SERUM CHANGES AND THE CAUSE OF DEATH IN EXPERIMENTAL PANCREATITIS.

STUDIES ON FERMENT ACTION. XXX.

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Incidental to a study of the ferment balance of the serum during various pathological conditions we have had occasion to observe the serum changes in a series of eighteen dogs in which an acute experimental pancreatitis had been produced.

Various theories have been advanced to account for the marked intoxication resulting from an acute pancreatitis. Opie (1) in this country, and Eppinger (2), Pólya (3), von Bergmann and Guleke (4), and numerous other workers in Europe have fully discussed the problem. The changes in the lipase titer have been reported by Whipple and Goodpasture (5).

Most workers are convinced that an activation (probably intracellular) of the trypic proenzyme occurs with a resulting intoxication of the animal because of the sudden formation and absorption of toxic split products. Coincident with this change there may occur a saponification of fats due to the simultaneous activation of the pancreatic lipase with a further injury to the pancreatic tissue by the soaps so formed. The means of activation of these ferments, resulting from a primary injury, may, of course, be diverse: bacterial infection, either through the ducts or lymphatics; mechanical blocking of the ducts and activation from bile; or activation from enterokinase and from tissue juice resulting from direct trauma, possibly from injury following vascular changes. While, therefore, the primary factor may be diverse, the resulting pathological lesions and the cause of death are uniform.
In the following illustrative experiments three different substances were injected as activators: bile salts, as first recommended by Flexner (6), active trypsin solutions, and sodium oleate solutions.

These experiments and the charts of the serum changes follow.

Dog 1.—Weight 4.5 kilos. 0.2 gm. of bile salts was injected into the pancreatic duct with subsequent ligation, at 9.30 a.m. on May 10, 1915. Serum samples were collected before the operation, at 10 and 11 a.m., and at 1 and 3 p.m. on each of the following 2 days and after about 3 weeks (June 3, 1915). The serum changes are shown in detail in Text-fig. 1.

The animal was killed on June 3, 1915. The pathological changes noted at autopsy were as follows: The pancreatic duct was occluded. The body of the pancreas was atrophic, fibrous, with large areas of fatty change and small necrotic foci containing caseous material. The tail of the pancreas showed less change. The viscera presented no pathological alteration other than fatty changes.

Dog 2.—Weight 5 kilos. 1 gm. of sodium oleate was injected into the pancreatic duct with subsequent ligation, at 11.30 a.m. (May 14, 1915). Serum samples were collected before the operation at 11.50 a.m., and at 1.30 and 3.30 p.m. on the 3 succeeding days, and after several weeks (June 4, 1915). The dog was killed after being used in another experiment. The serum changes are shown in detail in Text-fig. 2. The findings at autopsy were as follows: The pancreatic tissue was represented by a small remnant about one-fourth the size of the original tissue, rather firm, and pale yellow in color. The duct was occluded and there were numerous firm adhesions to the adjoining viscera. Scattered throughout the remnants of the gland were small more or less caseous areas of necrosis.

Dog 3.—Weight 5.1 kilos. 0.2 gm. of trypsin (purified) was injected into the pancreatic duct, with subsequent ligation, at 9.10 a.m. (June 7, 1915). Serum samples were collected before the operation at 9.45 a.m., noon, and 3 p.m., and at 8.30 a.m. and 2 p.m. the following day. The animal died at 2.15 p.m. (June 8, 1915). The serum changes are shown in detail in Text-fig. 3.

The autopsy findings were as follows: On opening the abdominal cavity a considerable amount of sterile, hemorrhagic, opaque fluid was found. This exudate contained 0.28 mg. of non-coagulable nitrogen per cc., and had a slight antitryptic action. Incubated under toluol the non-coagulable nitrogen increased 0.27 mg., and under chloroform 1.72 mg. in 16 hours, indicating the presence of considerable amounts of proteolytic ferments. The pancreatic tissue was hemorrhagic and contained numerous areas of necrosis throughout; there were numerous areas of fat necrosis scattered over the omentum. Fibrinous adhesions were found about the pancreas and adjacent viscera.

In the first animal the injection of bile salts caused only a moderate pancreatitis, although at the time the abdomen was closed after the injection a thorough infiltration of the pancreatic tissue was noted.
TEXT-FIG. 1. Serum changes accompanying acute pancreatitis due to bile salt injections.
Text-Fig. 2. Serum changes accompanying acute pancreatitis due to soap injections.
TEXT-FIG. 3. Serum changes accompanying acute pancreatitis due to trypsin injections.
No increase in temperature resulted; only a moderate leukocytosis and that only for a short period of time. Immediately after the operation the antiferment increased while the protease decreased; the balance was restored to a normal level the following day. The serum lipase increased slightly. There was noted a marked increase in serum proteoses during the period following the operation; after 3 weeks a normal value was again found. The amino nitrogen in this, as in the other animals, showed only very slight changes.

In the third dog the injection of the trypsin resulted in a rapidly fatal intoxication and it will be observed that the serum changes were different. There was a marked leukocytosis—80,000—as an index of the intoxication, with a progressive decrease in temperature. The antiferment, after a short rise, declined progressively, while the serum protease increased and remained high. The proteoses, after a slight initial decrease, frequently observed in the period following the mobilization of protease, increased markedly. There was only a slight change in the lipase.

The picture closely resembles the condition found in true trypsin shock (7), except in the behavior of the serum lipase. In conjunction with Experiment 2 it would seem that the decrease in the antiferment and the increase in protease have had some relation to the fatal outcome in this case.

In the second dog in which soap was injected, we find the reverse of the preceding changes, as might be expected from the difference in the action of the substances. The tissue destruction was quite marked and the whole pancreas even before closing the abdomen presented a deeply engorged, hemorrhagic, semitranslucent mass almost twice the normal size. It will be observed that the leukocyte count was also high—100,000 after 24 hours. Despite the severity of the local process the serum changes were slight and the animal showed little evidence of a general intoxication. The antiferment increased immediately, but the serum picture was practically unaltered after 24 hours. The lipase remained low. As contrasted with the two previous animals it will be seen that the increase in proteoses was not only delayed but actually less in amount.
DISCUSSION.

From the series of animals, of which these three are representative, we believe that we are justified in assuming that death is due to the sudden flooding of the blood stream with the higher split products formed at the expense of the pancreatic tissue, of which the proteose increase is an index. Except in the experiments in which active trypsin is used for injection there is no increase in serum protease at any time, as would be expected if the intoxication were a true trypsin shock, nor is there much change in serum lipase (esterase), the condition in this respect resembling closely the results observed following the injection of protein split products (8).

Here, as in other protein intoxications (9) the increase in antiferment seems to be of distinct value in the protection of the animal; in the experiment in which soap was used for the injection this becomes apparent. The increase in antiferment was marked, while the delay in the digestion of the pancreas and the consequent lessening of the shock is indicated by the gradual and relatively small increase in the amount of proteoses present in the serum.

In view of Whipple's results concerning the non-toxicity of the abdominal exudate (5) and our own experiments, it would seem that the only beneficial effects which might possibly have accrued from operative interference in cases of human pancreatitis have resulted from the prolonged anesthesia rather than from the surgical drainage. The inhibitory effect of anesthetics on the development of toxicity for protein intoxication is well known.

CONCLUSIONS.

1. The serum changes observed during acute experimental pancreatitis indicate that the shock and death are due to an intoxication from protein split products, and not to an intoxication from pure tryptic ferment.

2. When the pancreatitis is produced by the injection of an antiproteolytic substance (sodium oleate), the degree of intoxication bears no relation to the degree of tissue destruction.

3. The increase in serum antiferment apparently favors the recovery of the animal.
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BIBLIOGRAPHY.