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Influence of Secretin and Insulin on Pancreatic Secretion in Healthy Human Subjects.

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The intravenous administration of highly purified secretin is known to stimulate the secretion of pancreatic juice which is low in both organic material and enzymatic activity. On the other hand vagus stimulation results in the secretion of pancreatic juice with a high enzyme concentration.[1] Central vagus stimulation induced by insulin hypoglycemia has been shown to be without effect on the secretion of fluid by the pancreas in both man[2] and the unanesthetized dog[3] providing adequate precautions are taken to exclude the acid gastric contents from the intestine. However, less consistent have been the studies on the influence of insulin hypoglycemia on the secretion of enzymes by the pancreas. Both inhibition[4,5] and excitation[6,7] of enzyme secretion have been reported.

Methods. The subjects comprising this study were 22 men and women who were either volunteers or clinic patients with no evidence of either gastro-intestinal or metabolic disease. About 15 to 18 hours after the previous meal the stomach and intestine were intubated with a single double-lumen tube of the type described by Agren and Lagerlof.[8,9] Exact location of the tube was always verified by fluoroscopy. Separate gastric and duodenal samples were collected by continuous aspiration at a negative pressure of 30 to 50 mm Hg.

The secretin used was prepared either in our laboratory or by Wyeth Incorporated by the procedure of Friedman and Thomas.[10] For the purpose of this study it is important to note that no evidence for the presence of pancreozymin[11] in this secretin preparation was found. The secretin had no effect on the blood sugar level, and did not stimulate either emptying of the gall-bladder or the secretion of intestinal juice.*

Following collection of a basal sample during a 20 minute control period the secretin was administered intravenously at a dosage level of 1.1 clinical units per kilogram body weight. Continuous collection of separate gastric and intestinal contents was carried out for the next 60 minutes, the samples being divided into the fractions obtained at the end of 10, 20, 40 and 60 minutes. A second standard dose of secretin was then given and collection of gastric and duodenal contents continued for the next hour. In one series of patients the second intravenous dose of secretin was combined with crystalline insulin, 0.1 unit per kilogram body weight. In some experiments a third injection of either secretin alone, or of secretin combined with insulin in the doses stated, was made at the end of the second hour and collection of digestive

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TABLE I.

	1st hr Secretin			2nd hr Secretin		
	cc	Output	Conc. K	cc	Output	Conc. K
Highest	213	48140	.434	253	59720	.477
Lowest	82	7870	.072	127	9982	.072
Avg	143	22658	.158	186	29244	.157
Increase, %				30.1	29.1	0
	Secretin			Secretin + insulin		
Highest	283	67354	.238	287	57680	.288
Lowest	94	9580	.056	119	16070	.093
Avg	163	24910	.153	195	37812	.194
Increase, %				19.2	51.8	26.7

fluids continued during the third hour. Blood samples for sugar determinations were taken immediately before the combined injection of insulin and secretin and at 30 minutes and 60 minutes after the injection. All experiments involving the use of insulin were terminated by giving the subject dextrose solution through the gastric tube. Bicarbonate was determined by the titrometric procedure of Van Slyke.[12] Lipase concentration was determined on a tributyrin substrate by a phototurbidometric method,[13] and expressed in terms of percent standard substrate hydrolyzed by 0.1 cc of duodenal fluid in 20 minutes. Amylase concentration was determined by the picric acid method of Myers, Free and Rosinski.[14] Trypsin concentration was determined on an albumen substrate by the turbidometric method of Riggs and Stadie[15] as modified by Friedman.[16] Blood sugar concentration was determined by the Folin-Wu procedure.

Results. Following the injection of secretin the secretion of pancreatic juice reached its maximum rate during the second ten minute period and amounted to 82 to 213 cc (average 143 cc) during the hour (Table I). The concentration of enzymes was also greatest during the second 10 minute period but decreased thereafter at a more rapid rate than did the volume. In some instances the fluid recovered from the intestine during the last 20 minutes was pratically free from trypsin while amylase and lipase were still present in measurable concentrations.

A second dose of secretin in 22 experiments yielded from 127 to 253 cc (average 186 cc) of intestinal content during the hour, with the maximum rate of secretion usually occurring during the first 20-minute period. The secretory rate fell less rapidly during the hour following the second injection of secretin than during the hour following the first injection. The concentration of enzymes following the second secretin injection usually reached a maximum during the first 10 minute period. In all except 3 of the 22 experiments the concentration of enzyme following the second dose of secretin was less than that following the first dose (Table I).

In 17 other experiments the second secretin injection was combined with the injection of insulin. The blood sugar levels before insulin ranged from 66 to 93 mg %, 30 minutes after the administration of insulin from 23 to 48 mg %, and at the end of one hour from 30 to 105 mg %. In only one patient did the blood sugar level at the end of the hour exceed the initial value. During the first hour, when secretin alone was given, the volume secreted ranged from 94 to 283 cc (average 163 cc) while during the second hour, when insulin was combined with the secretin, the volume ranged from 119 to 287 cc (average 195 cc). The

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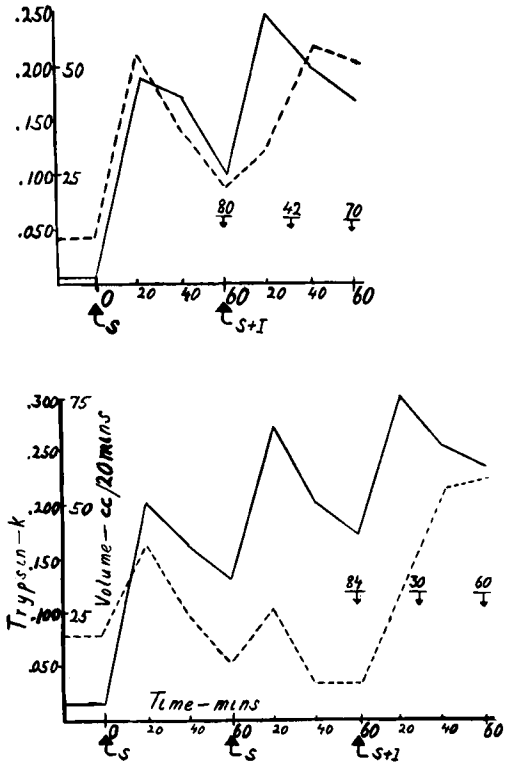
rate of secretion following the administration of insulin combined with secretin was thus not different from that occurring following a second dose of secretin alone. However, in contrast with experiments in which secretin



Mr. L. L., psychoneurosis, no gastrointestinal disease demonstrated. Underscored figures in each graph represent mg % blood sugar before and after insulin. Solid line shows volume, dotted line shows trypsin concentration.

FIG. 1a (upper) Pancreatic response to a dose of secretin (S) followed one hour later by a dose of secretin combined with insulin (S + I).

FIG. 1b (lower). Pancreatic response to 3 hourly injections of secretin (S), the last one being combined with insulin (S + I).

alone was given, in each of these experiments the concentration of enzymes secreted during the second hour was higher than during the first hour. The average increase in output of enzymes was 51.8% (Table I).

In 6 experiments 3 hourly injections of secretin were given. In 3 of these experiments the third secretin injection was combined with insulin. Three consecutive hourly injections of secretin alone resulted in a fairly steady increase in rate of secretion with a progressive decrease in the concentration and total output of enzymes. Combination of insulin with the third secretin injection had little influence on the rate of secretion but resulted in a very definite increase in the enzyme output (Fig. 1).

Discussion. The intravenous administration of secretin to the healthy fasting subjects evoked the typical pancreatic response attributed to the hormone. After a second dose of secretin the volume of juice secreted was greater than after the first dose, probably due to the cumulative effects of both secretin injections. After each injection of secretin the concentration of enzymes gradually diminished following an initial transitory rise. Since secretin is believed to excite active secretion of bicarbonate and water only, but not of enzymes, the initial transitory increase in enzyme concentration has generally been attributed to the washing out of the enzyme from the acinar cells and ducts by the flow of water. According to some investigators[17] a constant synthesis of protein material would make available new enzyme substances which would be similarly washed out by the flow of water that is put into operation by a second dose of secretin. Experimental evidence for this process, however, is still wanting.

Another explanation has been advanced by Thomas[18] and recently by Wang *et al.*[19] An increase in the dose of secretin, as well as a new injection of a submaximal dose of secretin, as was done in our experiments, may bring previously resting secretory elements into activity. This would result in the initial transient increase in enzyme output after each secretin injection.

Compared to the effects of secretin alone, the addition of insulin to the secretin did not influence the volume response. However, the output of enzymes by the pancreas secreting in response to secretin was increased by about 60% when a hypoglycemic state was induced by means of insulin. It is well-known that vagus excitation may stimulate the se-

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cretion of pancreatic juice of high enzyme concentration, and that insulin hypoglycemia may excite vagus centers. The latter has been proved abundantly by studies on gastric secretion and motility. It may be assumed that the excitatory effect of insulin on the secretion of pancreatic enzymes is due to a generalized hypoglycemic excitation of visceral centers, including those of the vagus.

Summary. Healthy human subjects were given 2 or 3 hourly intravenous injections of secretin. In some of the experiments insulin was given intravenously during the course of the pancreatic secretion evoked by the secretin. It was found that during insulin hypoglycemia the concentration and output of pancreatic enzymes was increased but that the volume of secretion was not influenced.

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Heat Stability of Hemagglutinin of Various Strains of Newcastle Disease Virus.*

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Determination of the heat stability of the hemagglutinin was selected as the first method of approach to the problem of characterizing the antigenically homologous strains[1] of Newcastle (NDV) virus. A method of identifying strains was deemed necessary for proposed studies of virulence and immunogenicity of the virus. For purpose of survey, 24 strains of virus obtained from widely distributed points in North America and Europe were cultured in embryonating eggs and the stability of the hemagglutinin (HA) to heating at 56°C determined.

The heat stability of the influenza hemagglutinin[2] has been extensively studied. It was the demonstration by Salk[3] of differences in heat stability of the influenza strains which influenced our choice of approach. Scott and Lauffer[4] described the inactivation of hemagglutinin of influenza virus as a first order reaction by assuming a multicomponent system. The demonstration that the site of inactivation of the hemagglutinin and the site of infectivity for embryos were independent was, therefore, not surprising.[5] The Henles[6] have shown that with heat and ultraviolet treatment, certain properties of influenza virus can be arranged in a descending order of susceptibility to inactivation. The capacity to infect embryos was lost first, then, in order, the ability to interfere with infection, to elute from agglutinated red blood cells, to agglutinate red blood cells, and subsequently, the ability to fix complement in the presence of immune sera. Antigenicity could not always be fitted into this order, but sometimes it persisted until after the hemagglutinin had been destroyed. With certain strains of influenza virus Salk[7] demonstrated the protec-

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