There are also many sources of potash other than those included in the probable reserves that may be developed when economical methods of extraction are devised. This latter point again emphasizes how conservative these estimates are, for no allowance was made for technical improvements, which are sure to come in the fertilizer industry.

Here, then, is an affirmative answer to the question: Do we have the natural resources to meet world food goals by 1960? This answer is a challenge to all men, not to scientists only, for it raises immediately an even more critical question: Can we mobilize these resources to produce the needed food? This question begs many answers, because it involves the whole field of human relationships.

Science may discover and point the way, but it cannot dictate. The full measure of success in economic, social, and political action comes only with the will of the majority—not from the desires of one group.

If the people of the world really have the determination to give battle to the problem of hunger, if they are willing to extend a small part of the energy and capital poured into World War II, only then can we see hope of victory.

Modern Concepts of Inflammation

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INFLAMMATION IS THE PHYSICAL BASIS OF infectious diseases, although inflammation and infection should not be considered as synonymous terms. Inflammation implies a more inclusive concept. It is a manifestation of severe cellular injury in higher forms. As such, the inflammatory reaction requires the presence of vascular and lymphatic structures as well as tissue cells. The reaction, which is initiated by a disturbance in fluid exchange, manifested primarily by an increase in capillary permeability, tends to be stereopatterned. It can be modified by the nature of the irritant, which, per se, has its specific chemical affinity with the tissues of the host. Furthermore, the topographical location of the injury doubtless alters the ultimate picture of the lesion. Nevertheless, close scrutiny reveals throughout a fundamental pattern which is largely referable to various basic common denominators or biochemical units liberated by injured cells, irrespective of the nature of the stimulating irritant. It therefore behooves us to concentrate on a study of the biochemistry of injured cells.

The initial increased capillary permeability and the early migration of polymorphonuclear cells is primarily caused by a polypeptide to which there may be attached a prosthetic group. This substance, called *leucotaxine*, was identified in exudative material some 10 years ago. It is not possible here to go into the details employed in its isolation and properties. Suffice it to say that leucotaxine has no similarity to histamine and, as such, has no relation to the so-called hypothetical H-substance of the late Sir Thomas Lewis. It evidently is wholly different from hyaluronidase, acetylcholine, or adenine compounds. Cullumbine and Rydon in Great Britain have recently confirmed by a somewhat different procedure of extraction its presence in exudates and also its properties (*Brit. J. exp. Path.*, 1946, **27**, 33).

Leucotaxine fails to alter the number of circulating leucocytes when administered intravenously. It appears as if the state of leucocytosis accompanying a number of inflammatory processes is caused by a wholly different basic factor or common denominator. When exudative material, particularly, though not always, at an alkaline pH, is injected into the blood stream of a normal dog, a rise in the number of circulating leucocytes occurs. This rise may take place in an hour in some animals, whereas in others it may be significant in only three to four hours. Thus, a leucocytosis-promoting factor is liberated by injured cells, which can in turn be recovered from exudates. Neither normal blood serum nor saline can produce any such prompt response as exudative material. The factor abbreviated as the LPF is thermolabile and nondiffusible. It can be extracted in the pseudoglobulin fraction of exudates by fractionation with $(NH_4)_2SO_4$. Recent cataphoretic studies in collaboration with Dr. Gerald Cooper and Mr. Dillon, of the Duke University School of Medicine, suggest its association with the α^1 and α^2 globulins of exudates. In as yet unpublished studies by the writer, it has been found that by aging the LPF the material seems to denaturate spontaneously, and then it becomes insoluble. The active principle, however, splits off from the original protein molecule as a soluble component, which in preliminary tests appears to be polypeptide in nature.

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The leucocytosis-promoting factor, or LPF, of exudates reasonably explains the mechanism of leucocytosis with inflammation. The LPF induces a discharge into the circulation of immature granulocytes. It is also present in human exudates, but, as already mentioned, it is absent from normal blood serum except when there is a concomitant acute inflammation.

The LPF has, likewise, a specific growth effect on some of the elements of the bone marrow. Its administration is rather quickly followed by a hyperplasia of granulocytes and of megakaryocytes. These various properties possibly imply some clinical application, for it is well known that the prognosis of infectious processes depends to a large extent on the number of circulating leucocytes.

Recent studies at Duke University indicate that the canine LPF is both innocuous and active on human beings (*Arch. Path.*, 1946, **41,** 376) when administered intravenously. New studies by the writer demonstrate that with an already-existing inflammation the superimposed intravascular introduction of a single injection of LPF induces a synergistic effect, so that the number of circulating leucocytes remains elevated for markedly longer periods (on the average, about 9 times longer) than in control animals with an inflammation alone or in animals which have received only a single injection of LPF. These studies definitely point toward clinical implications in an endeavor to reinforce the commonly used antibiotics. The LPF can be assayed conveniently on guinea pigs. The canine material is likewise promptly active on these animals, even when injected subcutaneously.

The reaction of injury with inflammation is basic and fairly stereotyped. It includes the four cardinal features of Celsus, the loss of function of John Hunter, and the chemical breakdown of proteins, namely, proteolysis. Although, as pointed out earlier, the irritant and the location of the lesion may alter its ultimate appearance, a basic similarity can, nevertheless, be roughly discerned. This injurious reaction by the tissues of the host has been found to be referable to the euglobulin fraction of the exudative material. There is thus liberated by injured cells a toxic substance which has been termed *necrosin*. Necrosin is either a euglobulin or is associated with this fraction of exudates. Its cutaneous injection is followed by swelling, redness, varying degree of central necrosis, lymphatic blockade, injury to the endothelial wall of blood vessels, and swelling of collagenous bundles. Necrosin is absent in normal blood serum, but it can be recovered frequently from the serum of an animal with a concomitant inflammation. This fact may be of significance in revising our views on so-called foci of infections, with their repercussions on organs at a distance. For this reason, observations were undertaken to determine the effect on various structures of intravascular injections of necrosin (*Arch. Path.*, 1943, **36,** 269). There is almost constant injury to the liver. This may be in the form of a curious stippling granulation in the hepatic cords, or the liver cells may display a prominent degree of vacuolation with scattered areas of leucocytic infiltrations. Dogs were also repeatedly injected intravascularly with this toxic material over a space of weeks. Large amounts of either glycogen or fat replaced a good deal of the normal hepatic tissue. These deposits of glycogen were found not to be referable to feeding. It has been found that injections into the circulating blood of exudative material or of necrosin induce a small rise in the blood sugar level. Whether this small but constant augmentation in sugar concentration is referable to the apparent specific effect of necrosin on the liver remains to be determined. Varying degrees of injury to the kidneys following necrosin injection may also occur.

The whole euglobulin fraction of exudates not only induces a conspicuous degree of cellular damage but also causes both a rise in temperature and a marked drop in the white cell count—a state of leucopenia.

By a method of differential solubility the fever-inducing factor has been dissociated from the true euglobulin fraction of usually acid exudate, which in turn is, or at least contains, necrosin (*Arch. Path.*, 1945, **39,** 28). This pyrogenic factor, which can reasonably explain the mechanism of fever with inflammation, has been termed *pyrexin*. It is capable of increasing the temperature of a rabbit or of a dog 2° or 3° F. It is a thermostable factor; boiling fails to inactivate it. It is conceivable that its action is central, for nembutal and antipyretics tend to reduce its action. Its frequent occurrence from nonpyrogenic necrosin by merely incubating the latter suggests that pyrexin may perhaps be the end-product of proteolytic degradation, especially since some protein enzymatic activity is found to be present in necrosin. It appears to be eliminated to some extent in the urine. Some studies in collaboration with Frederick Bernheim, of Duke University, indicate the possibility that pyrexin is a glycopeptide, but further studies are necessary before this view becomes a certainty.

The leucopenic factor of exudates seems to be closely associated with pyrexin. It can be dissociated from the latter by hydrolyzing it briefly with 0.1 N HCl and subsequently neutralizing it with N NaOH. The presence of such a factor in exudative material, particularly if the exudate is at an acid pH, may be of help in explaining the leucopenia attending numerous inflammatory processes, such as influenza and typhoid fever. The presence of this factor in exudates, probably liberated by injured cells, opposes the LPF in its mode of action. The actual level of white cells in the circulation may prove to be the resultant of these opposing tendencies on the part of the two different factors. The mode of action of the leucopenic factor, which appears to be a polypeptide, seems to be a trapping of leucocytes in various organs such as the alveolar walls of the lungs, the sinusoids of the liver, and

the spleen. The trapping of leucocytes in the spleen may help in our understanding of the mechanism of the acute splenic tumor which is frequently seen with many inflammatory processes.

I believe that sufficient material has been presented to stress the necessity of studying thoroughly the biochemistry of cells injured previously by an irritant. The several common denominators already identified in exudative material are shown in Fig. 1. Doubtless, further studies

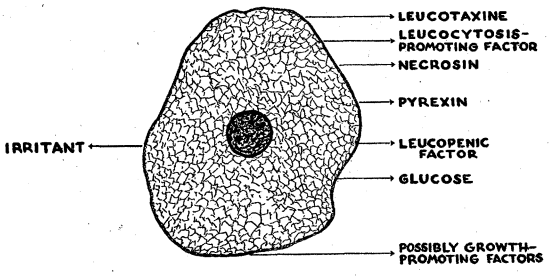

FIG. 1

will unfold other types of common denominators or biochemical units which, per se, help in explaining the stereotyped reaction with inflammation.

A recapitulation of the salient points in the development of the acute inflammatory reaction, which localizes an irritant and finally disposes of it, may be useful. Such an outline may be presented in brief as follows:

(1) *Disturbance in local fluid exchange:*
  (A) Increased capillary permeability, referable to liberation of leucotaxine, a crystalline nitrogenous substance.
  (B) Initial increase in lymph flow.

(2) *Localization of irritant (fixation)*, referable to lymphatic blockade by occluding thrombi and a fibrinous network at the site of severe inflammation:
  (A) The inflammatory reaction may be considered as the regulator of bacterial invasiveness, *i.e.* $D = \frac{Kt}{I}$ where D refers to dissemination; I, to degree of local injury; t, to time; and K is a constant.

(3) *Migration of leucocytes:*
  (A) Diapedesis of polymorphonuclear leucocytes, referable to liberation of leucotaxine. In this way phagocytosis, stressed by Metchnikoff, can operate readily. The mechanism whereby macrophages assemble at the site of injury is still not exactly known.
  (B) Cytological sequence at the site of inflammation conditioned by the local pH, in turn referable to a disturbance in carbohydrate metabolism; glucose formed by injured cells by deamination of proteins.
  (C) Leucocytosis in the circulation, referable to liberation of a leucocytosis-promoting factor demonstrable in association with the pseudoglobulin fraction of exudates. The LPF induces a concomitant growth of granulocytes and of megakaryocytes in the bone marrow.

(4) *The pattern of injury in inflammation*, referable to the liberation of a toxic substance in the euglobulin fraction of exudates, termed necrosin. This fraction contains proteolytic activity.
  (A) Fever with inflammation, referable to liberation of pyrexin in exudative material.
  (B) Leucopenia with inflammation, possibly associated with the liberation of a leucopenic factor in exudates.

  Both pyrexin and the leucopenic factor are, with necrosin components, recovered from the euglobulin fraction of exudates.

(5) *Repair*, possibly referable to the liberation of one or several growth-promoting factors in exudates.