the thickness of the sac, results may be obtained varying from total retention to complete passage of the active substance.

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The activation of pancreatic extract.

By **A. R. DOCHEZ.**

[*From the Laboratory of the Rockefeller Institute for Medical Research.*]

Many years ago Heidenhain demonstrated that the pancreas does not contain trypsin in an active form, but that it exists in the pancreatic tissue as a proferment or zymogen. Heidenhain was able to convert pancreatic zymogen into active trypsin by treating pancreas with weak acids. This fact was later confirmed by other investigators. Hekma, who used pancreatic juice obtained from a fistula, observed that the trypsinogen of the juice cannot be activated by treatment with acid. In 1899, Pawlow and Schepowalnikow discovered, in the mucosa of the small intestine, a specific substance which converts trypsinogen into active trypsin, and which activates both pancreatic extract and pancreatic juice. Vernon, in a series of papers published in 1901 and 1902 studied the activation of trypsinogen. His observations were largely upon pancreatic extract, although in some instances he used pancreatic juice. His conclusions are as follows: fresh pancreas shows no enzymotic activity; upon standing a few days extracts suddenly develop nearly their maximal tryptic activity; the addition of small quantities of active pancreatic extract increases enormously the rate of conversion of zymogen into active enzyme; fresh pancreas treated for twenty hours with 0.2 per cent. acetic acid develops active trypsin. Using dog's pancreatic juice, Vernon claims that one per cent. active pancreatic extract liberates three times more trypsin than one per cent. succus entericus. The same result is obtained with glycerine extract of fresh pancreas. Bayliss and Starling, who worked with large quantities of exceptionally pure pancreatic juice, contradict Vernon's results upon the activation of pancreatic juice by any other agent than the enterokinase of succus entericus. They were not able to activate the trypsinogen of the juice with active trypsin, or by means of any simple chemical

agent. They, therefore, look upon the activation of trypsinogen in pure pancreatic juice by enterkinose as absolutely specific. Larguier des Baucels, Delezenne, and Wohlgemuth have been able to activate the trypsinogen of pancreatic juice with a limited number of substances other than enterokinase. From this short historical sketch, one sees that though trypsinogen of fresh pancreatic extract can readily be activated by a large number of substances, trypsinogen of pure juice is activated with but few agents other than enterokinase.

It is well known that pancreatic juice when secreted is strongly alkaline. In the course of the experiments here detailed, it has been found that when fresh pancreas is brought in contact with alkali, the activation of trypsinogen cannot be obtained by the use of agents which are capable of activating fresh pancreas. In short, the alkali-treated pancreas resembles pancreatic juice in regard to its behavior toward activators.

Fresh normal pancreas of the dog was allowed to stand on ice in one flask in a concentration of 0.2 per cent. acetic acid; in another, at neutral reaction, and in a third, in a solution of 0.2 per cent. sodium hydrate. After twenty-four hours, the acid and alkali were carefully neutralized and the proteolytic activity of the mixtures tested in acid, neutral and alkaline medium. Degrees of digestion are expressed in terms N/10 H_2SO_4. Bacterial growth was prevented by the addition of toluol. The same quantity of pancreas was used in all experiments. The duration of digestion was, in every instance, twenty-four hours at 37° C. Beef serum denaturalized by heat served as substrate.

Medium.	Treated with 0.2 per cent. acetic acid.	Untreated.	Treated with 0.2 per cent. sodium hydrate.
0.2 per cent. acetic acid	11.0 c.c.	12.4 c.c.	0.2 c.c.
Neutral	16.4 "	4.8 "	0.9 "
0.2 per cent. sod. carb.	11.2 "	0.6 "	0.3 "

In this experiment, treatment with 0.2 per cent. acetic acid has developed proteolytic activity in all media. In untreated pancreas maximum proteolysis is observed in acid medium, and only slight proteolysis in neutral. In all portions of pancreas coming in contact with alkali, proteolysis has been paralyzed. This is especially marked in that portion of pancreas pretreated with 0.2 per cent. sodium hydrate.

In another experiment fresh dog's pancreas was inactivated by treatment with 0.2 per cent. sodium hydrate as above. The sodium hydrate was neutralized, and an attempt made to activate the alkali-treated pancreas with various agents. The inactive pancreas was allowed to stand for twenty-four hours at 37° C. in contact with the substances used for activation, and proteolysis was subsequently tested in acid, neutral and alkaline medium. The quantities of pancreas used and the technic were the same as in the experiment described above.

Activation of Pancreas Inactivated by Treatment with 0.2 per cent. Sodium Hydrate.

Medium.	Substances used for activation.				Heated pancreas.
	0	Enterokinase.	0.2 % acet. ac.	Active pancreas.	
0.2 % acetic acid	0.5 c.c.	8.8 c.c.	1.2 c.c.	0.0 c.c.	0.8 c.c.
Neutral	0.5 c.c.	19.0 c.c.	2.6 c.c.	0.9 c.c.	2.3 c.c.
0.2 % sodium carbonate	0.6 c.c.	21.5 c.c.	0.9 c.c.	0.1 c.c.	0.8 c.c.

From this experiment it is observed that pretreatment of fresh pancreas with 0.2 per cent. sodium hydrate completely prevents subsequent proteolysis. The enzyme of alkali-treated pancreas is, however, not destroyed inasmuch as it can subsequently be activated by the addition of enterokinase. Acetic acid (0.2 per cent.) which readily activates fresh pancreas is not able to effect to any appreciable extent activation of pancreas treated with alkali. Active pancreatic extract, Vernon's most effective agent for activating inactive pancreatic extract develops no activity in alkali-treated pancreas.

From these results it would seem that the activating effect of acid and the inactivating influence of alkali upon fresh pancreas do not represent a direct action upon the proteolytic zymogen, but probably exert their influence through the destruction of secondary substances which are necessary for the preservation of enzymotic equilibrium. The suggestion is made that the enzyme complex upon coming in contact with the alkaline reaction of the pancreatic juice undergoes a change analogous to that observed in the treatment of fresh pancreas with alkali, so that it is no longer readily activated by any agent other than the enterokinase of succus entericus.