more frequently in those cases which develop cold agglutinins than in those which do not. Studies on this point are in progress.

Summary. Significant titers of cold agglutinins were demonstrated in a large proportion of cases of primary atypical pneumonia. Similar titers were not observed in sera from patients with a number of other respiratory diseases.

The author wishes to acknowledge the assistance of the Medical Staff of the University of California Hospital and of the visiting and laboratory staffs of Cowell Memorial Hospital.

14358

On the Mechanism of Fever Production with Inflammation.*

VALY MENKIN.

From the Department of Pathology, Harvard University Medical School, Boston, Mass.†

Recent studies undertaken by the writer have demonstrated the presence of a substance in exudates which offers a reasonable explanation for the basic pattern of injury in inflammation.[1,2] This substance, which is either a euglobulin or is at least associated with that fraction of exudates, has been termed "necrosin." It is presumably liberated from the cell which has been initially injured by an irritant. The internal chemistry of the damaged cell is doubtless altered yielding as a result various common denominators, which in turn are responsible for the unfolding of a fundamentally stereo-pattern in inflammation. Leukotaxine, the leukocytosis-promoting factor, and necrosin belong to such a category of chemical units formed by the injured cells.[3] In this connection necrosin has been found to induce a severe inflammatory reaction accompanied by lymphatic blockade.[1,2] This substance introduced into the circulating blood is followed by a prompt leukopenia replaced several hours later by a leukocytosis.[2] The internal organs are injured; notably the liver and to some extent the kidneys.[2] Besides fatty deposits in the parenchyma of these structures, small foci of leukocytic infiltration may be found irregularly scattered throughout these organs.[2]

The present communication summarizes further data indicating that the intravascular injection of necrosin is accompanied by a rapid elevation in temperature. This hyperthermia is not induced by other protein fractions derived from either exudate, ascitic fluid, or normal blood serum. Inasmuch as necrosin seems to penetrate from the site of inflammation into the circulating blood,[2] it is conceivable that the basis of fever production with inflammation may be referable in large part to the absorption of necrosin from the site of injury into the blood stream. Owing to limit on space the earlier literature on fever will be omitted in the present short communication.

In the present experiments dogs were injected with necrosin either in the form of an aqueous suspension or as the desiccated material which was taken up in several cubic centimeters of physiological saline. The injections were made into the circulating blood by cardiac puncture. The rectal temperature was recorded at approximate hourly intervals. The chemical preparation of necrosin from canine exudates has been described in earlier

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. The studies were also aided in part by a grant from the Jane Coffin Childs Memorial Fund for Medical Research.

This article represents Paper XXVII of a series entitled "Studies on Inflammation."

† Present address, Fearing Research Laboratory, Free Hospital for Women, Brookline, Mass.

1 Menkin, Valy, *Science*, 1943, **97**, 165.

2 *Idem, Arch. Path.*, 1943, **36**, 269.

3 *Idem, Dynamics of Inflammation*, Macmillan Company, 1940.

TABLE I.
Effect of Necrosin or the Euglobulin Fraction of Exudate on the Temperature Level of Dogs.

Dog No.	Dose of necrosin injected into the circulating blood	Temperature prior to injection of necrosin, °F	Max. temp. level within about 5 hr after inj. of necrosin, °F	Increase in level of temp.
7-92	8 cc of necrosin suspension*	101.4	104.2	2.8
7-92	10 " " " "	101.6	105.3	3.7
7-91	10 " " " "	101.8	105.3	3.5
7-83	10 " " " "	100.9	103.7	2.8
7-40	10 " " " "	101.0	106.2	5.2
7-92	100 mg of desiccated necrosin taken in 10 cc saline	101.4	102.0	0.6
7-92	Same as above	101.0	104.1	3.1
7-94	About 75 mg of desiccated necrosin taken in 6 cc saline	101.1	104.1	3.0
7-75	50 mg of desiccated necrosin taken in 10 cc saline	102.2	104.4	2.2
Avg elevation in temp.				3.0

* Preserved on ice under layer of toluene.

TABLE II.
Effect of Various Protein Fractions Derived from Exudates (Except Necrosin), from Blood Serum, and from Ascitic Fluid, on the Temperature Level of Dogs.

Dog No.	Type and dose of material inj. into circulating blood	Temp. prior to inj. of material, °F	Max. temp. level within about 6 hr after inj. of material, °F	Change in temp. as result of inj. of material
7-80	40 cc of aqueous suspension of leukocytosis-promoting factor (pseudoglobulin of exudate)	101.0	101.4	+0.4
7-91	100 mg of desiccated leukocytosis-promoting factor (pseudoglobulin of exudate) in 10 cc saline	101.1	101.0	—0.1
7-94	142 mg of desiccated LPF (leukocytosis-promoting factor) in 10 cc saline	102.3	101.8	—0.5
7-91	15 cc of LPF in water	102.2	102.4	+0.2
7-92	20 cc of albumin solution derived from an exudate	101.5	101.7	+0.2
7-78	65 mg of euglobulin from ascitic fluid in 10 cc saline	103.2	102.3	—1.0
7-80	25 mg of euglobulin from normal blood serum in 10 cc saline	101.0	101.0	0

communications and will therefore not be repeated here.[1,2]

The results are tabulated in Table I. It is clear that the introduction into the circulation of necrosin is accompanied by an appreciable elevation in temperature, averaging three degrees (Fahrenheit). The rise occurs very promptly and is very definitely perceived within about an hour or two after injection of the material (Chart 1). In this connection it is to be noted that the injection of 20 cc of whole exudate in normal dogs induces a sharp and marked elevation in temperature. In contrast, the injection of normal blood serum fails to augment the temperature.

On the other hand, the euglobulin fraction of normal blood serum, the euglobulin derived from a sample of ascitic fluid from a human patient, several fractions of pseudo-globulin from canine exudates (*i.e.*, the leukocytosis-promoting factor), and finally the albumin fraction of exudates, have all failed to induce

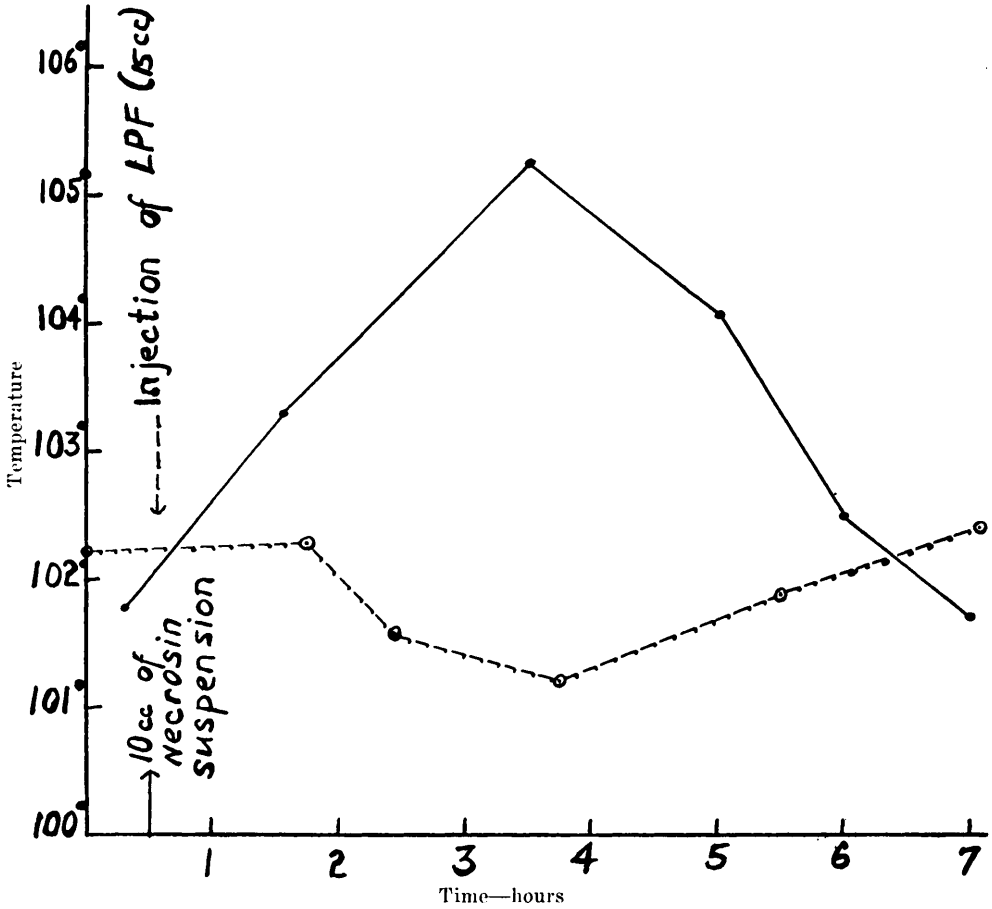

CHART 1.

The effect of necrosin and of the leukocytosis-promoting factor on the temperature level in the dog.

•————• Effect of necrosin on temperature level—Dog 7-91 (Degrees in Fahrenheit scale).

— — — • — — Effect of the leukocytosis-promoting factor (LPF) on temperature—Dog 7-91 (Degrees in Fahrenheit scale).

any detectable fever in dogs (Table II, Chart 1). These facts indicate that evidently it is only the euglobulin fraction of exudates, *i.e.*, necrosin, which contains the active principle capable in turn of evoking an appreciable rise in temperature. Whether this fever production by necrosin occurs through the mediation of the heat centers remains to be determined. These studies are being pursued in an endeavor to elucidate further the mechanism involved in the development of fever with inflammation.

In conclusion, the observations presented indicate that necrosin, the euglobulin fraction recovered from exudates and which is *per se* primarily responsible for the basic pattern of injury in inflammation, in turn induces, contrary to other protein fractions of exudates, an appreciable degree of fever when injected into the circulating blood of dogs. The absorption of this substance into the blood stream from the site of an acute injury offers a reasonable explanation for the probable factor largely responsible in the development of fever with inflammation.