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Renal and Hepatic Injury in Trypsin "Shock".*

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Among the various features of the shock syndrome which develops in consequence of extensive tissue damage (burns, traumatic injuries, abdominal emergencies, severe infections, anoxia) are the negative nitrogen balance and the characteristic renal and hepatic changes. These, and other aspects of the shock syndrome have been attributed to or associated with a variety of "poisons" such as histamine, H-like substances, adenyl compounds, abnormal globulins, vasoconstrictor substances and numerous other products.

It has been demonstrated that the administration of proteolytic enzymes can induce the liberation of a variety of catabolic products, such as histamine[1] "slow reacting muscle stimulant substance" and adenyl compounds[2] and other pharmacologically active substances. Consequently, it occurred to us that with extensive tissue damage a proteolytic enzyme may be released locally, and it in turn be responsible not only for the production of toxic substances but also for an increased proteolysis and the consequent development of a negative nitrogen balance such as is observed in practically all types of shock. In order to test this hypothesis we studied the effects of injections of a known proteolytic agent.

The present preliminary report is concerned only with the renal and hepatic changes observed in rats and rabbits which received injections of a crude preparation of trypsin.† The intraperitoneal injection of a sterile 2% to 4% solution of trypsin in saline resulted in the development of the shock-like syndrome in from 3 to 36 hours, when from 5 to 10 cc was administered to rats and 10 to 20 cc to rabbits. A simlar syndrome could be induced in rabbits by the repeated intravenous injection of a dilute solution of trypsin. Thus, when young rabbits were injected 8 times daily for 2 days with 10 to 20 cc of a 0.25% trypsin solution, collapse and death occurred in from 24 to 36 hours after the last injection.

Postmortem examination of rats which died with the shock-like syndrome revealed some degree of peritonitis in some animals and not in others. The majority of 16 rats thus studied showed a marked congestion of the liver, soft and somewhat swollen kidneys and usually, a pale contracted spleen. A similar picture was observed in the rabbits which died, though signs of peritoneal irritation were not found.

Microscopic examination of the kidneys of both rats and rabbits revealed various degrees of damage from cloudy swelling and vascular congestion to degeneration of the cells of the collecting and distal convoluted tubules, massive deposition of eosinophilic granular and fibrillar material in the tubules and glomerular spaces, and focal collections of lymphocytes in the interstitial tissue about the degenerated distal convoluted tubules and arterioles. In some tubular spaces the contained material formed rounded hyaline bodies resembling red blood cells. The similarity to the pathologic changes observed in the kidneys of man dying from "crush injuries"[5] or burns is striking.

The liver showed various degrees of damage from cloudy swelling and vascular congestion to focal or massive necrosis and infiltration of the portal areas with neutrophiles and lymphocytes.

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1 Roche e Silva, M., *Arch. Exp. Path. u. Pharmak.*, 1940, **194**, 335.

2 Trethewie, E. R., *Austr. J. Exp. Biol. Med. Sci.*, 1942, **20**, 49.

† Fairchild's Trypsin and Wilson's Trypsin were employed. We are indebted to Dr. David Klein of the Wilson Company, Chicago, Ill., for generous supplies of a potent trypsin preparation.

In addition to the morphologic data herein reported, we have observed that the urine from animals in shock frequently contained large quantities of R. B. C., hyaline, and granular casts. Conclusive evidence of an hemoglobinuria was not obtained.

It must be emphasized that the intravenous injection of concentrated trypsin solutions (2% to 4%) in rabbits results in rapid death, within a few minutes after the injection, or even while the injection is in progress. Examination of such animals reveals extensive intravascular clotting, all chambers of the heart being filled with thrombus. In some respects this response is similar to the anaphylaxis-like syndrome produced by trypsin as described by Roche e Silva[3] and Dragstedt[4] although they do not attribute the collapse and death to the intravascular clotting which we have observed.

Data not yet reported lend support to the possibility that with extensive tissue damage some proteolytic enzyme is released or activated which in turn may be responsible not only for changes at the site of injury, but also for the production of catabolic factors whose effects may be reflected in renal, hepatic, and other systemic functional and structural depressions.

[3] Roche e Silva, M., *Arquivos d. Inst. Biol.*, 1939, **10**, 93.

[4] Dragstedt, C. A., and Wells, J. A., *Quart. Bull. Northwestern Univ. Med. Sch.*, 1944, **18**, 104.

[5] Bywaters, E. G. L., and Beall, D., *Brit. Med. J.*, 1941, **1**, 427.

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Paroxysmal Pulmonary Edema: A New Experimental Method.

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We have studied pulmonary edema following rapid infusion of massive doses of fluid into the circulation of dogs. Infusion into either the femoral or the jugular veins, or the femoral arteries was tried in 14 dogs with inconstant results. The rapid infusion of fluid into the carotid arteries toward the brain was therefore used to induce pulmonary edema constantly.

Technique. Experiments were performed on 18 dogs weighing from 8 to 20 kg, under morphine (3 mg/kilo)-urethane (1 g/kilo) anesthesia. Infusions were given simultaneously into both carotid arteries under a pressure of 280-300 m/m Hg. The total quantity of fluid injected amounted to 2.3 times the animal's estimated blood volume (on the basis of an assumed blood volume equal to 10% of body weight). A first infusion amounted to 85% of the blood volume and required from 1 to 2.5 minutes. A second infusion equivalent to 80% was given 10 minutes later. A third infusion equivalent to 65% of the blood volume was given 5 minutes after the end of the second. If the animal survived, it was sacrificed 7 minutes after the end of the last infusion.

Edema of the lungs was evaluated by: (a) weighing the lungs and calculating the lung/body index; (b) examining the gross appearance of the lungs and the presence of foam in the trachea; (c) studying the fluid pouring out of the cut parenchyma. Venous pressure, arterial pressure, X-ray of the chest and electro- and phonocardiograms were studied in some animals.

Results. 16 of the group of 18 dogs studied developed severe pulmonary edema after infusion with: (a) Tyrode solution; (b) physiologic salt solution; (c) bovine albumin solution; (d) oxygenated dog's blood.

Pulmonary edema occurred in all 4 types of infusion, with increasing severity from (a) to (d), but dyspnea was more severe with saline than with the other fluids.

Having obtained a reliable technique, we