig. 1).

The liver also contains some macrophages which are located in the extravascular connective tissues of the portal tracts.

SPLEEN

The spleen contains more macrophages per gram of tissue than any other organ, and they are situated predominantly in the red pulp and the marginal zones, together with small numbers scattered within the Malpighian bodies comprising the white pulp (Fig. 4).

It would appear that the blood passing through the spleen is effectively 'filtered' by exposure to macrophages within the red pulp. The venous sinuses are lined by littoral macrophages (macrophages which form the walls of blood channels) which are supported by reticulin fibres forming an incomplete membrane, and the striking feature of the sinuses is the large gaps which exist between the littoral cells and which appear to

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