A STUDY OF THE EFFECT OF INTRAVENOUS INJECTIONS OF SOLUTIONS OF PANCREATIC TISSUE; WITH ESPECIAL REFERENCE TO THE CAUSE OF COLLAPSE IN ACUTE PANCREATITIS.*

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Blood-pressure in disease and especially in its relation to shock and collapse has been the subject of much experimental work. There is a particular phase of this subject dealing with the influence of tissue extracts and products of tissue degeneration in disease that is of special interest. Powerful toxins can be extracted from certain organs and others are formed in the process of auto-digestion or breaking down due to bacterial action.

There is evidence to show that autolysis differs somewhat from the ordinary decomposition of tissue. Biondi believes there are several ferments differing from trypsin at work in self-digestion. They are specific for certain proteid molecules of the nature of globulins and cause the formation of end products rather than of albumoses. Salkowski believes a ferment is set free at time of death. Salkowski, Jacobi and others have shown that the cells of the animal body contain ferments capable of digesting these cells under certain conditions. Schwiening and Jacobi do not consider the ferment identical with trypsin.

Claypon and Schryver have published some experiments on autolysis. They show that there is a latent period of twenty-four hours after extraction before autolysis begins. The authors believe the ferments active in this process do not exist preformed in the cells, but as zymogens. On the liberation of the enzymes autolysis begins. The fact that they found the latent period diminished

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1 Biondi, Virchow's Arch., 1896, cxliv, 373.
2 Claypon and Schryver, Jour. of Physiol., 1904, xxi, 169.
or absent in organs of fasting animals suggests that liberation of those enzymes is a normal mechanism for the intra-vitam utilization of the proteids of the tissues. Even in the earliest stages the maximum amount of degradation products is in the form of the lower molecular compounds.

It has been proved that extracts from certain organs possess a depressing effect on the blood pressure. Osborne and Vincent, and Vincent and Sheen have studied this phenomenon. Vincent and Sheen found that the extracts of nervous tissues produce a marked temporary fall of blood-pressure occurring after section of both vagi and after doses of atropine sufficient to abolish vagus action. They do not believe choline is the active principle of nervous tissue extracts. They found extracts from muscle tissue, kidneys, testes, pancreas, liver, spleen, ovary, lungs, and intestinal mucous membrane produce depressor effects.

Vincent and Cramer showed that normal blood of the ox and rabbit produced frequently as great a fall of blood pressure in cats and rabbits as Halliburton observed when he used pathological blood. It can then be seen that many organs possess substances that are capable of influencing the blood-pressure.

In regard to certain products of decomposition or autolysis Hamburger has found that peptones and albumoses exert on the organism first a narcotic action resembling that of chloroform; second, an anticoagulative effect when injected intravenously; third, an effect on the blood-pressure. In the form of Witte's peptone it produced a fall in pressure. All the ingredients of Witte's peptone with the exception of anti-peptone possess undoubted vaso-dilating properties. Pick and Spiro found it possible to obtain typical albumoses and peptones after cleavage of proteids by trypsin, autolysis, and alkalis, but these authors found that when such products are introduced into the blood no effect was shown on the blood-pressure. They believe active products prepared by acid or pepsin and acid lose their typical action after purification by a method which apparently does not alter their chemical character.

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8 Osborne and Vincent, *Jour. of Physiol.*, 1900, xxv, 283.
Mendel and Underhill\textsuperscript{7} doubt some of these conclusions. They found that all proteose preparations introduced in doses of from 0.3 to 0.5 gram per kilo of body weight into the circulation of dogs produced a fall in arterial pressure, diminished coagulability of the blood, a transitory stage of excitation followed by narcosis, by a degree of immunity, and in a single experiment so far tried by lymphagogic effect.

The collapse so characteristic of acute pancreatitis has been the subject of considerable study of late. Several have offered explanations. Opie\textsuperscript{8} believes some toxin is the cause; Guleke\textsuperscript{9} says it is due to trypsin; Doberauer\textsuperscript{10} believes it is caused by some toxin derived from the pancreatic tissue. Involvement of the cælic plexus is advanced by others as the cause. That the stretching and irritation of the sensitive peritoneum, and involvement of the cælic plexus are important contributing factors seems very probable in view of the exceedingly severe pain seen in the disease. Some lowering of blood-pressure can be produced by irritating these parts experimentally. This was done on four dogs using mechanical irritation and three per cent. nitric acid. Although the blood-pressure fell and there was considerable disturbance in respiration and pulse tracings, there was not sufficient evidence to indicate that the collapse could be explained on the basis of irritation of the peritoneum or involvement of the cælic plexus alone.

We have in the products of tissue decomposition of the pancreas substances capable of producing marked toxic symptoms and fall in blood-pressure. The general opinion seems to favor a toxin as being the cause of this collapse or at least as being the main cause. That the pancreas will undergo a very rapid autolysis is well known. There is marked tendency for a small injury to spread, there is breaking down of tissue and more or less necrotic material tends to form. In many cases the peritoneal cavity is partially or completely filled with fluid. That the conditions for absorption of toxic substances are favorable is evident.

\textsuperscript{7}Mendel and Underhill, \textit{Amer. Jour. of Physiol.}, 1902-3, viii, 377.
\textsuperscript{8}Opie, Diseases of the Pancreas, Philadelphia, 1903.
\textsuperscript{9}Guleke, \textit{Archiv. f. klin. Chir.}, 1905-6, lxviii, 845.
\textsuperscript{10}Doberauer, \textit{Beiträge z. klin. Chir.}, 1906, xlviii, 456.
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It has been suggested that the glycerine formed in the production of fat necrosis is responsible at least in part for the collapse. However after repeated trials on dogs and rats obtaining no satisfactory results I came to the conclusion that it played an unimportant part.

As already stated, trypsin has been advanced as a possible cause of the collapse. That it has a depressing effect is obvious from the results obtained. But the effect is not as pronounced as with peptone and other tissue extracts of the pancreas, and is more transient. So experimentally at least I do not regard trypsin as important. Cathcart has found that normal serum has an antitryptic action which is associated with the albumin fraction. It was found in all varieties of sera examined by the author and is destroyed by exposure to 55° C. for one half hour. Globulins do not possess this action.

In acute pancreatitis the toxin or toxins causing the marked collapse are probably derived from the broken down pancreatic tissue, disintegration being brought about by the action of bile salts in case of retrojection of bile, and possibly through the action of ferments contained in the gland itself. Bacterial action also would readily lead to the formation of necrotic material in this gland, so readily broken down. Peptones and albumoses would be the early substances formed, later on aromatic compounds as indol and skatol, and certain phenyl-compounds would appear. Finally, according to Levene, the amino-endproducts are in case of self-digestion of the pancreas, alanin, amino-valerianic acid, leucin, glutaminic acid and aspartic acids, tyrosin and phenylalanin; α-pyrrolidin-carboxanic acid could not be established with certainty.

That the degradation of tissue is rapid even in cases of pure autolysis is seen from Hamburger’s experiments. He found that often the increase of nitrogenous extractives in case of the liver after an incubation of twenty-four hours amounted to more than fifty per cent. of the total.

Peptone is an early product formed in the breaking up of cellular substances either through autolysis or bacterial action. This was injected into the femoral vein of three dogs, causing a fall slightly

*Cathcart, *Jour. of Physiol.,* 1904-5, xxxii, 299.
*Levene, *Amer. *Jour. of Physiol.,* 1904, xii, 276.*
Experiments.—To test the effect of pancreatic extracts on the blood-pressure the following experiments were undertaken. These can be divided into two classes. The testing of extracts (1) giving the biuret reaction, (2) those not giving the biuret reaction. The extracts were prepared as a watery solution of fresh ground pancreas obtained from dogs. Ten dogs were used for the experiment. A canula was inserted into the left carotid artery and tracings taken on a slowly revolving drum. The injections were made into the femoral vein in most experiments.

Injections of pancreatic extracts giving the biuret reaction had a marked effect on the blood-pressure. The rapidity and extent of the fall was more pronounced than after the injection of either trypsin or peptone, or after mechanical irritation. Doses from 2.5 c.c. to 2 c.mm. were employed and were always followed by a rapid fall of about 20 mm. in the mercury column. Although there was a considerable difference in the amounts injected at different times, the difference in response was not as great as might have been expected. The results obtained showed that there was present in the extracts a depressor substance of considerable toxicity. The trypsin and peptone present had possibly some effect, but the fall in pressure was considerably in excess of that produced by trypsin or peptones used alone; therefore there must be present some other substance or substances in the gland tissue which is more powerful than those mentioned. The same results were obtained when one or both vagi were cut.

The inoculation of pancreatic extract not giving the biuret reaction gave more pronounced results than that giving this reaction. The fall of the heart beat and respiration was more rapid, the fall lower, and the recovery slower. Since in this solution no proteid was present, all having been converted into simple chemical structures as aromatic and amino compounds, we must look among these for the main cause or causes of the marked fall in blood-pressure. As in the preceding experiments the same results were obtained with one or both vagi sectioned.

We have thus in the products of the decomposed pancreas substances that experimentally at least are capable of producing a
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marked fall in blood-pressure. This substance or these substances are present in the gland shortly after necrosis begins, in combination with the trypsin, the peptones, and albumoses. The biuret reaction tends to disappear after the lapse of a short time, and there is left the aromatic and amino compounds.

In addition to the experiments on dogs, thirty white rats were inoculated intraperitoneally with pancreatic material in various degrees of decomposition, with the result that twenty-one died, nine recovered; but those that recovered showed marked evidence of severe effects for a day or two after inoculation. The material not giving the biuret reaction seemed especially toxic. Seven died within twelve hours after inoculation with this solution. However it appeared that when the material had stood for three or four weeks the toxicity was not as great and recovery was more likely.

Bacteriological inoculations were made from the peritoneal cavities of all the animals dying, and from only one was a pathogenic germ isolated, namely Micrococcus pyogenes aureus. The blood-vessels of the peritoneum of most of the rats were injected, but no exudate was present.

CONCLUSIONS.

From these results it is permissible to draw the following conclusions which may be used to explain certain phenomena associated especially with the onset of acute pancreatitis.

1. The sudden marked collapse of acute pancreatitis has as its most important cause a toxin or toxins derived from broken down pancreatic tissue. This toxin or toxins seem to be most powerful in the stage of degradation just after the disappearance of the biuret reaction and are probably of the nature of aromatic and amino-compounds.

2. There are various contributing factors of toxic action as peptone and trypsin, but these are to be regarded as of secondary importance.

3. Mechanical irritation as stretching of the peritoneum and irritation of the celiac plexus is a secondary cause.

4. The glycerine produced through the action of steapsin cannot be regarded as an important cause of collapse.