were transplanted to the mesentery, estrus failed to occur, but if the same ovaries were retransplanted into the axilla then estrus occurred normally.

Summary and Conclusions. 1. We have studied 8 patients with hepatic cirrhosis in whom gynecomastia occurred late in the disease, confirming the findings of Silvestrini, Corda and others. 2. In all of these cases bilateral gynecomastia was preceded by the development of ascites. 3. The histological changes in these hyperplastic mammae are similar to the changes seen in experimental estrone stimulation (growth of ducts). 4. Sevringhaus, Israel, *et al.*, have shown experimentally that the liver normally plays a rôle in the inactivation or destruction of estrogen. Accordingly, it is reasonable to suspect that organic liver disease may result in abnormalities in estrogen metabolism. The increased urinary excretion of total estrogen in 2 cases and of free estrogen in 2 cases tends to justify this assumption. 5. An explanation of the absence of gynecomastia in acute hepatic necrosis and in the majority of cases of cirrhosis is not as yet apparent. The effect of testicular atrophy upon androgen excretion also is not clear.

10813

Changes in the Parenchymatous Organs Produced by Artificially Induced Fever.

E. v. HAAM AND T. T. FROST.

From the Departments of Pathology of Ohio State University, Columbus, Ohio, and the City Memorial Hospital, Winston-Salem, N. C.

The purpose of this experimental study has not been to investigate the pathological changes which could be produced by lethal doses of artificially induced fever, as has been done previously by Hartman, Jacobsen and Hosoi, Baldwin and Nelson, and a few others,[1] but to make a quantitative comparison between the organ changes occurring in fatal and non-fatal doses of fever, and to investigate the fate of these changes after recovery of the animal. In our series of experiments male adult rabbits of a healthy standard breed were used. Nine animals died after a rapid high rise of temperature induced by the diatherm or radiotherm in a short period of 30 minutes (Group

[1] Hartman, F. W., and Major, R. C., *Am. J. Clin. Path.*, 1935, **5**, 392; Jacobsen, v. G., and Hosoi, K., *Arch. Path.*, 1931, **11**, 744; Baldwin, W. M., and Nelson, W. C., PROC. SOC. EXP. BIOL. AND MED., 1928, **26**, 588.

TABLE I.

		A Lethal Temp. 30-60′	B 109° 8-9 hr	C 107° 40 hr	D 106.5° 3 hr 6 times	E Nembutal control	F Healthy control
Heart	Hemorrhages	+	+++	+	+	0	0
	Fatty degeneration	+++	++++	+++	++	+	0
	Necrosis	+	++	+	0	0	0
Lung	Hemorrhages	+++	++++	+++	+	+	0
	Atelectasis	0	+	+	0	0	0
	Pneumonia	0	+	0	0	0	0
Liver	Hemorrhages	0	+	+	0	+	0
	Loss of glycogen	++++	++++	+++	++	+	0
	Fatty degeneration	+	++++	++	0	0	0
	Focal necrosis	0	+	+	0	0	0
Spleen	Congestion	+	++	+++	++	+	0
	Hemorrhages	+	++	+	+	+	0
	Follicular necrosis	+	+++	++	0	0	0
Kidney	Hemorrhages	++	+	+	0	0	0
	Tubular degen.	++	++++	++	+	++	0
	Glycogen infiltra.	+	++	+	0	0	0
Adrenals	Hemorrhages	+	++	0	+	+	0
	Lipoid depletion	++	++++	++	+	0	0
	Cortical necrosis	0	++	+	0	0	0
Testis	Atrophy	+	++	++	+	+	+
	Necrosis	0	+++	++	0	0	0

A); 9 animals succumbed to a fever of 108° to 109° in a time interval from 8 to 9 hours (Group B); 5 animals were kept at a temperature of 107° until death occurred after an estimated time of about 40 hours (Group C); and 5 animals were exposed once a week 6 times and killed by air embolus one week after the last exposure. Twelve animals served as controls, 6 of which received similar doses of nembutal as used in our fever experiments in order to study the effect of this drug (Group E).

The principal pathological changes in the parenchymatous organs have been grouped in Table I. The frequency of their occurrence in each experimental group is indicated by a plus sign: 1+ indicates a frequency from 5 to 25%; 2+ a frequency up to 50%, 3+ to 75%, 4+ to 100%. Because of the relatively small number of animals used, this was thought to be a more truthful index than the quotation of actual percentage figures.

The most important changes in the heart were scattered interstitial hemorrhages of the myocardium and severe degenerative processes of the muscle fibers. The cells lost distinctness of cross striations and intercalated discs, and with the Sudan stain a fine emulsion of fat droplets could be noted in many of the muscle fibers. Small focal areas of necrosis with hyalinization and fragmentation of muscle fibers could be observed in the animals exposed to prolonged lethal doses of fever. The principal changes found in the lungs were acute venous hyperemia and intra-alveolar hemorrhage. The arterioles and small bronchi appeared constricted, the small veins dilated. Varying degrees of atelectasis, sometimes severe but not widespread or complete, were present in Group B. In this group a small percentage showed development of pneumonia. In the liver evidence of hemorrhage or congestion was only slight. The most significant change was the complete depletion of the liver cells of glycogen in the animals exposed to lethal doses of fever. The protoplasm of the liver cells in Group B showed the typical coarse granular appearance of parenchymatous degeneration with numerous small fat droplets present in the cytoplasm. Scattered areas of patchy focal necrosis could be found in the groups exposed to longer lasting lethal doses of temperature. They were usually located in the mid-zone of the liver lobules and consisted of acidophil hyalinized cellular debris invaded by leukocytes and macrophages. The most characteristic change in the spleen was the necrosis of lymphocytes in the Malpighian follicles and in the splenic pulp in the animals of Group B. Marked congestion was present in the spleen of all fever animals and in the nembutal controls. The hemosiderin pig-

ment in the pulp was slightly increased in the chronic fever animals. In the kidney, congestion with hemorrhage was present in all fever animals except in the recovery group, while degenerative processes of tubular epithelium were most marked in Group B. These consisted of irregular enlargement of the tubular epithelium with obstruction of the tube lumen, an increased desquamation of epithelial cells, and the formation of cellular casts. An interesting finding was the appearance of glycogen in the tubular epithelium of the animals with depleted liver glycogen—a histological evidence of fever glycosuria. The adrenals showed a marked depletion of lipoid in fatal doses of fever and the presence of extensive cortical necrosis, which was most marked in the group exposed to 109° over 8 to 9 hours. Small hemorrhages were present in all fever animals and some of the nembutal controls. Necrosis of germinal epithelium with edema and hemorrhage in the interstitial tissues was found in the testicles of the animals exposed from 8 to 40 hours to high fever. The nuclei of the germinal epithelium showed changes varying from simple pyknosis to complete lysis. Giant cells with dense peripheral nuclei and a hyaline cytoplasm were frequently present. Acidophilic cell debris filled the lumina of the tubules. The changes seemed to affect the spermatids first, the spermatocytes second, and the spermatogonia last. Frequently an intact layer of spermatogonia could be found in tubules in which all other elements were destroyed. The interstitial cells showed only a slight swelling with some vacuolar degeneration. The thyroids of all fever animals showed moderate to severe depletion of colloid with corresponding hyperplasia of the epithelium lining the acini. Examination of the thymus, lymph glands, striated muscle, and omentum showed small petechial hemorrhages which were most frequently present in Group B. Examination of the intestinal tract, pancreas, bladder, ureters, and the larger vessels showed no significant change.

In summarizing, we can therefore state that the most frequent pathological changes observed in animals exposed to fever were vascular phenomena: congestion and hemorrhage. These, however, were present also in some of the animals which received nembutal alone and may have been at least partly caused by the drug itself, although their prominence in Group B undoubtedly points to fever as an important etiological factor. Degenerative changes of the cytoplasm and cellular necrosis were present especially in those animals which suffered a temperature of 109° over several hours and were less frequent or even absent in animals which died after a

short-lasting exposure with rapid excessive rise in temperature. This observation would indicate that some time must elapse before the cells of the various parenchymatous organs show evidence of damage, and that fever over a brief period is apparently not very harmful to those cells although it produces death of the organism from some other cause. The difference in the cellular changes occurring in animals exposed to fatal and non-fatal doses of fever is very striking. No parenchymatous necrosis or replacement fibrosis was observed in animals who survived repeated short-lasting exposures to 106.5°. Since this is the condition we are meeting daily in the fever therapy of the human, we may emphasize the rather encouraging conclusions which can be drawn from these observations.

10814

Calcium Creosotate: V. Nature of Phenols Eliminated in Urine.*

EDWIN J. FELLOWS. (Introduced by Edward Larson.)

From the Department of Pharmacology, Temple University, School of Medicine, Philadelphia, Pa.

Investigation[1-4] of calcium creosotate appeared desirable on account of its admission to U.S.P. XI without published reports on its clinical and experimental behavior. Volatile phenols could not be detected in sputum of hospitalized patients or in expired air of rabbits after oral administration of calcium creosotate.[2] It has been found, however, that calcium creosotate phenols are eliminated in rabbit urine[1] and also in human urine[2] after oral administration. Although calcium creosotate is advocated as a urinary antiseptic no clinical or experimental data have been found in the literature to indicate that its administration by mouth produces a bacteriostatic urine. It seemed, therefore, that the ability of *calcium creosotate* to produce a bacteriostatic urine, and the *form* in which it is eliminated should be investigated; especially since Knapp[5] reported that

* I wish to express my thanks to Dr. A. E. Livingston for the helpful suggestions received during these experiments.

1 Fellows, *J. Pharm and Exp. Therap.*, 1937, **60**, 183.

2 Fellows, *Am. J. Med. Sci.*, 1939, **197**, 683.

3 Fellows, *J. Pharm. and Exp. Therap.*, 1937, **60**, 178.

4 Fellows, *J. Am. Pharm. A.*, 1939, **26**, 609.

5 Knapp, *Schweiz. Wchschr.*, 1911, **49**, 229, 245, 257.