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

type of beef liver. Condemnations of livers for telangiectasis represent a tremendous waste of a valuable food since the condition occurs in nearly 3 per cent. of a total of nine million cattle marketed each year in the United States.[1]

The livers from affected animals show dark red or purplish sunken areas throughout the entire organ. Attempts to ascertain the cause of this liver condition by histopathological studies[2] have been quite unsuccessful and since the literature does not report any diagnosis of the condition in living animals, obviously treatment has not been prescribed.

The toxicity to weanling rats of a large number of different telang livers has been investigated. These studies revealed that about 20 per cent. of the diseased livers were toxic to rats when fed as the sole diet plus a daily supplement of twenty-five milligrams of calcium carbonate. The calcium carbonate was added to correct the undesirable Ca : P ratio (about 1 : 16) in the beef liver. Constant symptoms observed in young rats fed the toxic telang liver were growth failure and the development of multiple spontaneous fractures of the extremities. Usually bone fractures were observed in the animals after a week to ten days of liver feeding and fatalities occurred about a week after the onset of the symptoms.

The close similarity of these toxic effects of telang liver to those observed in rats fed high amounts of vitamin A[3] suggested that abnormally high stores of this vitamin might be present in some of the telangiectatic livers. Previous studies in this laboratory[4] on the comparative vitamin content of telang and normal livers had disclosed that vitamin A storage was in general greater in the former type of liver. Vitamin A was determined colorimetrically by the method of Davies[5] in a specific series of six telang livers, two of which had been toxic to young rats. The results of these analyses and the growth and toxicity data for rats fed the livers are shown in Table 1. These data revealed that the toxicity of a liver and its vitamin A content were closely correlated and that the amount of the vitamin ingested by rats receiving the calcium supplemented liver as their sole dietary was in excess of the reported toxic dosage of 15,000 I.U. per day.[3]

[1] H. R. Smith, *Proc. 23rd Ann. Meet. Amer. Soc. Animal Prod.*, 272–276, 1940.

[2] A. Carta, *Profilassi*, 11: 43–53, 1938; F. Schote, *Inaug. Disa.*, Friedrich-Wilhelma University of Berlin, 1936.

[3] A. W. Davies and T. Moore, *Biochem. Jour.*, 28: 288, 1934; C. A. Baumann and T. Moore, *Biochem. Jour.*, 33: 1639, 1939; K. Rodahl and T. Moore, *Biochem. Jour.*, 37: 166–168, 1943; H. W. Josephs, *Amer. Jour. Dis. Child.*, 67: 33, 1944.

[4] Unpublished data.

[5] A. W. Davies, *Biochem. Jour.*, 27: 1770, 1933.

TABLE 1

VITAMIN A CONTENT AND TOXICITY OF WEANLING RATS OF TELANG LIVERS

No. of telang liver	Vitamin A content	Intake of vitamin A per rat per day*	Time for symptoms to develop	Growth of rats
	I.U./100 gm	I.U.	days	gm/wk.
1	121,000	22,990	7	0
2	132,000	25,080	7	0
3	68,400	12,996	no symptoms	15
4	50,800	9,652	"	20
5	45,200	8,488	"	29
6	59,000	11,210	"	26

* Intake of vitamin A calculated from food consumption data.

Subsequent experiments in which crystalline vitamin A suspended in corn oil was fed to weanling rats as supplements to a complete stock ration, or to non-toxic liver, have demonstrated that the telang liver toxicity was a hypervitaminosis A. Identical symptoms of bone fragility and growth failure were observed in rats fed 20,000 I.U. of crystalline vitamin A as a supplement to the grain stock ration. If non-toxic liver supplying 10,000 I.U. of vitamin A per rat per day was fed, the symptoms of toxicity could be produced by a daily supplement of 10,000 I.U. of the crystalline vitamin.

Relative to use of telang livers in human and animal diets, there is little probability that the amount of liver usually eaten would furnish sufficient vitamin A to produce toxic symptoms. Certainly prolonged ingestion of large amounts of telang liver would be necessary to produce any irreversible changes such as noted in the rat experiments reported herewith.

SUMMARY

(1) About 20 per cent. of fresh telang livers were toxic to weanling rats receiving the calcium supplemented livers as their sole dietary.

(2) The symptoms observed in rats were growth failure and multiple spontaneous fractures of the bones of the extremities.

(3) The toxicity of certain telang livers was due to their abnormally high stores of vitamin A. When these livers, supplemented only with calcium carbonate, were fed to weanling rats, the daily intake of vitamin A was in excess of the toxic dosage of 15,000 I.U. per day.

(4) Identical symptoms of toxicity were observed in weanling rats fed 20,000 I.U. of crystalline vitamin A per day in conjunction with a standard stock ration.

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