

1910

Eugene L. Opie, 1910

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INFLAMMATION *

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THE obvious causal relationship of bacterial infection to inflammation has tended to obscure the broader significance of the inflammatory reaction. An immense number of sterile substances, both fluid and solid, soluble and insoluble, organic and inorganic, incite a reaction which differs in no essential respect from that which follows the invasion of micro-organisms. Even so-called physiological salt solution introduced into the body may cause acute inflammation; absorption of a protein such as egg albumen or of a fatty substance such as sterile olive-oil is in part dependent on the same process. Views concerning the nature of inflammation are widely diverse, but all are agreed that inflammation accomplishes the destruction and solution of a variety of substances, and notably of those proteins which form the bodies of parasitic invaders.

Although absorption from the tissue, so-called parenteral resorption, is made possible by processes which resemble those occurring within the digestive tract, recent compendiums of biochemistry are almost silent concerning the nature of such processes and limit their discussion to a consideration of the part of filtration, osmosis, and the secreting activity of lining membranes. The pathological problems are unfamiliar to the physiological chemist, and the pathologist is poorly prepared to solve them.

It is well known that there is no agreement on what shall be regarded as inflammation, and some have wished to discard the word. I shall cite historical data with the sole purpose of showing that its historical associations offer little aid in deter-

* Presented before the Harvey Society, New York, Feb. 19, 1910.

mining its application; that accepted usage furnishes no more definite criterion.

The cardinal symptoms of inflammation—heat, pain, redness, and swelling—described by the classical writers, have reference to inflammatory conditions affecting the surfaces of the body; perhaps well illustrated by erysipelas or by a boil. By a series of analogies the term has been applied to changes in the internal organs which exhibit, in some instances, none of these symptoms. Virchow, in the "Cellular Pathology," shows that each one of the cardinal symptoms at some period has been used as a test of the true nature of inflammation. The name, which implies taking fire, shows that the early writers attached greatest significance to the increased heat of the inflamed part. At a later period, the condition of the blood-vessels indicated by congestion and redness, attracted more attention, and Boerhaave taught that inflammation was the result of stasis caused by obstruction of blood-vessels. This view prevailed during the period when, in France, pathological anatomy was studied with greatest industry. Ponfick cites the aphorism of Cruveilhier: "Phlebitis dominates pathology." Yet Cruveilhier defines inflammation as a blood-stasis in the capillaries which is associated with exudation at times of coagulable lymph, at times of pus, perhaps finally of caseous or tuberculous substance. As a criterion of inflammation, accumulation of exudate received increased attention, and the swelling or tumor of inflammation held a predominant place in the views of Rokitsansky.

The experimental studies of Cohnheim inaugurate modern views on the nature of inflammation. Inflammation is the reaction which follows an injury affecting the wall of blood-vessels; increased permeability facilitates the escape of plasma and corpuscles into the surrounding tissue. Attempts to study the effect of various injurious substances upon a tissue devoid of blood-vessels, such as the cornea, have shown that well-known inflammatory changes occur in the adjacent vascular tissues and hence flood the injured part with exuded fluid and corpuscles.

Most of the substances which act as inflammatory irritants cause obvious injury to tissues with which they come into contact. At first sight it may appear unimportant to decide whether injury to tissue, including its blood-vessel, is the stimulus which puts in motion the numerous processes grouped as inflammation; or if the irritant itself acts directly on the structures with which it is in contact, and attracts to itself elements of the blood or of the tissues capable of neutralizing or destroying its toxicity. The decision will modify any interpretation of the phenomena of inflammation. One group of writers who have regarded injury to tissues as the inciting cause of inflammation, have included within its domain all those phenomena which tend to restore to normal the injured part; formation of fibrous tissue replacing elements which have been destroyed becomes a part of the inflammatory reaction. Inflammation is regarded as a process adapted to diminish the harmful consequences of an injury. This is the view expressed by the well-known definition of Burdon Sanderson; it represents the opinion maintained by Cohnheim, Weigert, Ziegler, Neumann, Letulle, Adami. Another group of writers, including Leber, Metchnikoff, Marchand, Ribbert, Councilman, Klemensiewicz, regard inflammation as a reaction excited by the presence of something injurious to the tissues; inflammation is adapted to counteract and destroy the injurious substance. Study of the phenomena by which bacteria are destroyed and dissolved has given this view a predominant place.

All inflammatory irritants produce some form of injury, and moreover, tissue which has been destroyed may act as an inflammatory irritant; nevertheless, there is a fundamental distinction between a reaction which repairs an injury, and reaction which renders harmless an injurious substance. Certain invertebrates with simple structure (hydra, planaria) repair an injury by rapid regeneration of a part removed; phenomena suggesting an inflammatory reaction are wholly lacking. Those who believe that inflammation is adapted to neutralize and destroy the injurious body usually exclude those regenerative changes which replace with fibrous tissue structures which have

been destroyed, for all writers agree in excluding the regeneration which affects the surviving parenchyma when part of an organ has been removed or destroyed.

To determine if inflammation is dependent on changes in the blood-vessels attempts were long made to study the process in tissues such as the cornea or cartilage, which contain no vessels. The nearest vascular tissue became inflamed and the attempt failed. Directing his attention from the vertebrates which had heretofore served as objects of experiment to the lowest invertebrates, Metchnikoff has found the long-sought opportunity to study inflammation in tissues containing no blood-vessels. His well-known treatise on the comparative pathology of inflammation defines the relatively simple reaction which follows application of injurious agents to such animals.

Throughout the animal kingdom methods used to obtain food are often employed to destroy enemies. The amoeba survives because it can destroy and digest the bacteria which it takes into its substance. In certain sponges, phagocytic cells, which digest the food of the animal, accumulate about a foreign body thrust into its substance. The lower orders of invertebrates, such as the medusa, the starfish, and certain worms possess no vascular system; situated between the outer covering and the digestive cavity are mesodermic cells which, having no part in the digestion of food, approach, engulf and often digest foreign particles, bacteria, and other organisms which have found their way into the tissues of the animal. By means of amoeboid movement they accumulate about any substance capable of exciting their activity. Shall this reactive accumulation of phagocytic cells be designated "inflammation"? Those who believe that inflammation is a response of blood-vessels to injurious agencies are unwilling to include it. With a broader view, those processes by which protective elements are drawn from adjacent tissues cannot be separated from those changes by which similar cells are drawn from adjacent blood-vessels. Nomenclature of the process is relatively unimportant. Yet study of what is universally designated "inflammation" in animals with fully developed blood-vessels shows that phago-

cytic cells which react in response to the inflammatory irritant are not necessarily derived from the blood-vessels.

To illustrate the chaotic state of prevailing views concerning inflammation, the status of tuberculosis may be cited. Cohnheim, who attached prime importance to vascular changes, excluded the infectious granulomata; yet many of those who believe that inflammation occurs only in vascular tissue regard tuberculosis as inflammation. Marchand, on the contrary, separates such processes from inflammation, because he believes that they are characterized by multiplication of fixed cells of the tissue.

Inconsistencies of accepted nomenclature are readily found. The term parenchymatous nephritis, a survival of Virchow's conception of inflammation now long abandoned, is applied to a lesion which exhibits none of the vascular and cellular changes which are associated with inflammation of other organs. Injury to the spinal cord is designated as inflammation when it is called traumatic myelitis; yet the secondary occurrence of inflammatory changes common to all forms of injury merely serves to emphasize the confusion of two distinguishable conditions (Marchand¹). The name "acute hemorrhagic pancreatitis" has been applied to a lesion which is essentially necrosis, and not inflammation of the pancreas, and its use has hindered a rational classification of pancreatic disease.

Should we assume that inflammation occurs in order that injurious substances may be destroyed or removed, the nature and action of the fluid and cells which accumulate acquire predominant importance. The swelling of inflammation is in great part referable to accumulation of fluid derived from the plasma of the blood; yet the wall of the vessel controls this transit, for the protein content of the fluid which passes through the wall of the blood-vessel into the tissue is constantly less than that of the blood-plasma. The proteins of the plasma do not enter the spinal fluid nor the aqueous humor, yet with inflammation they are found in both fluids.

Studies of Klemensiewicz² have shown the effect of increased pressure exerted by exudate within the tissue on local

vascular tension. By an ingenious device he has been able to measure directly under the microscope the pressure capable of producing stasis within the capillaries. When an inflammatory irritant is applied to the tissue under examination, accumulation of exudate increases extravascular tension, and a smaller pressure is now capable of causing capillary stasis. This observation may help to explain the obvious truth that accumulation of fluid in the subcutaneous tissue in response to an irritant, is quickly self-limited; whereas the same irritant causes an immense serous exudate when introduced into a serous cavity. Later it will be shown that this difference has an important influence on the outcome of the inflammatory reaction and may determine whether suppuration or resolution occurs.

During the last ten years an immense amount of laborious study has been devoted to the character and origin of the various cells which accumulate at the site of inflammation. The studies of Cohnheim and of Von Recklinghausen have afforded convincing evidence that the common pus corpuscle is the polynuclear leucocyte of the blood which, under the stimulus of the inflammatory irritant, passes through the walls of blood-vessels. Some of the earlier observers have believed that such polynuclear leucocytes may become cells of the fixed tissue, colonize the part, as it were, but there is now universal agreement in the view that they may degenerate but undergo no progressive transformation after they have left the bloodstream. The origin and fate of the numerous mononuclear cells which accumulate in the inflamed tissue, on the contrary, is doubtful. The subject, repeatedly investigated by histological methods, often uninteresting because they are inconclusive, has great biological importance, for it deals with the significance of lymphatic tissue and the normal and pathological relationship between lymphatic and other tissues of the body. It seeks to determine if a cell formed in one part of the body may establish itself in a distant part and there form an integral constituent of the tissue.

Insight into the changes associated with inflammation assumes an accurate knowledge concerning the tissue in which

the inflammatory reaction occurs. All of these changes have their origin within the connective tissues of the body whence inflammatory exudates may find their way into other situations. There are yet many defects in knowledge of the connective tissues of the body. In early stages of embryonic life this tissue is represented by a network of cells with branching processes which are continuous with one another. Within the substance of this protoplasmic syncytium, and hence within the cells, according to observations of Fleming, and in recent years of Mall,³ the white fibres are laid down. At first all the cells which compose this tissue are fixed, but later cells make their appearance within the meshes of the network. Since these unattached cells exhibit irregular projections which suggest that they are capable of amœboid movement, and since they resemble amœboid cells of the circulating blood, they are regarded as wandering cells. Part of them have all the characters of lymphocytes and in many situations form small collections about the blood-vessels. Part of them are larger than lymphocytes and resemble the large mononuclear cells of the blood; they are frequently collected about blood-vessels.

Von Recklinghausen has maintained the opinion that the spaces which, filled with fluid, exist in the meshes of the network formed by the fixed elements of the tissue, are in direct communication with lymphatic capillaries and constitute the origin of the lymphatics within the tissue. Nearly half a century ago (according to Sabin) Langer showed that these lymphatics grow as blind sprouts of endothelial cells. Ranvier has confirmed this almost forgotten observation in recent years, and Sabin⁴ and others have shown that the entire lymphatic system sprouts from the endothelial lining of veins and gradually pushes its way into various tissues and organs to form a closed system everywhere lined by endothelial cells. Endothelium separates the lymph within the lymphatic capillaries from fixed cells of a part. This well-known relationship, usually little considered, has much pathological significance; indeed early observers (Hering, Heller, Thoma⁵) of the movements of amœboid cells within the tissues, have noted the important

truth that leucocytes which have wandered from the wall of the blood-vessels and have passed through the spaces within the fixed tissue, may penetrate the endothelial wall of a lymphatic vessel.

Embryological study of the lymphatic nodes has explained the relationship of lymphatic tissue to lymphatic vessels. Gulland,⁶ Sabin,⁷ and others have shown that lymphoid tissue makes its appearance in the walls of lymphatic channels which have already been formed; and consequently a layer of endo-

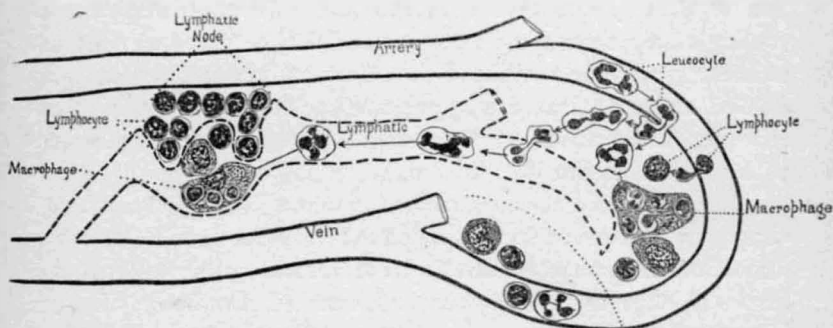


FIG. 1.—Diagram showing the relation of the site of inflammation to the regional lymphatic node. An artery is shown dividing to form a capillary which in turn enters a vein; within the capillary loop is a lymphatic vessel which becomes the sinus of the adjacent node and finally discharges its contents into the venous system. Within the capillary loop to the left of the dotted line is shown the normal position of wandering cells. To the right of the dotted line are shown cells having part in the inflammatory reaction. Polynuclear leucocytes which migrate from the blood-vessels may be ingested by macrophages or may enter the lymphatic, pass to the adjacent lymphatic node and perhaps undergo ingestion by a macrophage within the sinus of the node. The data on which the diagram is based are described in the text.

thelial cells separates the lymphatic tissue from the lumen of the lymphatic vessel, and later from the tortuous sinus to which the primitive channel gives place. The lymphocytes of the lymph-node appear within the meshes of a fibrillated network and in their relation to lymphatics are analogous to the lymphocytes in the meshes of connective tissue elsewhere.

The local changes which with inflammation occur in the lymphatic vessels of the affected part and in the tributary lymphatic nodes (see Fig. 1) are not separable from the changes which have their seat in the blood-vessels and in the interstitial

tissue. Muscatello⁸ has shown that finely granular material, such as carmine powder, introduced into the peritoneal cavity of a dog, appears within ten minutes in the retrosternal lymphatic nodes; the two retrosternal lymphatic channels which follow the internal mammary arteries are quickly rendered conspicuous by the injected material. Within these lymphatic vessels some of the granules are free in the lymph, whereas others are contained in wandering phagocytic cells which, as MacCallum⁹ has shown, penetrate the endothelial lining of the diaphragm. Within three-quarters of an hour after injection of *Staphylococcus aureus* into the subcutaneous tissue of the leg of a guinea-pig, Bezançon and Labbé¹⁰ found that the afferent lymphatic vessels of the adjacent lymphatic node were dilated and contained many polynuclear leucocytes which were entering the sinuses of the node. The subsequent changes within the node are well known.

The well-known studies of Maximow¹¹ have defined the changes which occur in and about a sterile foreign body, introduced into the subcutaneous tissue of various species of animals. In later experiments he has impregnated the body with an inflammatory irritant such as turpentine, or has infected it with pyogenic bacteria, namely, with *Staphylococcus aureus* and with streptococcus. He has pictured with great clearness the changes observable at intervals varying from a few minutes to many days after onset on the inflammatory reaction. The reaction caused by a sterile body differs from that produced by bacteria in its intensity and in the rapidity with which corresponding phenomena occur, but the character and sequence of events are identical.

Serous fluid quickly accumulates about the infected body and the surrounding tissues become œdematous. Within the first four hours polynuclear leucocytes emigrate from the blood-vessels in large numbers, and properly prepared tissue exhibits many leucocytes making their way through the endothelial lining of vessels. Early emigration of lymphocytes as well has so frequently been observed that its occurrence has been placed beyond doubt. The small round cells which migrate from the

blood-vessels quickly give place to larger cells with paler, larger nucleus and fairly abundant cell substance. Those cells which have a predominant part in the late stages of inflammation are known by no familiar name, and it is difficult to designate them conveniently. The term "macrophage," used by Metchnikoff, is applicable, for these cells exhibit phagocytic activity, but the name has a wide significance and may be applied to all large cells capable of ingesting solid particles. The attack on living virulent micrococci is apparently conducted wholly by polynuclear leucocytes. With the disappearance of micrococci, mononuclear cells increase in number and in size and begin to exhibit ability to ingest cells and cellular débris. Such phagocytic cells or macrophages may contain six, a dozen or more leucocytes in various stages of disintegration, together with a variety of inclusions whose origin is no longer recognizable. On the activity of these cells is in large part dependent the solution and removal of the leucocytes which have previously attacked the invading bacteria.

The serous cavities, particularly the peritoneal and pleural cavities, offer a convenient opportunity for study of the cellular phenomena of inflammation. The early changes, whether produced by various bacteria or by sterile irritants, do not differ materially. A noteworthy peculiarity of inflammation within serous cavities is the unobstructed and rapid accumulation of serum; the cells which accumulate are in part suspended in this fluid but a greater part adhere to the membranes, such as the omentum or mediastinum which are contiguous with the cavity. Numerous observations have shown that the changes which occur in the serous cavity during the first few hours after inoculation are identical with those which are demonstrable under similar conditions in the subcutaneous tissue.

The importance of vascular changes in inflammation has long been recognized; less has been written concerning the significance of the lymphatic system. The studies which have been cited show that the lymphocytes which are in great part at least derived from the lymphatic glands migrate from the blood-vessels and are perhaps transformed into macrophages.

At the same time lymphocytes and similar larger cells which are scattered in the normal tissue outside of the blood-vessels and often according to Ribbert form rudimentary lymphatic nodes mingle with the cells of the exudate and perhaps take part in the formation of macrophages. The intimate relationship of the local focus of inflammation to the adjacent lymphatic glands is well illustrated by the experimental pleurisy produced by injection of a sterile irritant such as the vegetable protein, aleuronat, into the pleural cavity. The lymphatic glands which are situated in the anterior mediastinum become greatly swollen and microscopic examination shows that changes which occur in the sinuses of these glands are identical with those in progress within the pleural cavity itself. At the end of four or five days the serous cavity contains abundant fluid in which polynuclear leucocytes are abundant; at this time mononuclear phagocytic cells are large and numerous and are engaged in ingesting and dissolving polynuclear leucocytes. The sinuses to the adjacent mediastinal lymphatic glands are much distended and closely packed with the same large phagocytic cells whose protoplasm often contains many polynuclear leucocytes in various stages of disintegration. In some instances almost the entire lymphatic gland is replaced by these cells. Ingestion of polynuclear leucocytes and other cells, essential to complete resolution of the exudate, is begun in the serous cavity and is completed in the regional lymphatic node. By the method previously described cells make their way along lymphatic channels from the primary site of inflammation to the adjacent node.

Studies of the fate of bacteria injected into the body have demonstrated the rapidity with which micro-organisms enter the regional lymphatic nodes, and the partial efficiency of these nodes as filters. Buxton and Torrey¹² have injected typhoid bacilli in considerable quantity into the peritoneal cavity of small animals and have estimated by the enumeration of colonies in agar plates the relative abundance of bacteria in the sub-sternal lymphatic nodes, in the blood and in various organs such as the liver, spleen, lungs, bone-marrow, and kidney.

Within ten minutes after inoculation, they found an enormous number of bacteria in plates prepared from the regional lymphatic node, and in sections prepared for microscopic examination bacilli are found in the afferent sinus, in part free, in part within phagocytic cells. Notwithstanding this regional fixation of those bacteria which had escaped from the site of inoculation, a not inconsiderable number had entered the blood and were scattered throughout the body. Within the interval from five to thirty minutes after inoculation, from twenty to thirty thousand bacteria per cubic centimetre were recovered from the blood. Nevertheless at the end of an hour, the number had fallen to several hundred. Likewise within the first half hour after inoculation the number of bacteria in the liver, spleen, lungs, and kidney was very great; but it fell suddenly and soon became relatively small. This initial rush of bacteria from the peritoneal cavity to the blood has been found to occur with equal readiness in normal and in immunized animals.

Experiments of Muscatello have shown that inanimate particles such as powdered carmine pass through the diaphragm into the lymphatic vessels of the mediastinum and reach the circulating blood only through the lymphatic system. Wells and Johnstone¹³ have successfully attempted to show that bacteria do not pass into the blood-vessels of the peritoneum but reach the blood wholly by way of the lymphatic vessels. They have prevented the initial rush of bacteria from the peritoneal cavity into the blood by ligation of the thoracic duct. By estimation of the number of bacteria in the lymph they have shown that the thoracic duct, during the first hour after inoculation of the peritoneal cavity with *Bacillus coli* discharges an immense number of bacteria into the blood.

The foregoing observations show that the lymphatic nodes, during the first hour after inoculation, are not efficient filters for bacteria. Although two lining membranes are interposed between the peritoneal cavity and the interior of lymphatic vessels, solid particles pass with the utmost rapidity from one to the other; the greater part of these particles are not contained within phagocytic cells. The membranes separating the

cavity and the lumen of the vessel are uninterrupted but solid particles pass as if there were direct communication. Furthermore, both bacteria and inanimate particles at first pass the lymphatic nodes, but later at the end of the first half hour or hour after inoculation, although the peritoneal cavity and the regional lymphatic nodes contain an immense number of bacteria, their escape is obstructed and they have almost completely ceased to enter the circulating blood. At this time an inflammatory reaction has begun both at the site of infection and within the lymphatic node. There is little doubt that the quiescent lymphatic node is an inefficient filter whereas the inflamed node, containing even at this early period many phagocytic cells, is effective in restraining the dissemination of bacteria.

Noetzel¹⁴ injected *Bacillus pyocyaneus* into the knee-joint of rabbits, and from five to ten minutes later found the organism both in the inguinal, lumbar, and crural lymphatic nodes and in the circulating blood. Pawlowsky¹⁵ has demonstrated the presence of staphylococci in the blood and organs of guinea-pigs from twenty-four to forty-eight hours after inoculation of the knee-joint, but has been able to show that this dissemination is inhibited or wholly prevented if before inoculation acute inflammation of the joint has been produced by the injection of some sterile irritant such as turpentine, alcohol or solution of quinine. His observation recalls the studies of Issayeff, who showed that the peritonitis induced by a variety of sterile irritants such as foreign blood-serum, bouillon or normal salt solution, temporarily increases resistance to subsequent intra-peritoneal inoculation of bacteria. Such observations help to explain the well-known resistance to infection exhibited by a granulating wound.

A great variety of substances which are either non-dialyzable or insoluble in water are dissolved and removed when introduced into the tissues of an animal. It is difficult, perhaps impossible, to cite any substance which introduced from outside of the body into the tissues of an animal fails to excite an inflammatory reaction; physiological salt solution introduced

into the peritoneal cavity produces active emigration of leucocytes. Comparatively little systematic observation has been made on the pharmacology of inflammation and we are as yet ignorant of the factors on which depend peculiarities in the intensity of the reaction and in the character of the exudate which is produced. The reaction is in all instances characterized (a) by a stage of leucocytic emigration followed when resorption begins, (b) by accumulation of macrophages. It is noteworthy that tubercle bacilli and typhoid bacilli, whose presence in man is usually associated with peculiar lesions exhibiting little resemblance to acute inflammation, produce the same changes during the first twenty-four hours after introduction as *Staphylococcus aureus* (Helly) and other pyogenic cocci.

Nevertheless one large group of substances, unlike bacteria, excite the large mononuclear phagocytes with much greater activity than polynuclear leucocytes. The cells of one animal introduced into the body of another of the same or of a different species are attacked by large mononuclear cells and are gradually dissolved within their substance. This experiment has been repeated under a great variety of conditions by Metchnikoff and his pupils. The same process occurs under physiological conditions, for in the spleen red blood-corpuscles, perhaps those which have undergone some degenerative change and are no longer useful to the body, are ingested and destroyed by large mononuclear phagocytes. When hemorrhage occurs into the tissues, phagocytic cells of similar character, by taking red corpuscles into their substance, aid in the process of absorption. Necrotic tissue in the liver or in other organs is absorbed by aid of the same cells. A similar process occurs when degenerative changes affect the central nervous system. Absorption of tissues no longer useful to the body, and perhaps already the seat of degenerative change, is accomplished by the aid of mononuclear phagocytes and has many analogies throughout the animal kingdom. Metchnikoff, studying the progress of the metamorphosis of insects, has lately found evidence that the organs and tissues first undergo degenerative changes, and

later become the prey of phagocytes. Furthermore, one large group of parasitic invaders, including protozoan micro-organisms such as malarial parasites and trypanosomes, excite almost exclusively the activity of the mononuclear phagocytes.

The observations which have been cited show what cells accumulate about a foreign substance introduced into the body. The more important of these cells are capable of engulfing solid protein particles, and of dissolving them. By what means is this absorption accomplished?

The occurrence of products of protein digestion in inflammatory exudates was recognized almost fifty years ago; Eichwald in 1864 found in pus what was then called 'peptone'; and later, Maixner found peptone in the urine in association with a considerable variety of suppurative conditions such as empyema, peritonitis, cerebrospinal meningitis, pyelitis, etc. An observation of Friedrich Müller has explained the constant presence of so-called peptone in purulent phthisical sputum; a glycerin extract of such sputum is capable of digesting fibrin or coagulated albumin in a weakly alkaline medium. Other purulent sputum has the same property; the sputum of a patient with pneumonia does not exhibit this digestive action before crisis has occurred, but later when it has assumed a white pus-like appearance, the enzyme may be demonstrated. The pus of an abscess contains the same enzyme, but the pus-like fluid from a tuberculous lesion, a so-called cold abscess, fails to contain it. Various observers have shown that enzyme of pus is capable of digesting a considerable variety of protein substances, such as gelatin, fibrin, coagulated egg albumen, and casein. The well-known studies of Salkowski first showed that animal tissues preserved under conditions which prevent the growth of bacteria undergo changes similar to those which occur during the digestion of protein. Friedrich Müller showed that the pneumonic lung consolidated by the presence of inflammatory exudate within the alveoli is especially susceptible to such autolysis. By the self-digestion of this inflamed pulmonary tissue at body temperature are formed albumose, leucin, tyrosin, and other products of protein disintegration; nuclei

of the autolyzed tissue quickly disappear as a result of decomposition of nucleins. These observations have been used to explain the solution of fibrin and the disappearance of leucocytes and other cellular elements which occurs with resolution of the exudate.

Biondi,¹⁶ Hedin and Rowland,¹⁷ and others have found that various normal organs of the body autolyze with greater activity in weakly acid than in alkaline solutions, and in this respect resemble pepsin rather than trypsin.

Studying the cells of an inflammatory exudate obtained by injection of aleuronat or other sterile irritant, I have repeatedly confirmed the observation that they digest coagulated protein with greatest activity when they are suspended in an alkaline medium. Digestion may be accurately measured by allowing the cells to act at body temperature on blood-serum coagulated by heat; the amount of protein which goes into solution may be accurately determined. Testing the liver, kidney, spleen, lymphatic node, and bone marrow, it is noteworthy¹⁸ that the bone-marrow alone resembles the cells of an acute inflammatory exudate, and digests with greater activity in alkali than in acid.

The cell which is predominant in the inflammatory exudate produced by the injection of aleuronat is the polynuclear leucocyte, and histologists are agreed that this cell has its origin in the bone-marrow. In other words, polynuclear leucocytes which, constituting the greater part of the white corpuscles of the blood, migrate during the early stage of the inflammatory reaction, and approach and digest solid particles, contain an enzyme which resembles trypsin of the pancreas. They carry this enzyme from the bone-marrow to the site of inflammation. Dochez has shown that this enzyme, unlike trypsin, exists within the cells in an active state, and will, without further change, act on protein in the presence of alkali. Trypsin, on the contrary, exists in the pancreatic cells as zymogen, and requires activation by enterokinase or by acid before it is able to attack protein.

The enzyme of the polynuclear leucocytes, which may be

conveniently designated "leucoprotease," may be purified by precipitation with alcohol, and after drying may be preserved almost indefinitely.¹⁹ In the moist state, the enzyme thus prepared is destroyed by heating at a temperature between 70° and 75° C. Temperatures between 50° and 65° C. acting on the enzyme during half an hour increase its activity. It acts in an alkaline or in a neutral medium, but is inhibited by acid. Sodium carbonate in concentration of 0.2 to 0.5 per cent. favors its action; greater concentration is destructive. The enzyme is much less active than trypsin, but it is not improbable that its activity, tested outside the body, is less than its activity under the favorable conditions which doubtless exist within the leucocyte.

Examination of the properties of the enzyme which has been described, demonstrates that it is not identical, as several writers have claimed, with the alexin or complement of the blood-serum, for the latter, it is well known, is destroyed by heating to a temperature of 56° C. Jochmann²⁰ has shown that it has no bactericidal power and asserts that it digests bacteria which have been killed by chloroform or by heat, whereas it fails to dissolve living bacteria.

It is not difficult to bring proof²⁰ that the cells which accumulate in response to the presence of an inflammatory irritant contain a second enzyme capable of digesting albuminous substances; its properties are different from those peculiar to the enzyme of the polynuclear leucocytes. The enzyme which is obtained by treating the cells with alcohol, it has been mentioned, acts in both neutral and alkaline solutions, but is inactive in acid; the fresh cells, however, digest in acid as well as in alkali. This observation suggests that alcohol destroys a second enzyme, present in the fresh cells. Further study has shown that this second enzyme is more labile than leucoprotease; for whereas temporary heating to temperatures between 50° and 65° C. increases the activity of leucoprotease, it greatly diminishes the activity of the enzyme which digests in the presence of acid.

I have previously cited many observations which show that two types of cells are abundant in all inflammatory exudates

which exhibit a tendency to resolve. When aleuronat is injected into the pleural cavity of a dog the proportion of large mononuclear cells, which act as phagocytes, gradually increases and with this increase there is increasing power to digest in the presence of acid. I have already pointed out that the phagocytosis of micro-organisms, foreign particles, polynuclear leucocytes, red blood corpuscles, and cellular débris begun in the pleural cavity is completed in the regional lymphatic nodes. At the end of four or five days after the onset of inflammation incited by aleuronat the retrosternal lymphatic nodes are enormously enlarged beyond their normal size and their sinuses are distended with large cells identical with those in the pleural cavity and actively engaged in the phagocytosis of polynuclear leucocytes and other cellular elements. An emulsion prepared from such a lymphatic node in which mononuclear phagocytes are predominant, fails to digest protein in an alkaline or neutral medium but exhibits active proteolysis in the presence of acid. Moreover, this form of enzymotic activity increases with the duration of the changes in the node. The regional lymphatic node contains in almost pure form that enzyme which in the exudate increases with the increased number of macrophages. I have suggested for this enzyme the name "lymphoprotease."

This enzyme, like pepsin, acts in an acid medium and is inhibited by alkali; but it is not identical with pepsin, for it acts with greatest activity in a very weak concentration of hydrochloric acid and is destroyed by that strength (0.2 per cent.) which is favorable to the action of pepsin. It is more closely related to the autolytic enzyme of various tissues. The factor of essential importance is the increase of this enzyme which is associated with an increase of large mononuclear phagocytes in the exudate or with an increase of similar cells in the lymphatic nodes tributary to the inflamed area.

The enzymes which have been found in the cells of the serous inflammatory exudate just described are present as well in fibrinous exudates.²¹ When a small quantity of turpentine is injected into the pleural cavity, coagulable fluid accumulates and reaches a maximum at the end of two or three days. The

exuded fibrin, which contains polynuclear leucocytes during the first three or four days of inflammation, undergoes solution when suspended in an alkaline medium, whereas at a later period when polynuclear leucocytes have disappeared, this property is lost. On the second or third day after onset of the inflammatory reaction, products of proteolytic digestion appear in the serum; reactions indicating the presence of albumose are readily obtained. Such decomposition products are doubtless absorbed with great rapidity, for large quantities artificially introduced disappear from the exudate within twenty-four hours.

Although leucocytes contain active enzymes, serous inflammatory exudates containing cells in abundance fail to undergo autolysis. Experiments which I made several years ago have explained the absence of such autolysis and have disclosed a mechanism by which the activity of the enzyme is limited to the locality in which it is needed. The cells of the exudate separated from the serum undergo autolysis and are capable of digesting foreign protein; but if to the cells the exuded serum is added, digestion is wholly inhibited.

The serum contains some substance capable of restraining the action of the enzyme; it is convenient to designate this substance "antienzyme," without implying thereby that it is a specific antibody adapted to combine with enzyme in accordance with laws of chemical union. The antienzymotic action of the exuded serum is exhibited by the serum of the blood as well; it passes with the serum into the inflammatory exudate. The observation of E. Müller²² that the antienzyme fails to enter the normal cerebrospinal fluid has a considerable interest.

The antienzyme is destroyed by heating to 75° C. It is apparently attached to the albumin fraction of the serum for the globulin exhibits no antienzymotic action, whereas the albumin fraction is active. The antiaction occurs in an alkaline or neutral medium, but is destroyed by acid. The phenomenon can be accurately studied by adding to weighed quantities of leucoprotease different volumes of serum. Such experiments do not afford evidence that enzyme and antienzyme com-

bine in definite quantities. Nevertheless, if to a fixed quantity of serum, increasing quantities of enzyme are added, a point is reached at which the serum fails to restrain completely the activity of the enzyme. In the study of suppuration this observation has considerable importance.

Antienzymes in the blood serum similar to that which restrains the action of leucoprotease have long been known. Hahn in 1897 showed that the blood-serum inhibits the action of trypsin. It is not improbable that the inhibitory effects on trypsin and on leucoprotease are dependent upon some peculiarity of the same substance, for Jochmann and Kantorowicz²³ have found that blood-serum which has abnormally high anti-tryptic action exhibits an increased ability to restrain the action of leucoprotease. Furthermore, there is no specific relationship between the enzyme of one species and the antienzyme of the same species; the serum of the rabbit has greater antienzymotic action on dogs' enzyme than dogs' own serum.²⁴ Birds' serum, unlike mammalian serum, fails to inhibit leucoprotease, which is peculiar to mammals.

The relationship between leucoprotease and its antienzyme in the serum furnishes a mechanism by which the action of the enzyme is limited to the locality in which it accomplishes its function. The polynuclear leucocyte is suspended in a fluid which neutralizes the effect of its enzyme, should this enzyme be set free by disintegration of the cell or by other means. When the polynuclear leucocyte ingests a solid particle of protein matter, for example, a bacterium, it removes it from contact with the serum and brings it into contact with its enzyme.

The mononuclear phagocytes are subject to a similar influence, for numerous experiments have shown that the enzyme which they contain is restrained by the serum of the blood, and similarly by the serum of an inflammatory exudate. In what degree this antienzymotic action depends on the apparent alkalinity of the serum, and in what degree on a thermolabile antibody, has not been established.

The relation between leucoprotease of the polynuclear leu-

cocytes and the antienzyme of the serum has served to explain the essential nature of abscess formation. Ribbert²⁵ defines suppuration as follows: "It is an intense inflammation with which polynuclear leucocytes wander from the blood-vessels in unusually great quantity; the tissue is softened and the serum between the collected pus cells does not coagulate." It may be added that solution of tissue in some instances has a beneficial result, for softening of the least resistant tissues may result in superficial rupture with healing; without escape of pus, it is well known there is little tendency to heal.

The peculiar appearance of pus is in part dependent on the presence of a great quantity of pus cells suspended in a relatively small proportion of fluid. A serous or serofibrinous exudate, on the contrary, contains abundant fluid and a relatively small proportion of cellular elements. Whereas the serum of the serous or serofibrinous exudate inhibits the digestive action of leucoprotease, the serum obtained from pus not only fails to inhibit leucoprotease, but itself contains unrestrained enzyme.²⁶ By disintegration of leucocytes, doubtless referable to the inflammatory irritant, increasing quantities of leucoprotease have been set free, so that the antienzymotic activity of the exuded serum is finally overcome. The proteolytic enzyme may now come into contact with tissue and with fibrin, and softening is the result.

The following experiment serves to explain why the same irritant in the same quantity may cause two different types of inflammation. If a small quantity of turpentine is injected into the subcutaneous tissue of a dog, a large fluctuating abscess filled with creamy pus is formed within four days; there is wide-spread undermining of the skin. The same quantity of turpentine injected into the pleural cavity causes a serofibrinous inflammation which undergoes resolution so that the pleural cavity is restored to its normal condition after about ten days; there is no destruction of tissue and a scar is not formed. In the subcutaneous tissue only a small amount of œdematous exudate can accumulate; the undiluted irritant causes active migration of leucocytes so that the antibody of the exuded

serum is soon overbalanced by the enzyme set free by disintegrated pus cells. In the pleural cavity, on the contrary, a large quantity of serum quickly accumulates and the exudate is serofibrinous instead of purulent; the antienzyme it contains is capable of holding in check the leucoprotease of the accumulated leucocytes. If a bit of the fibrinous exudate is suspended in the exuded serum, it is preserved intact. Nevertheless, by repeated injection of turpentine at short intervals into the pleural cavity, accumulation of leucocytes may be prolonged so that finally a condition is produced in which antienzyme can no longer restrain the enzyme. The softened fibrin of such an exudate quickly disintegrates in the serum of the exudate.

The foregoing observation introduces a new factor into the discussion concerning the pyogenic activity of many bacteria. It helps to explain how the typhoid bacillus produces abscesses in certain situations such as the kidney and bone; how the pneumococcus, which rarely causes abscess of the lung, in which conditions are somewhat similar to those within the pleural cavity, may cause suppuration in other localities, such as the middle ear, or in the subdural space; how the tubercle bacillus may, under peculiar conditions, cause true suppuration.

It is noteworthy that the normal spinal fluid, unlike other body fluids, contains neither enzyme nor antienzyme, and for this reason, Dochez²⁷ has made a special study of the changes which occur in association with inflammation. With epidemic meningitis, antienzyme may enter the spinal fluid and quickly leaves it. With more virulent infection caused by pneumococcus or streptococcus, enzyme derived from disintegrated polynuclear leucocytes gives to the fluid well marked power to digest protein. Such active enzyme itself doubtless acts as an irritant and increases the severity of the disease.

A few writers, notably Marchand, exclude the infectious granulomata from the domain of inflammation; they are those who, on the one hand, accept the opinion of Baumgarten that the tubercle is formed from elements of the fixed tissue, and on the other hand, do not apply the term "Inflammation" to regenerative changes in the fixed tissue. Nevertheless, the

greater number of pathologists give weight to the truth that the tubercle is formed by a reaction in response to the presence of an invading parasite, and this reaction, in its early stage, is identical in character with that which follows the entrance of other bacteria into the tissues. Tuberculous tissue, moreover, is composed in large part of so-called epithelioid cells; these cells have the anatomical structure and phagocytic activity of the large mononuclear cells which predominate in the later stages of an acute inflammatory reaction. With present knowledge, it is impossible to define clearly the relationship of the tubercle to the later stage of inflammation, for the available evidence has permitted no agreement concerning the origin of the epithelioid cells. Study of acute inflammations produced by a sterile foreign body or by bacteria demonstrates with considerable certainty that lymphoid cells leave the blood-vessels and, it is probable, assume the characters of macrophages. In the immense accumulation of cells which follows, the identity of various elements is lost and only the uncertain means of tracing transitions from one form to another is available for determining origin of various types. Large mononuclear cells are accumulating in the tuberculous and in the non-tuberculous inflammation after the first twenty-four hours. There is no doubt that small round cells with the character of lymphocytes accumulate in the neighboring blood-vessels and migrate from them during the formation of the tuberculous lesion. Though transitions from this lymphoid cell to epithelioid cells are not wanting, there is no convincing evidence that one is derived from the other.

Polynuclear leucocytes occur in scant number in tubercles found at autopsy; yet in man (Benda), as in other animals, they are the first cells to accumulate about tubercle bacilli which are free in the tissues. Within an hour after injection of tubercle bacilli into the blood or into a serous cavity, they are surrounded or ingested by polynuclear leucocytes; mononuclear cells subsequently appear. In some animals, polynuclear leucocytes are very numerous in tuberculous tissue. In the dog, during the first few weeks after inoculation of the pleural

cavity, polynuclear leucocytes occur in immense number in the tuberculous tissue which is formed in and on the mediastinum. The relative abundance of these cells is dependent on the character of the bacillus, and in some degree is an index of the activity of resistance upon the part of the host. Virulent tubercle bacilli excite a more active emigration of polynuclear leucocytes than non-virulent organisms.

If the lesions which are classed as infectious granulomata are passed in review, various conditions intermediate between the tubercle and a simple abscess are found. The actinomycotic nodule has many of the characters of the tubercle, yet polynuclear leucocytes are so abundant that a small abscess is formed in the immediate neighborhood of the micro-organism. Glanders, in man and in lower animals, is usually characterized by abundant accumulation of polynuclear leucocytes with necrosis and suppuration. Duval and White²⁸ have shown that the character of the lesion produced in animals varies with the virulence of the micro-organism. Very virulent strains of the bacillus of glanders rapidly cause necrosis of tissue and formation of small abscesses in the liver, lungs and other organs, whereas less virulent organisms produce nodules which are composed of epithelioid and giant cells and have all the characters of tubercles.

The specificity of the tubercle is impaired by the observation that various sterile foreign bodies produce somewhat similar nodular lesions. When, for example, finely powdered meal (Kopec²⁹) in suspension is introduced into the peritoneal cavity, the particles are collected together in clumps and tubercle-like nodules are formed about the clumps scattered upon the peritoneal surface. In other respects these foreign body tubercles do not accurately reproduce the histological peculiarities of the true tubercle. Similar foreign body tubercles have been found scattered throughout the peritoneal cavity when, under conditions which cannot be accurately defined, food particles have entered the cavity through a perforation in the wall of the gastro-intestinal tract.

It is well known that the tubercle bacillus contains an insol-

uble wax-like substance on which, in part at least, depends its ability to resist solution in the tissues; it is not improbable that its peculiar staining properties are dependent on the same substance. Such wax may be obtained by extraction from tubercle bacilli and introduced in suspension into the body of an animal first attracts polynuclear leucocytes; later mononuclear phagocytes accumulate, and among them occur giant cells. At the periphery a fibrous capsule is formed; the wax remains undissolved (Tschistowitsch³⁰).

One form of pseudo-tubercle accurately reproduces the histological characters of the true tubercle. About the eggs of the blood-fluke *Schistosoma japonicum* deposited in the liver and in the intestinal wall nodules with all the characters of true tubercles are formed. Through the kindness of Dr. Henry J. Nichols,³¹ I have lately had opportunity to examine tissues from a case of schistosomiasis occurring in the Philippine Islands. The nodules are composed of epithelioid cells containing giant cells; at the periphery of the nodule lymphoid cells are abundant. Coagulation necrosis with the histological characters of caseation occurs in the centre of the nodules in contact with the egg, and the epithelioid cells at the margin of the necrotic area assume the arrangement frequently seen in true tubercles, namely, with long diameter at right angles to the margin of necrosis.

The observations just described suggest that the tubercle has a close relationship, on the one hand, to the late stage of acute inflammation at a time when absorption is in progress and, on the other hand, to the changes which occur about an insoluble substance. The histological data which are available, fail to furnish conclusive evidence concerning the origin of the macrophage, which has an important part in acute inflammation, nor of the epithelioid cell of the tubercle. Both cells are capable of ingesting and dissolving protein bodies, and both contain enzymes with similar properties.

The dog offers a favorable opportunity for study of the enzymes of tuberculous tissue and for comparison of these enzymes with those present in the sterile inflammatory exudates

which are readily obtainable from the same animal.³² When tubercle bacilli are injected into the pleural cavity, an immense mass of tuberculous tissue is formed in the mediastinum and the adjacent lymphatic glands undergo enormous hypertrophy. The power of this tissue to digest protein material exhibits certain noteworthy peculiarities. During the first two or three weeks after its formation polynuclear leucocytes are abundant and it exhibits the ability inherent in the leucoprotease of these cells to digest in the presence of an alkaline medium. At a later period with the disappearance of polynuclear leucocytes, this property diminishes and is finally lost. In the early period of its formation the tuberculous tissue digests in weak acid as well and at a later period when leucoprotease is no longer demonstrable the power of energetic digestion in acid persists. The enzyme which has this property may be extracted from the cells with water and preserved during a limited period of time. There is little doubt that it is contained in the epithelioid cells which digest within their substance tubercle bacilli, polynuclear leucocytes, red blood-corpuscles and other cellular elements; for such cells constitute almost the entire bulk of the newly formed tuberculous tissue. Moreover, when the tuberculous tissue undergoes caseation and the epithelioid cells undergo necrosis so that a fibrous capsule alone persists, protein-digesting activity disappears from the tissue.

Autolysis in the presence of acid is exhibited by the liver, spleen, and kidney, and these organs exert a limited power to digest foreign protein. There are at present no available means of determining if the enzyme of tuberculous tissue is a peculiar enzyme or is identical with the autolytic enzyme of certain other tissues. Of especial interest is the observation that the enzyme of phagocytic cells which are capable of intracellular digestion is more active than the autolytic enzymes. Opportunity for an accurate comparison is afforded by the liver studded with innumerable miliary tubercles. Such tissue contains much more enzyme than normal liver.

A peculiarity of the serous effusion which accumulates in the infected pleural cavity in contact with the tuberculous tissue

previously described emphasizes what has been said concerning the character of the enzymes contained in this tissue. Such serous effusion, like other serous effusions, inhibits the enzyme of the polynuclear leucocytes but unlike the serum of all other inflammatory exudates which have been tested, fails to restrain the enzyme which is abundant in the tuberculous tissue.

To complete the study of enzymes produced during the course of an inflammatory reaction, it is necessary to examine the adjacent lymphatic nodes. Such tuberculous nodes show enzymotic action which differs in no respect from that of the tuberculous mediastinum. The sinuses of the node are filled with large mononuclear phagocytes, many of which contain tubercle bacilli. Before caseation has begun, the histological appearance resembles that of the same node during the late stages of pleurisy produced by a sterile irritant such as aleuronat; and in both instances there is active enzymotic power of the same character.

Evidence of the existence of lipolytic enzyme in the cells of tuberculous exudates and in similar mononuclear cells from other sources has been obtained first by Bergel.³³ On plates of wax small excavations are produced after a period of incubation by exudates containing lymphocytes and especially by the exudate obtained from so-called tuberculous abscesses; ordinary pus produces no superficial solution of the wax plate. Tuberculous pus-like exudates, moreover, are capable of splitting neutral fat obtained from butter. Lymphatic gland and spleen pulp have similar lipolytic action, but bone-marrow, according to Fiessinger and Marie,³⁴ who have confirmed the observations just cited, fails to exhibit it. These authors have injected wax and various fats into the subcutaneous tissues and peritoneal cavity of animals and have found that polynuclear leucocytes first accumulate; an intense mononuclear reaction follows and effects the absorption of the fat. They think that the wax-like substance of the tubercle bacillus is dissolved by the lipolytic enzyme of the mononuclear cells.

The conditions under which in the body the intracellular enzymes act and the factors which bring them into action are

not clearly understood. Intracellular digestion by amœbas and other protozoa occurs in the presence of an acid medium and granules of litmus, and other indicators ingested by amœbas undergo the usual color changes indicative of an acid reaction. When phagocytic cells of vertebrates are allowed to ingest such indicators in granular form, no such change of color occurs. Whatever change of reaction occurs is not indicated by this gross method.

The enzyme of the polynuclear leucocytes is active in a neutral or alkaline medium and its behavior *in vitro* indicates that the reaction of the normal body fluids is favorable to it. The acids, such as acetic acid, which have usually been employed to demonstrate the activity of the enzyme of the mononuclear phagocytes are not present in the cells or in the serum. Nevertheless, other acidifying substances such as carbon dioxide, or lactic acid, are capable of bringing the enzyme into action. It is not improbable that conditions which diminish the oxidation of pathological tissue or inhibit its gaseous interchange increase its acid content and produce conditions favorable to the action of the enzyme.

Solution of bacteria, such as pyogenic cocci, is doubtless effected by the proteolytic enzymes contained within the polynuclear leucocytes. Metchnikoff has brought abundant proof that living bacteria are ingested by the leucocytes, but it is uncertain what part enzymes have in destroying bacteria. The proteolytic enzyme of the leucocytes and the bactericidal complement of the serum are not identical. Abundant histological evidence previously cited has shown that the mononuclear cells which accumulate at the primary site of inflammation dissolve within their substance polynuclear leucocytes, many of which have probably undergone degenerative changes before they have been ingested; this process is continued and completed in the adjacent lymphatic nodes. Indeed, it is not improbable that polynuclear leucocytes, together with other products of tissue degeneration, serve as the principal stimulus to the activity of the mononuclear cells. Such intracellular digestion of polynuclear leucocytes is the first step in the resolution of an

inflammatory exudate. There is scant evidence that polynuclear leucocytes disappear by autolysis unless suppuration occurs.

Absorption of fluid constitutes a second factor in the resolution of an exudate. When, with diminishing activity of the inflammatory irritant, exudation from the blood-vessels ceases, the physiological factors which favor absorption of tissue juices rapidly diminish the accumulated fluid unless the inflammatory irritant or inflammation itself has produced changes which alter the adjacent vascular and lymphatic structures; necrosis, suppuration, which is always accompanied by necrosis, and new formation of fibrous tissue, three conditions which are usually associated, produce such structural changes.

The large mononuclear cells which act as phagocytes are at first only slightly larger than the cells which they ingest, but those which are engaged in digesting many cells attain great size. The fate of these large cells after they have accomplished their function is probably not always the same. Some may enter lymphatics and reach adjacent lymphatic nodes. According to Maximow, some undergo degenerative changes, whereas others remain in the tissue. It is not improbable that disappearance of exuded fluid produces conditions unfavorable to their prolonged existence and many probably undergo autolysis. Diminished blood-supply and other factors which might impair oxygenation doubtless increase the acidity of their protoplasm and favor self-digestion.

Human pathology affords numerous instances in which inflammation pursues its course without noteworthy destruction of tissue and, followed by complete restoration to normal, is unaccompanied by any fibrous induration of the part. Lobar pneumonia, acute serofibrinous pleurisy and erysipelas may be cited. Such inflammatory reactions are well represented by the serofibrinous inflammation which follows the introduction of turpentine into the pleural cavity of an animal. The fibrin of such an exudate undergoes autolysis *in vitro* under conditions which indicate the presence of leucoprotease only during the first three days after onset of the reaction. During this early

stage autolysis occurs when the fibrin is suspended in weak acid and this ability to undergo self-digestion in acid persists at a later stage when fluid has completely disappeared from the chest. Fibrin obtained by whipping freshly drawn blood exhibits the same property. Since the blood-serum contains an enzyme exhibiting similar proteolytic activity it is probable that fibrin carries with it some of this enzyme when it is precipitated during coagulation. Autolysis referable to the presence of this enzyme may explain the disappearance of fibrin which persists after the fluid of an exudate has been absorbed. In some instances under conditions which are not understood, fibrin fails to undergo absorption and organization with new formation of fibrous tissue follows; fibrin is then slowly absorbed and replaced.

Further evidence that formation of scar tissue is not a necessary result of inflammation even when the reaction is inaugurated by extensive destruction is afforded by recent experiments of Whipple and Sperry³⁵ on the necrosis of the liver after poisoning by chloroform. The hepatic cells constituting a large part of the liver lobule undergo coagulation necrosis; a considerable number of large mononuclear phagocytes collect at the site of injury and accomplish the absorption of the dead liver cells. By active multiplication of adjacent liver cells, the parenchyma which has been destroyed is replaced and no new formation of fibrous tissue follows. The liver is restored to normal and there is complete absence of cirrhosis, though a bit of tissue removed three weeks before has demonstrated necrosis of three-fifths of each hepatic lobule.

Human pathology affords little evidence that tuberculous exudates may undergo resolution with restoration to normal; yet such resolution is doubtless possible and is probably accomplished by the same enzymotic action, which brings about the disappearance of an acutely formed exudate. Experiments of J. L. Nichols³⁶ have shown that the exudate of tuberculous pneumonia in immune rabbits undergoes complete resolution.

After suppuration has occurred, restoration to normal by the processes which have been described is no longer possible.

The inflammatory reaction pursues the course which brings it to an end only when enzymes set free by disintegration of polynuclear leucocytes are fully held in check by the serum which accumulates. When intensity of the irritant calls forth increasing numbers of leucocytes, and the density of the tissue affords restricted opportunity for accumulation of fluid, free enzyme overbalances antienzyme and fibrin, necrotic tissues, and perhaps to a limited extent adjacent living tissues undergo solution; in the wall of the abscess fibrous tissue is formed; what is the immediate stimulus to the new formation of fibrous tissue has not been determined.

Since long-continued inflammation is associated with new formation of fibrous tissue, such sclerosis has been commonly used as an index of chronic inflammation. Increase of interstitial tissue may furnish evidence of pre-existing inflammation even though the regenerative changes in the connective tissue are not included in the conception of inflammation. Nevertheless, the resulting confusion has introduced many inconsistencies into the nomenclature of disease.

In many instances of hepatic cirrhosis, the increased interstitial tissue is sclerotic and scar-like and all evidence of inflammation is wanting; the lesion, indeed, has all the characters of a scar and chronic hepatitis is not more applicable than is chronic inflammation to the scar from a burn of the skin (Marchand). The same remark is applicable to certain instances of granular atrophy of the kidney and to chronic lesions of other organs. Such diseases are a combination of degenerative change, notably necrosis, inflammatory reaction, regeneration of parenchymatous elements, and regenerative changes affecting the interstitial tissue. The relationship of these processes has not been sufficiently analyzed.

In most instances of so-called chronic endocarditis the existing lesion, perhaps preceded by inflammatory changes, is sclerosis of the valvular segments, and functional derangement of the valve is referable to peculiarities of scar tissue found in any part of the body. The same objection is applicable to fibrous myocarditis, applied to the lesion which occurs in asso-

ciation with arterial disease, impairing the vascular supply of the cardiac muscle. The common designation of chronic arterial disease does not have the affix "itis" indicating its inflammatory origin, but arteriosclerosis is used almost synonymously with endarteritis and mesarteritis, lesions in which degenerative and regenerative changes are conspicuous, whereas true inflammatory reaction is in most instances wholly absent. Thoma has pointed to the truth that the present use of the term "chronic inflammation," applied to the liver, kidney, heart, blood-vessels, and other organs, means nothing more than chronic disease. Study of pathological structure, eagerly pursued during the last two centuries, is not infrequently regarded as an unprofitable field for investigation and perhaps this view is correct should its scope be limited to the observation and description of pathological lesions; but examination of present knowledge concerning the nature and classification of various forms of inflammation shows how meagre is our knowledge concerning the significance of altered structure.

If it were possible to define the origin of the mononuclear cells concerned in the inflammatory reaction of all vertebrate animals as well as it is possible to define the character and source of the common polynuclear leucocytes concerned in the same phenomenon, it might be possible to describe with an accurate generalization the essential nature of the cellular accumulation which follows the action of substances foreign to a tissue. The possibility that the various mononuclear cells which accumulate are derived from the lymphocytes of the blood, offers attractive solution of the matter; but proof is wanting. A definition of inflammation, as Metchnikoff has pointed out, must be applicable to the entire animal kingdom unless it can be shown that the changes which follow the same stimulus in one group of animals are different from those which occur in another group. Metchnikoff has shown very clearly that the possession of a well-formed vascular system does not furnish this distinction.

In order that the cells which accumulate at the site of inflammation may preserve their vitality, a proper medium is

essential; exudation of serous fluid serves to dilute the inflammatory irritant and doubtless to furnish to migratory cells a suitable habitat.

To survive, an organism must prevent, or at least set a limit on, the entrance of foreign substance. Identical phenomena follow the entrance both of an insoluble foreign body and of a living invader capable of multiplication. The exclusion of inanimate material is relatively simple, but the struggle of one group of living beings to exclude other groups has been the source of almost infinitely complex relationships. The difficulty of distinguishing what is physiological and what pathological is here obvious. Since partial exclusion of bacteria is an essential condition of life, it is not inconceivable that special powers which accomplish no other physiological function may have developed. Phagocytosis of inanimate particles, such as carmine and charcoal, occurs equally well in serum and in normal salt solution, but most bacteria must be altered by the serum (acted on by opsonin) in order that phagocytosis attain its maximum activity. It is probable that agglutination and precipitation have a part in the phenomena which, during the course of an inflammatory reaction, fix and finally destroy certain inflammatory irritants. The bactericidal substances of the serum, both those which are normally present and those which are formed during the progress of immunization, are brought by exuded serum to the site of inflammation. Serum and cells co-operate.

From another point of view, cellular migration from the vessels and within the tissues may be regarded as a process by which certain enzymes are quickly concentrated at a point where they are needed. Study of the protein-digesting enzymes of inflammatory exudates has shown that cells and serum must maintain certain quantitative relations in order that the inflammatory reaction may accomplish its purpose and permit restoration to normal without excessive destruction and regeneration of tissue. Disturbance of this balance is followed by grave consequences which give to suppuration much of its ominous character.

Throughout the animal kingdom, the inflammatory reaction affords means by which various substances, notably enzymes, are delivered in unusual quantity in response to unusual local need. Inflammation may be defined as the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. In lower animals with no vascular system this process with little or no accumulation of fluid occurs in the supporting tissues. In higher animals, it begins in the supporting tissues, proceeds with the co-operation of the blood-vessels and is completed in the adjacent part of the lymphatic system.

SUMMARY

Inflammation is a process which tends to render harmless an injurious substance; it has its site in the interstitial tissue of the body. This tissue consists of fixed cells and fibrillated substances and is penetrated by closed lymphatic vessels. With inflammation certain cells migrate through the wall of the blood-vessels of the part and enter the spaces within the interstitial tissue. Some of these cells are destroyed; others penetrate the endothelial membrane which forms the lymphatic capillaries and hence are carried by way of lymphatic vessels to the regional lymphatic nodes.

Bacteria and many other injurious substances are attacked and ingested by the polynuclear leucocytes which migrate from the blood-vessels. These leucocytes, often injured by the inflammatory irritant, are in turn ingested by large mononuclear cells (macrophages) which quickly appear at the site of inflammation. The origin of these mononuclear cells is still undetermined. Ingestion of polynuclear leucocytes and other cellular material is begun at the site of inflammation and completed in the regional lymphatic nodes.

The ability of phagocytic cells to remove injurious material is dependent on the possession of proteolytic enzymes. Peculiar to the polynuclear leucocytes is an enzyme which, like trypsin, exerts its digestive action in an alkaline medium. The serum of the blood contains an antienzyme which restrains the

action of this enzyme should it be set free by disintegration of the leucocytes; the action of the enzyme is thus limited to the locality in which it accomplishes its proper function, namely, within the cell. When enzyme is set free in such quantity that it overbalances the antienzyme of the exuded serum, suppuration occurs, for the purulent exudate has in virtue of its unrestrained enzyme acquired the power to soften and erode the adjacent tissues.

The mononuclear phagocytes which appear in the late stages of acute inflammation, the similar cells which appear in the regional lymph-nodes, and the cells of similar structure which constitute the greater part of tuberculous tissue contain an enzyme which, like pepsin, digests in the presence of acid. Such phagocytes are active at the site of inflammation, but their work is completed in the regional lymphatic nodes.

Inflammation is the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. This process does not include the regenerative changes which replace injured tissue by newly formed parenchymatous elements or by new interstitial tissue. Present nomenclature of chronic disease contains many terms which are inconsistent with knowledge of the underlying disease. Terms such as "parenchymatous nephritis," "traumatic myelitis," acute "hemorrhagic pancreatitis" are applied to conditions which have not primarily the characters of inflammation; the term "chronic inflammation" is applied to complex morbid changes (*e.g.*, cirrhosis, chronic nephritis, myocarditis, arteriosclerosis, etc.) in which inflammatory processes have an insignificant part.

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- ³⁴ Fiessinger and Marie: Arch. d. mal. du cœur, 1909, ii, 545.
- ³⁵ Whipple and Sperry: Bull. Johns Hopkins Hosp., 1909, xx, 278.
- ³⁶ Nichols: Med. News, 1905, lxxvii, 638.