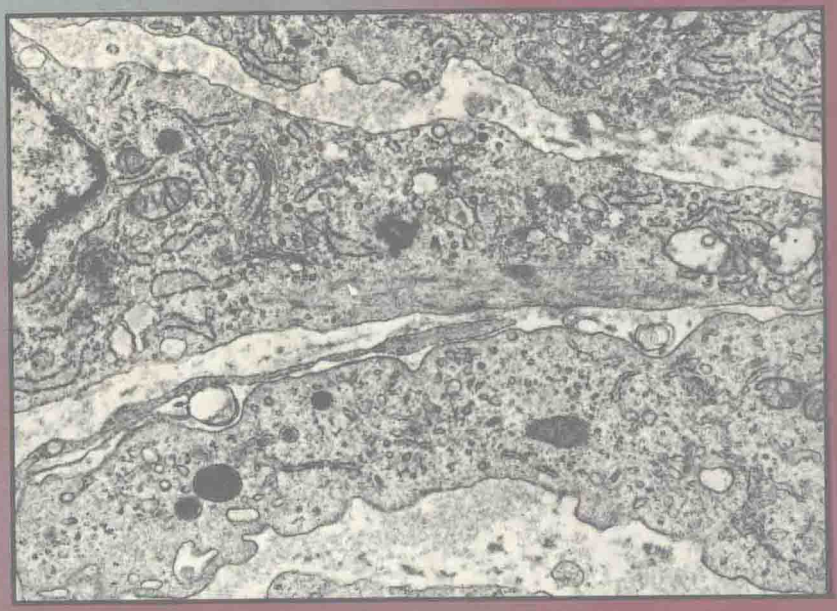
J.V. HURLEY



ACUTE INFLAMMATION

SECOND EDITION

Churchill Livingstone

Acute Inflammation

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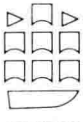
SECOND EDITION



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Preface to the Second Edition

Rapid advance in our knowledge of many aspects of the acute inflammatory reaction during the past eleven years has made it necessary to revise substantially almost every chapter of the first edition. The order of several topics has been changed and an account of healing by scar, an aspect of inflammation omitted in the original account, has been added.

As before, the book is based on the work of myself and my students and colleagues, and I should like to express thanks to all who have assisted me in various aspects of my experiments. Additional illustrations, all from our own work, have been added to this edition. Most have been published previously, and I am grateful to the editors of the journals in which they appeared for permission to reproduce them in this book. The source of individual illustrations is indicated in the text.

Finally, I acknowledge with gratitude the continued financial support I have received from the Medical Research Fund of the University of Melbourne and from the National Health and Medical Research Council of Australia.

Melbourne, 1983 J.V. H.

Preface to the First Edition

Inflammation was described by the late Lord Florey as the backbone of pathology. Knowledge of many aspects of the inflammatory process has increased substantially in recent years due to the introduction of new experimental techniques, especially electron microscopy. However, no relatively brief account of this new knowledge is available.

The aim of this book is to outline current views on the morphology and mechanisms of acute inflammation and of its local sequelae. It is hoped that the account is in a form that will prove of value to teachers of pathology and surgery, to research workers and to senior students of pathology.

The book is based on experimental work carried out in London and in Melbourne during the past twelve years. It emphasizes those aspects of inflammation in which I have been especially interested, but I have tried to relate my own findings and beliefs to those of others, and to provide a balanced picture of current views. All the illustrations are from my own experiments. Many have been published previously, and I am grateful to the editors of the following journals, in which they appeared, for permission to reproduce them in this book: *Annals of the New York Academy of Sciences; Australian Journal of Experimental Biology and Medical Science; British Journal of Experimental Pathology; Journal of Endocrinology; Journal of Pathology; Journal of Pathology and Bacteriology; Pathology.*

I should like to express my thanks to the many people who have assisted me in various aspects of my work. In particular I am grateful to Professor W.G. Spector, who first aroused my interest in inflammation when I was working with him in the late Sir Roy Cameron's department in London as a Nuffield Dominion Travelling Fellow in Medicine; to the late head of my own department, Professor E.S.J. King, and to his successor, Professor G.S. Christie; to all my collaborators in the experiments that form the basis of the book, and especially to Dr Kathryn Ham and Dr G.B. Ryan; to my technicians Trevor Davey and Mrs Estelle Shavin; to Jack Smith for photographic assistance; and to Miss Sandra Fehring for typing the manuscript with her usual meticulous accuracy.

Finally, I acknowledge with gratitude the financial support I have received from the Medical Research Fund of the University of Melbourne and from the National Health and Medical Research Council of Australia.

J.V. H.

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Contents

1

The nature of inflammation

Definition

It has been known since earliest times that when men or animals are injured, a characteristic series of changes follows in the damaged area. The reaction may last for hours or even days, and appears to be more or less independent of the nature of the damaging agent, a wide variety of types of injury being followed by a very similar response. This tissue response to injury is known as inflammation, the term being derived from the Latin, inflamare meaning to burn.

In Greek and Roman times inflammation was regarded as a single disease entity, the result of a disturbed state of the humours or body fluids. The discovery of the circulation of the blood by William Harvey (1628) provided the necessary basis for a more rational explanation of inflammation, but the essential nature of the inflammatory process was not appreciated until more than 150 years after the publication of Harvey's book. The first clear statement of the modern concept of inflammation was given by John Hunter (1794), who after first-hand study of injured tissues on the battlefield concluded that 'inflammation is itself not to be considered as a disease, but as a salutary operation consequent either to some violence or some disease.' All modern definitions of inflammation are restatements in a variety of forms, of this basic concept.

Most recent writers, including the present author, agree that it is wise not to attach too narrow a meaning to the term, and favour a definition such as that of Burdon Sanderson (1871): 'The process of inflammation is the succession of changes which occurs in a living tissue when it is injured, providing that the injury is not of such a degree of severity as to at once destroy its structure and vitality.' More recently Ebert (1965) expressed a similar idea when he proposed that: 'Inflammation is a process which begins following a sublethal injury to tissue and ends with complete healing.'

More limited definitions have been proposed by some authors. For example Spector and Willoughby (1963) defined inflammation as: 'the reaction to injury of the living microcirculation and related tissues.' This type of definition can be criticized on two grounds. First it excludes the reaction to injury of avascular tissues like the cornea, and secondly it implies an ability to separate the direct effects of a damaging agent on living tissues, so-called passive or regressive changes, from the tissues' reaction to injury, inflammation. Injury-induced death of cells, and the various degenerative changes which may appear in cells some time after injury, are treated in many textbooks as if they are phenomena quite distinct

from inflammation. However, separation between the direct effects of injury and the body's reaction to them is often difficult or impossible. For example, increased vascular permeability is regarded as one of the main features of the inflammatory response. However, the main part of increased permeability in both mild and severe thermal burns, and in many other types of injury as well, is now known to result from direct damage to the wall of small blood vessels, and not to be a reaction of the vessels to damage to surrounding tissues.

Again, direct injury to the wall of blood vessels may destroy part of their endothelial lining. If this occurs, platelets adhere to the damaged area and thrombosis commonly follows. Like regressive changes in cells, thrombosis is not usually regarded as a part of inflammation, but again the distinction is an artificial one. Indeed with the exception of neoplasia and related cell proliferations, virtually any portion of what is customarily considered as general pathology, can be regarded as a particular manifestation of the body's response to injury, and any subdivision must be, to a degree, one of convenience.

In the present book, only those aspects of the response to injury that are generally included under the term inflammation will be considered, and cell degeneration, necrosis and thrombosis will not be described except in so far as they relate to other aspects of the inflammatory process.

All the above definitions exclude any mention of the purpose of inflammation. Although John Hunter (1794) and many subsequent authors have claimed that the response to injury is a useful or purposeful process, there are serious objections to this concept of inflammation. To say that a reaction is beneficial and has a protective function explains neither the mechanisms underlying the reaction nor the links between the injurious stimulus and the body's response to it. Furthermore whilst the overall effect of the inflammatory reaction may be of survival value, both to the affected tissues and to the organism as a whole, many examples can be cited in which destruction of tissue is due not to the damaging stimulus, but to one or other component of the body's reaction to injury. For example, in both the Arthus and Shwartzman reactions, and in the local response of dogs to the bite of the tick *Rhipicephalus sangineus* the destruction of tissue is caused by substances liberated from polymorpho-nuclear leucocytes which accumulate at the site of injury as part of the inflammatory response. No tissue necrosis occurs in animals temporarily deprived of blood leucocytes by treatment with nitrogen mustard. Again whilst increased vascular permeability may be beneficial in local infections, because it allows passage of natural and immune antibodies into tissue spaces where they may come into contact with the invading bacteria, local fluid loss has no apparent protective value in physical injuries, such as thermal burns. On the contrary, the fluid loss, if excessive, may have severe effects on the circulation of the animal as a whole, resulting in shock and peripheral circulatory failure, and may also cause stasis and arrest of the circulation in the burnt area which, if unresolved, may lead to tissue necrosis.

It should be emphasized that the response to injury is a process and not a state and that dynamic and complex changes occur over long periods within the injured area. It is probably better to regard inflammation not as a single process but as a collection of distinct mechanisms, each of which is sensibly designed to aid, and may well have evolved for, the defence of the organism against external injury,

but each of which has other uses as well (Thomas, 1970). Phenomena such as sustained increase in the diameter of small blood vessels, increased vascular permeability, increased lymph flow, sticking of blood cells to one another and to the wall of inflamed vessels, and emigration of leucocytes from vessels and their accumulation in extravascular tissues all form part of the inflammatory reaction. Sometimes all occur together, but their relative prominence varies widely after different types of injury. Indeed, as will be shown in later chapters, many of these phenomena can, and not uncommonly do, occur quite separately from one another.

The cardinal signs of inflammation

Inflammation was known to the ancients by the appearances it produced in the skin and other surfaces of the body. Its manifestations in this situation were summarized by the Roman encyclopaedist Celsus (30 BC–38 AD) as Rubor et tumour cum calore et dolore—'redness and swelling with heat and pain', and these changes are commonly termed the Cardinal Signs of inflammation. Often a fifth sign, loss of function is added. For very many years this fifth sign was attributed to the Greek writer Galen (130–200 AD), until Rather (1971) pointed out that there is no mention of such a sign in any of Galen's works. It appears that the concept of a fifth sign originated, as did so much of modern pathology, in Virchow's Cellular Pathology, published in 1858. The sign was subsequently incorrectly attributed to Galen by the author of a German Handbuch of Pathology, and the error has been perpetuated in almost every textbook published since that time (Ryan and Majno, 1977).

The appearances of inflammation in living transparent tissues

Although he recognized the reactive nature of inflammation, John Hunter had no real knowledge of the changes responsible for the production of its cardinal signs. Understanding of the complex and dynamic changes which take place in living tissues in the first few hours after injury came only when studies were made of the effects of injury to living transparent tissues. The earliest workers to examine living inflamed tissues were a group of British pathologists, Thomson (1813), Wharton-Jones (1842), Addison (1843), and Waller (1846), who between them described all the essential features of the early stages of inflammation. However their accounts were largely neglected, and it was not until 1877 when Cohnheim published a full and graphic account of the changes seen after injury to the tongue or foot-web of the frog, that the basis of the cardinal signs was generally appreciated.

Cohnheim's account was so vivid and exciting that it won immediate acceptance. It has never been surpassed and has been copied more or less verbatim into most current textbooks of pathology. Cohnheim and the other early workers used frogs, which not only possess convenient transparent external parts in their tongues and foot webs, but, being cold blooded, do not have to be kept warm. Shortly after Cohnheim's work was published, Thoma (1878) devised a most complicated apparatus which enabled him to confirm Cohnheim's observations in warm blooded animals. Many years later the invention of the so-called ear-chamber by the Clarks (1930), Sanders and others, provided a simple means of examining the vessels of undisturbed mammalian connective tissue for periods of days, weeks or even months. Whilst extremely elegant, and allowing the production of beautiful

cine-films, these modern techniques have added relatively little to the observations of Cohnheim and his contemporaries.

It is not proposed to repeat Cohnheim's account once again—the reader is advised to consult the original. Instead a summary will be given of the behaviour of the normal microcirculation as seen in living transparent tissues, of its response to injury and of how the changes seen account for the classical cardinal signs of acute inflammation.

The normal microcirculation

Structure Although the detailed pattern of the microcirculation varies in different tissues, there is a common basic anatomical arrangement of small blood vessels throughout the body. This was described in detail by Chambers and Zweifach (1944). Blood enters the microcirculation via a vessel with a thick muscular wall, the arteriole, and leaves by way of a larger thin-walled venule. Arterioles and venules are joined to one another by metarterioles, which have a structure midway between arterioles and capillaries, and by capillaries. No smooth muscle fibres are present in the capillary wall, but at their origin muscle fibres encircle the metarteriole to form a pre-capillary sphincter. Some capillaries are large and are called preferential channels; others are small, the true capillaries.

Function Blood flow through capillaries is not continuous, but occurs in a series of spurts caused by intermittent contraction of metarterioles and pre-capillary sphincters. Erythrocytes pass along capillaries in a single file because of the small diameter and may be deformed during their passage along the smaller vessels. Not all capillaries are patent at any one time in resting tissues, and the proportion of red cells to plasma varies in different patent capillaries—a condition known as plasma skimming.

Within larger vessels, both arterioles and venules, blood flow is divided into two zones—a peripheral zone of almost cell-free plasma, and a central stream of closely packed red and white corpuscles. This pattern is a consequence of the laminar or streamline flow in all blood vessels larger than capillaries. In laminar flow, velocity increases and lateral pressure decreases progressively from the vascular wall to the centre of the stream. As a result particles such as blood corpuscles accumulate in the central low pressure part of the stream of flowing blood, producing so-called axial flow.

Total blood flow through tissues varies widely in different physiological states. Increased tissue activity—whether it be muscular exercise, glandular secretion or intestinal absorption—is accompanied by increased blood flow through the active area. It is generally agreed that the intrinsic myogenic activity of the vascular wall, and nervous and humoral factors, are the major controls of flow in arterioles and venules. However, these factors appear to be of minor importance in the intrinsic regulation of flow within the terminal vascular bed. Capillary flow appears to be modulated largely by locally released by-products of tissue activity.

The changes seen after injury

Immediately after injury there may be a transient constriction of arterioles. As Cohnheim realized, this initial constriction does not always occur, and most authorities regard it as of little importance. It is a prominent feature of mild ther-

mal burns (Allison *et al*, 1955) and of mechanical stroking of the skin (Lewis and Grant, 1924), but is not seen after injuries of more gradual onset, such as ultraviolet light (Grant *et al*, 1962). The next stage is a widespread dilatation of arterioles and venules and the opening up of many small blood vessels which had previously been carrying little or no blood. Blood flow through the injured area may increase as much as ten-fold (Ascheim and Zweifach, 1962). Initially, flow through the dilated vessels is extremely rapid, and as a consequence axial flow in both arterioles and venules is accentuated so that cells become packed more tightly into the central part of the rapidly flowing blood. This stage of rapid flow is of variable duration. After mild stimuli, such as the application of histamine, rapid flow lasts 10–15 minutes and then gradually returns to normal. After more severe injury, increased flow may last for hours and be followed by a gradual decrease in the rate of flow through still dilated vessels. As flow slows, the axial column of packed cells widens and the outer plasmatic zone shrinks progressively until flow may finally cease entirely in some vessels, which now form distended immobile columns of tightly packed cells. Stasis may persist and end in death and disintegration of the affected vessels, but in many instances flow gradually begins again and eventually returns to normal (Florey, 1970). Soon, often before flow slows, and long before stasis is apparent, leucocytes begin to appear in the marginal plasma stream of the venules, and to impinge from time to time on the venular wall. At first they stick momentarily to the wall, may roll along it for a short distance, and then fall off and pass back into the flowing blood. With injuries of moderate intensity, progressively more leucocytes pass to the periphery of the blood stream, hit the venular wall and adhere to it for longer periods, until the luminal surface of many venules within the injured area becomes covered with a layer of living, adherent leucocytes, an appearance graphically described by Cohnheim as pavementing of leucocytes.

Many of the adherent cells may subsequently pass out through the venular wall into extravascular tissues. This phenomenon, known as leucocytic emigration, and the further stages in the behaviour of leucocytes will be described in a later chapter. In injuries of mild or moderate severity, pavementing and emigration of leucocytes may last for several hours. They then gradually cease and, except in severe injuries, the affected vessels resume an entirely normal appearance.

At the same time as leucocytes are behaving in the manner just described, an increased loss of fluid occurs from the blood vessels into the extravascular spaces. It is not possible by study of living tissue preparations to see precisely how this fluid escapes, but as more and more fluid accumulates outside vessels the tissues swell progressively, and it becomes increasingly difficult to observe what is taking place in and around the still widely dilated vessels.

Summary of changes seen in early stages of inflammation

From the above account, it can be seen that the reactive changes that occur in the first few hours after sublethal injury involve, in varying degree, three processes:

1. Changes in vascular calibre and blood flow.
2. Increased vascular permeability which results in the formation of inflammatory exudate and local oedema.
3. Escape of leucocytes from the blood into extravascular tissues.

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In the immediately following chapters present knowledge of these three processes will be discussed in detail.

The basis of the cardinal signs

Current concepts of the changes responsible for the cardinal signs of acute inflammation may be summarized as follows:

Rubor

This is due to gross and persistent dilatation of all small blood vessels, arterioles, capillaries, and venules within the injured area.

Calor

An area of inflammation is hotter than surrounding tissues only when it is situated in a part of the body which is normally at a lower temperature than the interior of the body and circulating blood, for example, skin, nasal mucous membrane or conjunctiva. In such areas the rise in local temperature of the inflamed area is a direct result of the great increase in local blood flow. Inflamed skin also feels hot due to stimulation of heat sensitive nerve endings which occur only in the skin.

Inflammation of internal organs does not cause any rise in their temperature except as part of a general rise in body temperature, or fever, which occurs in some types of inflammation, especially those due to bacterial infections.

Tumour

The main factor responsible for the swelling of an acutely inflamed area is local oedema. This is due to increased permeability of small blood vessels which allows protein-rich fluid, known as exudate, to escape into the tissues of the damaged area. Inflammatory exudate not only has high protein content, but also commonly contains enough fibrinogen to clot spontaneously after its escape into the tissues, and as a result large amounts of fibrin may be deposited within the injured area.

Escape of leucocytes from blood vessels and their accumulation in extravascular tissues and swelling of damaged tissue cells also contribute to the swelling of an inflamed area, but, except in some types of chronic inflammation, the effect of these factors is small in comparison with swelling due to formation of inflammatory exudate.

Dolor

This is the least understood of the cardinal signs. Some endogenous chemical substances, which will be discussed later in the account of possible chemical mediators of inflammation, have very marked pain-producing properties. In particular bradykinin, 5-hydroxytryptamine (serotonin) and some prostaglandins, cause pain when applied in extremely high dilution to the base of a blister in human skin. These substances are widely distributed in human and animal tissues and are known to be present in areas of injury, but their precise role, if any, in pain production is still in doubt.

Another important factor that undoubtedly can cause pain and tenderness in an inflamed area is rise in tissue tension. Inflammation in areas which become tense after the formation of only small volumes of inflammatory exudate, as, for exam-

ple, the skin covering the anterior surface of the tibia, or the ala nasae, is much more painful than a similar lesion in a less tightly bound-down area of skin. Pus under tension in a boil or an abscess may be extremely painful. Evacuation of the pus, either surgically or by spontaneous rupture, produces an immediate and marked decrease in both pain and tenderness.

Loss of function

This appears to be due in part to reflex inhibition of muscular movement as a result of pain, aided by a variable degree of mechanical limitation of movement due to swelling of the inflamed area.

Inflammation in a glandular organ such as the liver or the pancreas, may cause loss of function due to death of some parenchymal cells and damage to others by the agent causing the inflammation. Whether there is in addition any interference with the function of apparently undamaged glandular cells is not known.

REFERENCES

Addison W. *Trans. prov. med. Surg. Ass.*, **11**, 233 (1843).

Allison F. Jr., Smith M. R., Wood W. B. Jr. Studies in the pathogenesis of acute inflammation. I. The inflammatory reaction to thermal injury as observed in the rabbit ear chamber. *J. Exp. Med.*, **102**, 655–688 (1955).

Ascheim E., Zweifach B. W. Quantitative studies of protein and water shifts during inflammation. *Amer. J. Physiol.*, **202**, 554–558 (1962).

Burdon Sanderson J. B. Inflammation. *In* a System of Surgery, edited by T. Holmes, 2nd edition. London: Longmans, Green and Company, 5, 728 (1871).

Chambers R., Zweifach B. W. Topography and function of the mesenteric capillary circulation. *Amer. J. Anat.*, **75**, 173–205 (1944).

Clark E. R., Kirby-Smith H. T., Rex R. O., Williams R. G. Recent modifications in the method of studying living cells in transparent chambers inserted in the rabbit ear. *Anat. Rec.*, **47**, 187–211 (1930)

Cohnheim J. Lectures on General Pathology, 2nd edition (translated from 2nd German edition), Vol. **I**. London, 1889: The New Sydenham Society (1882).

Ebert R. H. *In* The Inflammatory Process, edited by B. W. Zweifach, L. Grant and R. T. McCluskey. New York: Academic Press, p. 1 (1965).

Florey, Lord. General Pathology, 4th edition. London: Lloyd-Luke (Medical Books), p. 90 (1970).

Grant L. H., Palmer P., Sanders A. G. The effects of heparin on the sticking of white blood cells to endothelium in inflammation. J. Path. Bact., **83**, 127–133 (1962).

Harvey W. Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (with an English translation and annotations by Leake C. D.). London: Bailliere, Tindall and Cox (1928).

Hunter J. *In* The works of John Hunter FRS with Notes, Vol. **3**, edited by J. F. Palmer. London: Longman, Rees, Orme, Green and Longman (1835).

Jones T. W. *British and foreign medical Review*, **14**, 585 (1842).

Lewis T., Grant R. T. Vascular reactions of the skin to injury. Part II. The liberation of a histamine-like substance in injured skin: The underlying cause of factitious urticaria and of wheals produced by burning, and observations on the nervous control of certain skin reactions. *Heart*, **11**, 209–265 (1924).

Rather L. J. Disturbance of function (functio laesa): The legendary fifth cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus. *Bull. N. Y. Acad. Med.*, **47**, 303–322 (1971).

Ryan G. B., Majno G. Acute inflammation: A review. *Amer. J. Path.*, **86**, 185–276 (1977).

Spector, W. G., Willoughby D. A. The inflammatory response. *Bact. Rev.*, **27**, 117–154 (1963).

Thoma R. *Virchows Arch. path. Anat.*, **74**, 360 (1878)

Thomas L. Third Symposium of the International Inflammatory Club, Michigan. The Upjohn Company (1970).

Thomson J. Lectures on Inflammation, Exhibiting a View of the General Doctrines, Pathological and Practical, of Medical Surgery, Edinburgh, Blackwell (1813).

Waller A. Philosophical Magazine (3rd Series), **29**, 271, 397 (1846).

2

Changes in vascular calibre and flow

Until very recently surprisingly little was known of this aspect of the inflammatory response. Changes in vascular calibre and flow can be observed only in living tissues, and it is extremely difficult to make quantitative observations on such preparations. However in the last few years methods have been developed which permit accurate measurement of the blood flow through local areas of tissue, and by the use of these techniques considerable additional information has been acquired about the vascular changes which follow tissue injury. Local blood flow can be measured in two ways; either by the rate of accumulation of radioactively labelled microspheres injected into the arterial side of the circulation (Vadas and Hay, 1978), or by the rate of washout of radioactive ^{133}Xenon injected into the area whose blood flow is to be determined (Williams, 1976).

Present knowledge in this field may be summarized as follows:

1. Arteriolar constriction, when present, appears to be caused by a direct response of the smooth muscle of the arteriolar wall to be damaging agent.

2. Both nervous and humoral factors are concerned in the vasodilatation seen after injury to human skin. This was first shown by Lewis (1927) in his description of the so-called triple response to injury. Lewis found that three phenomena occur after mild mechanical or thermal injury to the skin:

a. An immediate reddening which is confined the area of injury. Lewis showed that this was due to release of a chemical substance, which he called H-substance, within the injured area. Lewis never identified H-substance. He suspected that it might be histamine, but this seems unlikely as prior administration of antihistaminics fails to abolish the effect. More recently it has been suggested that H-substance may be bradykinin.

b. A more extensive bright red halo, or flare, spreading outwards from the injured area. By most ingenious experiments, Lewis showed that this flare was due to arteriolar dilatation mediated via an axon reflex, the nerve impulses passing centrally along one branch of a cutaneous nerve, and then distally along another branch of the same nerve.

c. Formation of a wheal within the area of injury. This is due to local oedema resulting from increased permeability of small blood vessels. Lewis considered that this also was due to local release of H-substance.

To what extent these findings can be applied to other areas of the body is not clear. Similar axon reflexes have been identified in the cornea (Bruce, 1910) and in the tongue (Krogh, 1920), but not in the brain (Florey, 1925) or exposed

abdominal viscera (Lewis, 1927). Lewis's concept of the effector branch of the axon reflex terminating directly on an arteriole has never been proven. It appears more likely that the effector nerve ends on a sweat gland, and that bradykinin, or some other substance, liberated here diffuses out to affect adjacent arterioles.

Chapman and Goodell (1964) have summarized the role of the nervous system in inflammation. It is clear that all the features of acute inflammation may occur in completely denervated tissues. However, in some instances, the intensity of the reaction may be modified by nervous influences. There is little firm knowledge in this area. What is available was reviewed recently by Bonta (1978).

3. Inflammatory vasodilatation is usually resistant to vasoconstrictor agents, such as noradrenalin, and to stimulation of vasoconstrictor nerves.

4. Vasodilatation does not of itself cause increased leakage of protein from the dilated vessels. A good example of the separate nature of these two phenomena can be seen in the vascular changes which accompany muscular exercise. Here all small blood vessels are widely dilated, there is greatly increased local blood flow, and the hydrostatic pressure within the dilated vessels rises considerably. This rise in pressure causes increased filtration of water from the vessels. This water is carried away by the lymphatics and produces a marked increase in the volume of lymph draining from the region. However, the amount of protein escaping from the widely dilated vessels is not altered significantly during exercise. The total protein content of lymph draining from the exercising muscle does not increase significantly, the lymph protein concentration decreasing in proportion to the rise in lymph volume (Yoffey and Courtice, 1970).

5. Vasodilatation and increased vascular permeability are separable phenomena whose time course differs markedly in many types of inflammation. For example, after crush injury to muscle prominent vasodilatation is present for many hours after the permeability of vessels within the injured area has returned to normal (Hurley and Edwards, 1969). Similar temporal separation of vasodilatation and increased permeability occurs after thermal injury (Hurley *et al*, 1967), and chemical injury (Steele and Wilhelm, 1966). Recent quantitative studies have confirmed this separation. For example bradykinin has been shown to cause massive and immediate increase in vascular permeability but very little hyperaemia, whereas prostaglandins E1 and E2 cause marked hyperaemia but no significant increase in vascular permeability (Hay *et al*, 1977).

6. Although increased vascular permeability and hyperaemia are separate phenomena, for any given level of increased permeability the amount of protein lost into the injured area varies directly with the rate of blood flow through the leaking vessels. This effect can be seen very clearly in the interaction which occurs between prostaglandin E1 and bradykinin (Williams and Morley, 1973). Prostaglandin E1 causes gross hyperaemia but no significant change in vascular permeability; bradykinin produces little vasodilatation but induces an immediate and massive increase in vascular permeability. If the two substances are injected simultaneously into the same area, the hyperaemia induced by prostaglandin E1 increases the rate of leakage from vessels rendered permeable by bradykinin, and total protein leakage is almost one hundred times greater than if bradykinin is injected alone.

The opposite situation may be seen in areas of severe injury such as the central part of a moderate thermal burn (Movat *et al*, 1978). Here injury may be so severe

as to lead to complete vascular stasis, and in these circumstances, no protein at all escapes from the widely dilated vessels despite the presence of large defects in their endothelial lining.

7. Most of the permeability factors, to be considered in a later chapter, are also vasodilators, but there is wide variation in the relative potency of individual mediators as vasodilators and in increasing vascular permeability. In addition, many substances known to be present in injured tissues, notably certain prostaglandins and lactic acid are powerful vasodilators but cause little or no change in vascular permeability.

Clearly many substances known to be present in injured tissues are capable of causing sustained vasodilatations. However very little is known of their relative importance in different types of injury. Published reports show wide variation in the vasodilator powers of individual mediators in different species and in different organs and tissues. It is not clear how much of this variation reflects a genuine heterogeneity of vascular response, and how much can be explained by variations in the experimental models used (Altura, 1978).

All the vascular changes seen in injured tissues are superimposed on the normal physiological regulations which control pressure and flow within the microcirculation. These normal regulatory processes are very complex and are still not understood in any detail. Hence it is not surprising that, even with the aid of modern quantitative methods, little detailed knowledge is available of the factors responsible for the production of the sustained vasodilatation which forms such a prominent feature of the acute inflammatory response.

Slowing of flow and stasis in the dilated vessels

The main factor here is the increase in the permeability of the wall of inflamed vessels, which allows plasma to escape but retains erythrocytes within the vessels. The consequent rise in haematocrit leads to an increase in blood viscosity. More force is then required to drive blood through the small blood vessels, and slowing of flow, and, in extreme cases, stasis results. The rise in tissue pressure, which results from rapid escape of fluid into extravascular spaces, may slow blood flow further by external compression of, and consequent rise in pressure within, venules and small veins.

As will be described later, changes occur in the endothelium of inflamed vessels, but there is no evidence that these changes are important in the production of slowing of blood flow or stasis.

Axial flow—its loss in inflamed vessels

Because flow within small blood vessels is laminar, particles such as blood corpuscles normally accumulate in the central low pressure area of the blood stream. Such axial congregation is accentuated in the early rapid flow phase of acute inflammation, but as flow slows the axial congregation of cells becomes less marked and the peripheral zone of cell-free plasma narrows. Finally if flow ceases altogether cells and plasma become distributed evenly throughout the vessel.

It has been claimed that leucocytes, being the heaviest elements of the blood, tend to lie centrally in the axial column of cells, and that in acute inflammation red cells adhere to one another to form clumps or rouleaux, which displace the

now relatively lighter leucocytes to the periphery. It is suggested that this may account for the impingement of leucocytes against vascular endothelium which is the earliest phase of leucocytic adherence and pavementing. However, although these factors may play some role, Florey (1970) and others who have carefully observed living vessels in areas of inflammation consider that much of the phenomenon of pavementing results from chance contact of leucocytes with, and their subsequent adherence to, an altered vascular wall—much as a fly is caught to flypaper. Our own observations on living tissues support this conclusion.

REFERENCES

Altura B. M. Humoral, hormonal and myogenic mechanisms in microcirculatory regulation including some comparative pharmacological aspects of micro-vessels. *In* Microcirculation, edited by G. Kaley and B. M Altura, Baltimore: University Park Press. Vol. **11**, 431–502 (1978).

Bonta I. L. Endogenous Modulators of the Inflammatory Response. *In* Inflammation, edited by J. R. Vane and S. H. Ferreira, Springer-Verlag, Berlin, Chap. 15, 521–567 (1978).

Bruce A. N. Uber die bezichung der sensiblen Nervenendizungen zum intzundungsvorgang. *Arch. fur exp. Path. und Pharmacol.*, **63**, 424–433 (1910).

Chapman L. F., Goodell, H. The participation of the nervous system in the inflammatory reaction. *Ann. N.Y. Acad. Sci.*, **116**, 990–1017 (1964).

Florey H. Microscopic observations in the circulation of the blood in the cerebral cortex. *Brain*, **48**, 43–64 (1925).

Florey, Lord. General Pathology, 4th edition, London: Lloyd-Luke (Medical Books), p. 74 (1970).

Hay J. B., Hobbs B. B., Johnston M. G., Movat H. Z. The role of hyperaemia in cellular hypersensitivity reactions. *Int. Arch. Allergy*, **55**, 324–331 (1977).

Hurley J. V., Edwards B. Acute inflammation: A combined light and electron microscope study of the vascular response to incisional and crushing injury of skeletal muscle in the rat. *J. Path. Bact.*, **98**, 41–52 (1969).

Hurley J. V., Ham K. N., Ryan G. B. The mechanism of the delayed prolonged phase of increased vascular permeability in mild thermal injury in the rat. *J. Path. Bact.*, **94**, 1–12 (1967).

Krogh A. Studies in the capillariomotor mechanism. I. The reaction to stimuli and the innervation of blood vessels in the tongue of the frog. *J. Physiol. (Lond).*, **53**, 399–419 (1920).

Lewis T. The blood vessels of the human skin and their responses. Shaw and Sons, London (1927).

Movat H. Z., Kopaniak M. M., Johnston M. G., Hay J. B. The relationship between increase in vascular permeability, hyperemia, stasis and thrombosis in the microcirculation. *In* The recognition of anti-rheumatic drugs, edited by D. C. Dumonde and M. K. Jasani, p. 73–85. Lancaster MTI Press (1978).

Steele R. H., Wilhelm D. L. The inflammatory reaction in chemical injury. I. Increased vascular permeability and erythema induced by various chemicals. *Brit. J. Exp. Path.*, **47**, 612–623 (1966).

Vadas P., Hay J. B. Cutaneous blood flow measurements: A standardisation of the microsphere assay for vasoactive agents. *Agents Actions*, **8**, 505–508 (1978).

Williams T. J. Simultaneous measurement of local plasma exudation and blood flow changes induced by intradermal injection of vasoactive substances, using ^{131}I albumin and ^{133}Xe. *J. Physiol. (Lond.)*, **254**, p 4–p 5 (1976).

Williams T. J., Morley J. Prostaglandins as potentiators of increased vascular permeability in inflammation. *Nature (Lond.)*, **246**, 215–217 (1973).

Yoffey J. M., Courtice F. C. Lymphatics, Lymph and the Lymphomyeloid Complex, p. 171. Academic Press, London (1970).

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