esis is found in the recently reported activation of chymotrypsinogen by trypsin to form a new proteolytic enzyme, chymotrypsin (Kunitz and Northrop).[1]

8892 C

Effect of Cinchophen on the Liver and Other Tissues of the Dog.*

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During a study of peptic ulcers produced by the administration of cinchophen we had the opportunity of studying the effects of large amounts of cinchophen on the liver and other organs of the dog. In view of the divergence of opinions regarding the effects of cinchophen on the livers of experimental animals, it seems advisable to record our observations on this subject.

Specimens of liver were obtained from 131 dogs which were normal in every case before the experiment was begun. They were given the routine kennel care and were fed a balanced diet of a calculated weighed amount sufficient for their caloric requirements. Cinchophen was for the most part administered orally; in a few cases it was given rectally, parenterally, or through intestinal fistulas.

Thirty-one dogs, whose average weight was 17 kg., were daily given 2 gm. of cinchophen well mixed with their food for a period varying from 3 to 60 days. The average length of time over which administration of the drug to this group was continued was 27 days; the average total dose of cinchophen was 50 gm.

Fifty-four dogs were given 2 gm. of cinchophen daily, with an occasional rest day, for an average of 30 days but in a few cases over a period of time as long as 114 days. To this group the amount of cinchophen administered varied from 36 to 228 gm. during the course of treatment.

Thirteen dogs, whose average weight was 13 kg., were given varying doses of cinchophen by routes other than by mouth, the usual dose exceeding 1 gm. daily. To members of this group an average of 21 gm. of the drug was given in an average of 13 days.

[1] Kunitz, M., and Northrop, J. H., *J. Gen. Physiol.*, 1935, **18**, 433.

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Twenty dogs, whose average weight was 8 kg., were given 1 gm. of cinchophen mixed with their food 5 days of each week; no cinchophen was given on the last 2 days of each week. The smallest total dose given to a member of this group was 22 gm. in 30 days; the largest total dose was 423 gm. in 630 days. The average for the group was 198 gm. given in an average of 270 days.

The 13 dogs remaining were fed the same diet but were not given cinchophen. These dogs were killed at varying, comparable intervals and were used as controls.

The majority of the animals were killed at the end of the period of administration of cinchophen. Some were explored surgically at this time and the gross appearance of the organs was noted; a recovery period of variable time was allowed and these dogs were then killed. All dogs killed were given light ether anesthesia and were then bled from the femoral arteries.

At the time of necropsy a record was made of the gross appearance of all the organs. Multiple sections of the heart, lungs, liver, pancreas, spleen, kidneys, adrenal glands, and occasionally the gallbladder, were fixed for histologic study.

Gastric lesions developed in all but 2 of the dogs which received cinchophen. The greatest changes in the other tissues were always noted during the first 10 days of administration of cinchophen. During this time a toxic condition usually developed, followed by a gastro-intestinal disturbance associated with varying degrees of nausea, vomiting, tarry diarrhea, and in some cases, anorexia. Since these symptoms were all manifestations of the development of peptic ulcer, we shall not discuss them further. The toxemia produced in the first few days usually subsided and the dogs then tolerated the drug fairly well. The toxic manifestations increased in a few cases, however, but these dogs usually died.

A slight yellowish color of the entire liver and kidneys was noted in a few of the animals killed during the initial stage of toxicity. A variable degree of vacuolization of the hepatic cells and of the tubular epithelium in the kidneys was seen microscopically. A few dogs had similar fatty changes in the cardiac muscle, and at times some cloudy swelling was seen in the liver. No gross or microscopic changes were noted in the other organs.

These mild pathologic changes varied with the degree of toxicity, and the toxemia varied with the dose of cinchophen. If the animal was markedly toxic, and this was true in only 3 or 4 cases, fatty degeneration was marked; if, on the other hand, the toxicity was no greater than that ordinarily produced by peptic ulcer, the fatty

change was slight, although at the same time it was more than that seen in normal dogs.

Little change was noted in any of the organs at the end of from 30 to 60 days, and the dogs killed after the administration of cinchophen for from 100 to 630 days had normal-appearing organs both grossly and microscopically. At no time was jaundice seen, and at no time was cirrhosis produced or the structural framework of the liver altered. In the kidneys of dogs fed cinchophen there was no more evidenced nephritis than in the kidneys of control animals, although during the acute toxic stage there was slightly more tubular degeneration in the kidneys of these dogs than was seen in the kidneys of the control animals. Pancreatitis was not noted at any time, and the gallbladder, adrenal glands, lungs, and spleen were consistently normal.

8893 P

Blood Electrolyte Studies in Experimental Acute Liver Injury Produced by Arsphenamine in Dogs.*

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In the present investigation we have attempted to determine changes in the blood electrolytes following the production of hepatic parenchymal damage with arsphenamine. The studies included determinations of the blood non-protein-nitrogen, urea, sugar, CO_2 content, sodium, chloride, potassium calcium, phosphorus, magnesium, total proteins, and lactic acid, as well as complete hematologic studies.

Liver damage was produced in 6 dogs by injection of arsphenamine intravenously. Animals were kept on a diet of raw meat to which was added 2 gm. of salt daily for 2 weeks before the experiment was started. Arterial blood for determination of various electrolytes was collected anaerobically before injection of arsphenamine. Forty to 80 mg. per kilo of body weight of freshly prepared arsphenamine was then injected intravenously. About 30 minutes later this was followed by vomiting which lasted for a few minutes before subsiding entirely. In 2 animals, a single injection

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