instances (pls. 77–81) could have been improved by better spacing and slightly greater reduction of some of the drawings, without loss of detail.

These somewhat technical points will probably only bother the specialist slightly, and the general botanist will find Smith's "Marine Algae" as attractive and useful as his other books have shown themselves to have been. Since the time is not ripe for a flora covering the whole western coast line, Smith has done biologists a great service in providing them with an excellent algal manual covering the adequately known part of its flora.

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SPECIAL ARTICLES

CHEMICAL BASIS OF FEVER[1, 2]

FEVER, as a rule, is associated with some form of cell injury. The writer has recently demonstrated the presence of a substance in inflammatory exudate which *per se* offers a reasonable explanation for the pattern of injury in inflammation.[3, 4] This substance has been termed necrosin. It is located in the euglobulin fraction of exudates. Preliminary studies undertaken by Major A. Mirsky and the writer indicate that this toxic substance may well be a proteolytic enzyme or, at least in its present state of purification, it contains proteolytic activity. These earlier studies have also demonstrated that the euglobulin fraction of exudates, recovered by ammonium sulfate fractionation, is pyrogenic when introduced into the circulating blood of dogs.[4, 5] Moreover, it has been pointed out that none of the other protein fractions of exudates are fever-inducing. Inasmuch as the active material is also recovered in the blood stream of an animal with a concomitant inflammation,[4] it is conceivable that the absorption of the toxic euglobulin fraction of exudates from the site of injury may help in explaining the development of fever accompanying inflammatory processes.

The studies have been carried out on rabbits[6] with exudate and with various fractions extracted from it. The exudate, as a rule, has been obtained from the pleural cavity of dogs previously injected with an irritant as described in an earlier study.[4] In several instances the material was obtained from human sources.

The fraction to be tested is introduced into the marginal ear vein of rabbits, and the rectal temperature is recorded periodically during an interval of approximately six hours. The temperature of a normal rabbit scarcely varies during such a period, the maximum increase averaging 0.63° F. In excessively hot days, there may be in the rabbit an increase in temperature of about 1° F. The introduction of saline, the euglobulin fraction of normal human or canine serum, the pseudoglobulin fraction of exudates (*i.e.*, the leukocytosis-promoting factor)[7] and the albumin fraction of exudates have all been quite ineffective in inducing any appreciable rise in temperature. The average increase in such a series of rabbits has been 0.66° F.

The introduction, on the other hand, of exudative material into the ear vein of rabbits elicits within about an hour or two a conspicuous increase in temperature, averaging 2.37° F. This pyrogenic effect is duplicated by the euglobulin fraction of exudates, the average rise being 2.46° F. Normal non-hemolyzed serum induces a negligible rise averaging 1.05° F. Hemolyzed serum, on the contrary, induces a somewhat more conspicuous rise averaging almost two degrees Fahrenheit. This finding suggests the possibility that ruptured red corpuscles liberate an appreciable amount of pyrogenic factor into the general circulation. The observation deserves further consideration, especially in regard to various conditions, such for instance as are encountered in malaria. It may well be that the chills and fever manifested in this disease are in part referable to the release of the pyrogenic factor from red cells. Furthermore, the pyrogenic factor is recovered to some extent in the non-hemolyzed serum of an animal with a concomitant inflammation. This is suggestive that the factor is absorbed into the circulation from the site of injury.

In contrast to what is known of ordinary euglobulins, necrosin has been observed to be insoluble in the presence of NaCl or sulfate ions.[6] This finding, at first, had been interpreted as the possible manifestation of an atypical euglobulin.[6] Pursuing the study further it has recently been found that one can dissociate and obtain from the whole fraction a true euglobulin soluble in the presence of $SO_4^=$, leaving an insoluble residual fraction behind. The procedure adopted is as follows: The exudate, obtained usually from the pleural cavity of dogs, is treated with am-

[1] From the Fearing Research Laboratory, Free Hospital for Women, Brookline, Mass.

[2] These studies were aided by grants from the Johnson and Johnson Research Foundation, New Brunswick, N. J., and the Dazian Foundation for Medical Research.

[3] V. Menkin, SCIENCE, 97: 165, 1943.

[4] *Ibid.*, *Arch. Path.*, 36: 269, 1943.

[5] *Ibid.*, *Proc. Soc. Exper. Biol. and Med.*, 54: 184, 1943.

[6] *Ibid.*, *Federation Proc.*, 3: March, 1944.

[7] *Ibid.*, "Dynamics of Inflammation," Macmillan Company, New York, 1940.

monium sulfate at one-third saturation. The precipitate formed is treated with distilled water prior to dialysis of the $SO_4^=$ ions. A true euglobulin enters into the aqueous phase containing the $SO_4^=$ ions. This is necrosin in a further state of purification. It is lethal to mice and is capable of inducing a severe cutaneous inflammation in rabbits; but it is essentially non-pyrogenic. The pyrogenic factor seems primarily associated with the precipitate which has failed to dissolve in the aqueous phase containing the $SO_4^=$ ions. This highly fever-inducing substance is readily dried by freezing. For the sake of convenience it is termed *"pyrexin."* The liberation of pyrexin at the site of inflammation and its absorption into the circulation offers a reasonable explanation for the basic mechanism of fever with inflammation. In a series of 10 experiments it was found that pyrexin elicited a rise in the temperature of rabbits averaging 2.46° F. This is of the same magnitude as that obtained with the whole euglobulin fraction of exudate. On the other hand, purified necrosin, *i.e.,* in the form of a typical euglobulin, in a similar series scarcely increased the temperature level, the average enhancement being °0.94 F. Whole exudative material in this series of experiments caused a hyperthermia averaging 2.25° F. over the basal level. These experiments support the view that there is a pyrogenic factor in inflammatory exudates. This factor is associated with the euglobulin fraction, but contrary to a typical euglobulin or purified necrosin it is essentially insoluble in the presence of various salts. This pyrogenic factor is pyrexin. Smith and Smith[8] have recently described the toxic properties of the euglobulin fraction of menstrual fluid. Owing to the insolubility of the material in the presence of certain electrolytes, they have inferred that an atypical euglobulin was involved. The writer has demonstrated with the material of these investigators that it likewise contains marked pyrogenic activity. It is quite possible that this is referable to the presence of pyrexin alongside with the toxic material described by Smith and Smith. This view would probably account for the apparent atypical chemical behavior of the whole toxic euglobulin fraction of menstrual fluid.

Pyrexin is thermostable. Boiling fails to inactivate it appreciably, while ashing destroys all activity. Its heat stability may prove to be of clinical value in various central nervous system disorders, *e.g.,* luetic states, in the treatment of which there must also be assurance of all absence of even traces of necrosin impurity. The thermolability of the latter would dispose of any such possibility.

Purified necrosin is, as mentioned above, highly toxic and injurious to tissues; whereas pyrexin is innocuous to mice and it induces no appreciable cutaneous reaction in rabbits.

The formation of pyrexin may be closely linked to necrosin. The essentially non-pyrogenic property of the latter can often be transformed, by mere incubation for several hours, into a powerfully pyrogenic fraction. This evidence is suggestive that pyrexin may be an end product of proteolytic hydrolysis initiated by enzymatic activity associated with necrosin. Thus, pyrexin may perhaps be an enzymatic product of necrosin acting on a euglobulin substrate.

In a dog with an experimental pleurisy, pyrexin is eliminated, at least to some extent, in the urine whence it can be demonstrated in the untreated fluid or frequently be recovered as a precipitate which forms slowly in a refrigerator by the interaction of urine with ammonium sulfate at one-third saturation.

The nitrogen and phosphorus contents of pyrexin are about 11 per cent. and 1 per cent., respectively. The material is Biuret negative but Ninhydrin positive, except in the fraction recovered from urine, which is also usually Ninhydrin negative. It is Molisch negative. It is insoluble in ether and 95 per cent. alcohol. It seems to be soluble in weak alkali, but it is insoluble in strong acids. It fails to be inactivated by crystallized trypsin. Nevertheless, the possibility of a peptide attached to a nucleic acid derivative is not precluded by the available data. The exact chemical nature of pyrexin is, however, unknown and will therefore require further studies. Inhibitory action of barbiturates and antipyretics on the activity of pyrexin suggests that the possible mode of action of pyrexin is on fever centers presumably located in the hypothalamic region. This and various studies on the nature of pyrexin are being investigated further. The details pertaining to the present communication will appear elsewhere *in extenso.*

In conclusion it seems as if the basic mechanism of fever accompanying inflammatory processes is primarily referable to the liberation by injured cells of a nitrogenous substance, termed pyrexin, recovered in the euglobulin fraction of exudates; and which is possibly an end product of proteolytic activity associated with necrosin. The absorption of this active substance into the circulation offers a reasonable explanation for the development of fever.

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[8] O. Smith and G. van S. Smith, *Proc. Soc. Exp. Biol. and Med.,* 55: 285, 1944.

TELANG LIVER AND VITAMIN A TOXICITY

DURING the past two years we have been making an investigation of the nutritional value of the telang