The "unconscious" does not represent an upper limit to possible human mental development, but rather a lower limit, above which in the process of becoming civilized, mankind has raised itself, slowly to be sure, and not without backslidings, but nevertheless with some notable successes.

It is necessary for social scientists to see to it that at their hands the world does not perish. They need to learn the lesson of history told by Gibbon:

> If a man were called to fix the period in the history of the world during which the condition of the human race was most happy and prosperous, he would, without hesitation, name that which elapsed from the death of Domitian to the accession of Commodus. The vast extent of the Roman Empire was governed by absolute power, under the guidance of virtue and wisdom. The armies were restrained by the firm but gentle hand of four successive emperors, whose character and authority commanded involuntary respect. The forms of the civil administration were carefully preserved by Nerva, Trajan, Hadrian, and the Antonines, who delighted in the image of liberty, and were pleased with considering themselves as the accountable ministers of the laws. Such princes deserved the honor of restoring the republic, had the Romans of their day been capable of enjoying a rational freedom.

The historian will note the circumstances of the subsequent decline and fall of the Roman Empire; how for a long period the Roman emperors were without virtue or wisdom or that character which elicits involuntary respect; how they were unable or unwilling to control the evils of military power; how they ignored the abuses of public and of private revenues; how they were indifferent to the corruption of morals and the decline of learning. He will note, too, the circumstances of reform; how a new and uncorrupted people, whose character has been delineated by Tacitus and by Kingsley, brought the evils of the Roman system to an end; how a new and uncorrupt religion smoothed, in some measure, the processes of reform. If he does this he will add that the historian may yet again speak, in virtue of his profession, with all the moral authority that Gibbon was capable of. If the historian and the other social scientists are unable or unwilling to do this, others will, even though they may be less capable than social scientists might become. Socrates will be ignored and Thrasymachus exalted. Learning in the social sciences, indeed in all the sciences, will then undergo its last and inevitable eclipse.

What is needed is a genuine science of politics. The political scientist can not build such a science alone, for he is too much concerned with the empty formulae of constitutions. A genuine science of politics would have as its ideal a community, a commonwealth or a state, of free men cooperating in all the great concerns of life, achieving, that is, a rational freedom. It would so order its component sciences that each would be at once a support of the central idea and a system of thought useful in the solution of practical problems. It would not concern itself with the perpetuation of sophisms, but, undisturbed by shibboleths, it would deal in a realistic way with the work, wealth, health and happiness of mankind.

THE SIGNIFICANCE OF BIOCHEMICAL UNITS IN INFLAMMATORY EXUDATES[1,2]

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VARIOUS observations made in the last few years indicate the presence of some biochemical units in exudates, capable in turn of reasonably explaining a number of basic mechanisms concerned in the development of the inflammatory reaction.[3]

Inflammation is a fundamental phenomenon occurring in higher animals. It involves lymphatic structures, vascular channels and the locally affected tissue. It is initiated by a disturbance in fluid exchange. The normal capillary filtration equilibrium is markedly deranged. One of the major changes is an increase in capillary permeability. This is readily demonstrable by the seepage of material introduced into the circulation. Diazo dyes (*e.g.*, trypan blue), ferric chloride, graphite particles and bacteria will readily concentrate from the circulation into acutely inflamed foci.[3] Since the increased capillary permeability is an initial stage in the progress of inflammation it is of prime importance to obtain some understanding of the mechanism involved in order to clarify somewhat the development of subsequent sequences.

The early work of Lewis postulated that the increased capillary permeability in inflammation is referable to the presence in wheal fluid of a hypothetical H-substance which presumably is histamine

[1] From the Department of Pathology, Duke University School of Medicine, Durham, N. C.

[2] An address presented at the University of North Carolina Medical School on December 13, 1944.

[3] Valy Menkin, "Dynamics of Inflammation." New York: Macmillan Company. 1940.

or at least a substance closely related to histamine.[4] Without going into too much detail, subsequent studies have failed to substantiate this view.[5] The following observations have suggested that there is liberated into exudates a substance which seems to have no direct biological relation to histamine[6]:

Exudative material is introduced into the normal skin of a rabbit. This is immediately followed by the intravenous injection of trypan blue. The dye rapidly accumulates into the treated area, indicating the probable presence of a permeability factor in exudate. This factor is absent in blood serum and the reaction is not elicited by physiological saline. The active substance is heat stable and it is diffusible through a Cellophane membrane. By treating exudative material with pyridine and then acetone to remove proteins, a crystalline active material can be recovered in a butyl alcohol mother liquor. The active material is also carried down by treating exudative material with ammonium sulphate at one-half saturation. It is biuret negative, but ninhydrin positive. The xanthoprotein test for the phenyl group is positive. The Million test is negative, but the Adamkiewicz color reaction for the indole nucleus is positive. It seems to be a peptide to which a prosthetic group may well be attached.[7] Studies on the enzymatic effect of crystalline trypsin on an otherwise inert serum albumin or whole serum suggest that the biological activity may in large part be confined to the peptide linkage.[8] Amino nitrogen measurement before and after hydrolysis indicates the possibility that the active principle may be a relatively simple peptide. The factor not only increases capillary permeability, but it also induces the migration of polymorphonuclear leukocytes through the capillary wall. This chemotactic property can be demonstrated by *in vitro* studies as well as by *in vivo* observations.[3] The substance has been called *leukotaxine*. Its liberation offers a reasonable explanation for the primary mechanism of increased capillary permeability and migration of leukocytes. Chemically and physiologically, as mentioned previously, it seems to have no relation to histamine.[3] Increased capillary permeability allows the free passage of plasma proteins from the circulation into the extracapillary spaces. Fibrinogen is converted to fibrin with the release of thrombokinase following injury to cellular structures. A network of fibrin is formed in tissue distended with edema, and lymphatic channels become plugged with fibrin, thus inducing a lymphatic blockade. It is the early lymphatic obstruction which prevents the ready dissemination of material or microorganisms from a focus of acute inflammation. This phase of the earlier studies offers a significant contribution to our understanding of the rôle of inflammation in immunity.[9]

Leukotaxine accounts for the local migration or diapedesis of leukocytes to the site of injury. It has no effect on the number of circulating leukocytes. Yet a leukocytosis is the frequent accompaniment of numerous inflammatory or infectious processes. The whole exudate of an animal or of man having concomitant leukocytosis with inflammation is in turn capable of inducing a rise in the number of circulating leukocytes upon injecting the material into the blood stream of an otherwise normal dog. There is thus present in exudative material a *leukocytosis-promoting factor* liberated by injured cells.[10] The leukocytosis-promoting factor, or as termed the LPF, is non-diffusible and thermolabile. It is protein in character. It is obtained from the exudate by treating the latter with ammonium sulphate at one-half saturation after removal of the euglobulin fraction.[11,15] It seems to be either a pseudo-globulin or at least it is closely associated with that fraction of exudate. The LPF induces not only a discharge of immature leukocytes from the bone marrow, but it likewise causes a marked hyperplasia of granulocytic and megakaryocytic elements in the bone marrow.[12] The presence of the leukocytosis-promoting factor is demonstrable only in the serum of an animal having concomitantly an acute inflammation but not in a normal animal's blood serum. The liberation of the LPF into exudative material and its absorption into the circulation offers a reasonable explanation for the leukocytosis frequently associated with inflammatory processes. Its apparent non-antigenicity and its leukocytic forming property in the marrow suggest definite clinical application, especially since it is well known that the prognosis of numerous infectious processes is largely referable to the number of circulating leukocytes.[13]

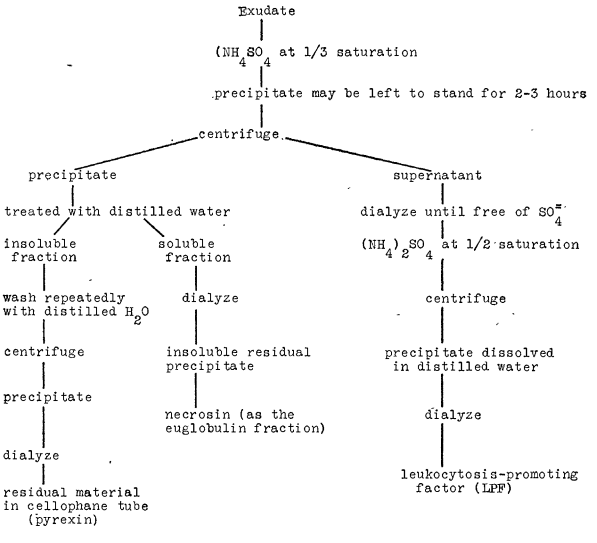
Inflammation is a manifestation of severe cellular injury. Neither leukotaxine nor the leukocytosis-promoting factor are *per se* capable of reproducing the pattern of injury discerned in acute inflammation. This, in turn, seems to be referable to the liberation of a substance located in or associated with the euglobulin fraction of exudate, particularly when the latter has an acid reaction when withdrawn

[4] Sir T. Lewis, "The Blood Vessels of the Human Skin and Their Responses." London: Shaw and Sons, Ltd. 1927.
[5] Valy Menkin, *Jour. Exp. Med.*, 64: 485, 1936.
[6] *Ibid.*, 67: 129, 1938.
[7] *Idem*, Alexander's "Colloid Chemistry," Vol. V, 917, 1944.
[8] *Idem, Jour. Exp. Med.*, 67: 153, 1938.
[9] *Idem, Physiol. Rev.*, 18: 366, 1938.
[10] *Idem, Am. Jour. Path.*, 16: 13, 1940.
[11] *Idem, Arch. Path.*, 30: 363, 1940.
[12] *Idem, Am. Jour. Path.*, 19: 1021, 1943.
[13] *Idem, Proc. Soc. Exp. Biol. and Med.*, 56: 219, 1944.

from the site of inflammation. This substance has been termed necrosin.[14] The introduction of necrosin into the skin of a rabbit is followed within several minutes by swelling and fusion of the collagenous bundles. This type of response is not duplicated by the euglobulin fraction derived from normal blood serum. When necrosin is maintained in cutaneous tissues for longer intervals, a marked inflammation develops characterized by intense redness, edema and superficial necrosis. An abundance of leukocytes may be found in such areas. Lymphatics are occluded by fibrin and evidence of thrombosis may be seen in vascular structures. The euglobulin fraction of normal blood serum fails to induce lymphatic blockade, which in turn is an evidence of severe damage. In contrast to the leukocytosis-promoting factor necrosin induces a marked leukopenia. Vomiting, diarrhea and general apathy are also not infrequent occurrences. The intravascular injection of necrosin may be followed by the formation of fluid in the chest cavities or of hemorrhage all along the length of the gastrointestinal tract. But more constantly, following intravenous injection of necrosin, one encounters damage to the liver in the form of areas of focal necrosis. The kidneys may show foci of leukocytic infiltration interspersed among tubules that reveal evidence of fuzziness of their epithelial lining and vacuolation of the cells. The picture is not wholly dissimilar to that seen in pyelonephritis. The leukopenia following necrosin injection is often followed after several hours by a rise in the number of circulating leukocytes.* It is possible that the latter is referable to secondary damage to visceral structures by necrosin liberating, as a consequence, an appreciable amount of leukocytosis-promoting factor. The fact that necrosin penetrates from an area of injury into the circulation and thus damages essential structures may prove of clinical significance in our further understanding of the significance of foci of infection. Necrosin is found also to be lethal to mice in contrast to other protein fractions of exudate.[15]

At first it was found that the whole euglobulin fraction of exudate reproduces not only the pattern of injury seen in inflammation, but that its intravascular injection was likewise followed by the development of fever. Subsequent studies have indicated that whereas necrosin is labile, its pyrogenic component is heat stable. It was soon recognized that the euglobulin fraction of exudate had a component insoluble in the presence of electrolytes. By differential solubility this component was dissociated from a true euglobulin, which in turn behaved as necrosin. The latter induced damage to the skin of rabbits and proved lethal to mice. Observations, still preliminary in nature, have suggested the possibility that necrosin is a proteolytic enzyme. After purification necrosin was found to be essentially non-pyrogenic. The present scheme utilized to extract the leukocytosis-promoting factor, necrosin, and the insoluble pyrogenic component is shown in Table 1. The pyrogenic component may well be an end product of proteolysis initiated by necrosin. It has been termed *pyrexin*. Besides its effect on the elevation of temperature in the dog, pyrexin induces appreciable fever in the rabbit.[16,17] The whole exudate causes an elevation of temperature in that animal. This, in turn, is duplicated by the whole euglobulin fraction of exudate. This is the only protein fraction of exudate capable of reproducing this phenomenon. Pyrexin, recovered from the euglobulin fraction of exudates, by its insolubility in the presence of electrolytes (in contrast to necrosin), induces marked fever. Its absorption may offer a reasonable explanation for the development of fever with inflammation. Pyrexin is heat stable. Boiling fails to alter essentially its activity. It seems to be excreted, at least in part, in the urine. Its exact chemical composition is unknown. The biuret reaction is positive only in minute trace. The xanthoproteic test is positive. It is ninhydrin positive except in the material recovered from urine. Studies are now under way in an endeavor to obtain

TABLE 1



[14] *Idem, Arch. Path.*, 36: 269, 1943.

* In more recent studies, which are now in progress and which will be subsequently reported *in extenso*, it appears as if the leukopenia-inducing factor of exudates is not referable to purified necrosin *per se* but rather that it is associated with its thermostable fever-inducing fraction or pyrexin.

[15] *Idem, Am. Jour. Med. Sci.*, 208: 290, 1944.

[16] *Idem, Proc. Soc. Exp. Biol. and Med.*, 54: 184, 1943.

[17] *Idem*, SCIENCE, 100: 337, 1944; *Arch. Path.*, 39: 28, 1945.

further information concerning the chemical identification of pyrexin.

The foregoing biochemical units present in exudates help in explaining, in part at least, some of the major sequences in the development of inflammation. The altered chemistry of the injured cell liberates various common denominators, such as described above, into the exudate. It is these biochemical units, in turn, that account quite adequately for the fundamentally stereotyped reaction of inflammation.

SCIENTIFIC EVENTS

AN "AIR AGE" MAP OF THE WORLD

THE aeronautical correspondent of *The Times*, London, calls attention to the fact that the British Overseas Airways Corporation has issued a new type of world map, designed to "re-teach" geography in a form more suited to the coming "Air Age."

It points out that because the earth is a sphere and maps of the world are flat, every type of map gives a distorted picture. On a Mercator projection, now commonly used for world maps, the distortion increases according to the distance from the equator. For instance, Greenland is shown as being about the same size as South America, whereas its area is only about one tenth of that continent. Distances between widely separated places also become exaggerated, particularly in high latitudes.

At present, maps drawn on the Mercator projection are used for both sea and air navigation, but whereas ships must follow tracks which may involve long detours to avoid land masses, the aeroplane can follow the shortest route—a straight line over the earth's surface. Now that airliners are being designed to fly non-stop over long distances, a new type of map is needed which will enable the intending passenger to read accurately the distance he has to cover.

To indicate the distance from London of places all over the world which will be served by British air services, the British Overseas Airways Corporation has prepared what is known as an azimuthal equidistant projection map centered on London. Straight lines drawn from London to any other point on the earth's surface will show accurately the distances separating them, though not necessarily the route which will be followed.

On the azimuthal equidistant map a straight line indicates a Great Circle course, but such a direct route is not likely to be followed by air services in the years immediately after the war unless it happens to serve big centers of population or important business areas. Such routes, in general, will not be used for air services until there have been further developments in the speed, range and economics of long-distance flying.

The British Overseas Airways Corporation's object in producing an "Air Age" map now is to encourage the teaching of this new conception of geography in schools, so that boys and girls will grow up to be air-minded.

PILOT TEACHING COURSES IN CANCER

THE need for the immediate establishment of "pilot teaching courses" in cancer for third and fourth year medical students was unanimously agreed upon by the National Advisory Cancer Council, which met on April 7 at the National Cancer Institute of the U. S. Public Health Service.

The council, headed by Surgeon General Thomas Parran, stated that definite emphasis should be placed on the early diagnosis of cancer which is now the second cause of death in the country. It was pointed out that the general practitioner is the "first line of defense" in cancer control and the courses should be "slanted" toward making graduating medical students "cancer conscious."

It is planned to stimulate the setting up of "pilot courses" with the working curricular committees of leading medical schools throughout the country. This will be done by the council joining hands with other foundations interested in cancer control and research.

Long-range postwar planning of cancer research programs was also considered and it was agreed that support for research programs should be guaranteed for periods ranging from five to ten years, instead of one year at a time, as has been done in the past.

In order to meet increasing demands for cancer specialists Dr. Parran explained that the Army has offered full cooperation in channeling news of Public Health Service fellowships in cancer to physicians in the armed forces possessing cancer experience. Dr. Parran said, "Of course, these men will be entitled to additional training under the GI Bill of Rights and when this is exhausted they can avail themselves of our fellowships."

Another topic discussed was the possibility of developing cancer specialists within each state to serve as consultants to physicians in rural and urban areas.

Three grants-in-aid for cancer research were approved at the meeting. They were made for one year to the School of Medicine of Washington University, St. Louis, for photometric histochemical study of tumors—$5,000; Barnard Free Skin and Cancer Hospital, St. Louis, for one year—$5,000 for the study of the integration of changes in experimental carcinogenesis; an additional grant of $5,000 was made for two years to the Barnard Free Skin and Cancer Hospital for the measurement of carcinogenicity of residue oils.