

ultraviolet irradiation during continuous ultraviolet irradiation of cytoplasm confers no degree of protection on cytoplasm or on longevity of the cell. (2) Nuclear protection from ultraviolet irradiation during continuous ultraviolet irradiation of cytoplasm prevents nuclear manifestations of ultraviolet induced nuclear damage.

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Received June 27, 1960. P.S.E.B.M., 1960, v105.

Constancy of Gastric Acidity with Variable Secretory Rates Induced by Insulin or Glucagon, with Histamine.* (26030)

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There is now considerable evidence to controvert the old concept concerning gastric acid secretion according to which concentration of acid in the primary secretion, as it arises from the parietal cell, varies with volume rate of flow(1). In the experience of our group, it has been found that the acidity of pouch juice may remain constant at high levels (*e.g.*, in the neighborhood of 150 meq/l) for significantly long periods of time and under a variety of experimental conditions. This was first observed in dogs with Pavlov pouches, following a single subcutaneous injection of histamine of very high dosage; in these experiments, acidity maintained a plateau level for a long time, during which rate of secretion rose and then fell to a level of about 10% of its maximum(2). Similar evidence has been adduced from secretion induced by low dosages of histamine and by ingestion of food, when the juice was collected in such a way as to minimize the concomitant secretion of mu-

cus(2); also during the diurnal hyper-secretory activity manifested by a bitch during lactation(3). Again, in experiments with Heidenhain pouch dogs in which both acidity and volume-rate were maintained at a fair degree of constancy, by repeated injections of histamine at short intervals (0.025 mg base every 10 minutes) for many hours, the superimposition of a single subcutaneous injection of atropine (0.4 mg/kg) about the middle of a 4-6 hour run, in order to inhibit the secretory response to the continuing administration of histamine, resulted in a drastic reduction in volume-rate without any marked change in acidity(4).

At no time, however, has it been reported that such essential lack of correlation between acidity and volume-rate obtains with purely vagal or vagomimetic stimuli, or even histamine at low dosage under ordinary collection conditions, but this may be ascribed to the fact that such stimuli evoke a gastric juice which is relatively high in organic matter—enzymes and mucus—and therefore relatively low in acidity. As a result of variations in these organic constituents, constancy of acidity is practically never attained, and time

* This work was supported in part by a grant from the Altman Foundation of New York.

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curves for HCl concentration and volume-rate manifest the usual parallelism. However, if one compares the acidities in such experiments at 2 or more times when the rates are identical, the lack of correlation is immediately evident. Thus, in histamine or food experiments with dogs, in which there was a manifest parallelism of the time curves for acidity and volume-rate, the data left no doubt that at 2 or more times during the experiment when volume-rate was the same (*e.g.*, near beginning and end of the secretory response), the acidities were so markedly different as to exclude any precise quantitative relation between the two variables(5). This same phenomenon can be seen from the data of an experiment on man by Olson and Necheles(6), in which the authors reported the usual stimulatory effect of an adequate insulin-induced hypoglycemia, along with a preceding inhibitory action of unknown mechanism. From the graphs in Fig. 1, it is evident that when a horizontal line, R-S, is drawn to transect the rate curve at 3 different positions or times, corresponding total acidity values, indicated by the verticals, are 53, 61 and 76 meq/l respectively. None of the experiments of these authors revealed a constancy of acidity like those with which we are dealing in the present report.

We recently completed a study of the inhibitory effect of insulin on histamine-stimulated canine gastric secretion in fully vagal pouches of the Hollander-Jemerin type(7) as well as in completely vagotomized (Heidenhain) pouches. The histamine was administered in repeated 10-minute subcutaneous doses of 0.1 mg of base for a total period of at least 4 hours. Some time after volume-rate of secretion had reached its maximum and leveled off (about 2 hours after start of experiment), a single dose of insulin (0.75 U/kg) was injected intravenously. This was followed promptly by a marked drop in secretory rate, similar to that reported by Olson and Necheles. In the case of the illustrative experiment shown in Fig. 2, volume-rate rose progressively during the first 75 minutes of repeated histamine injection, after which it remained constant for a full hour. Insulin in-

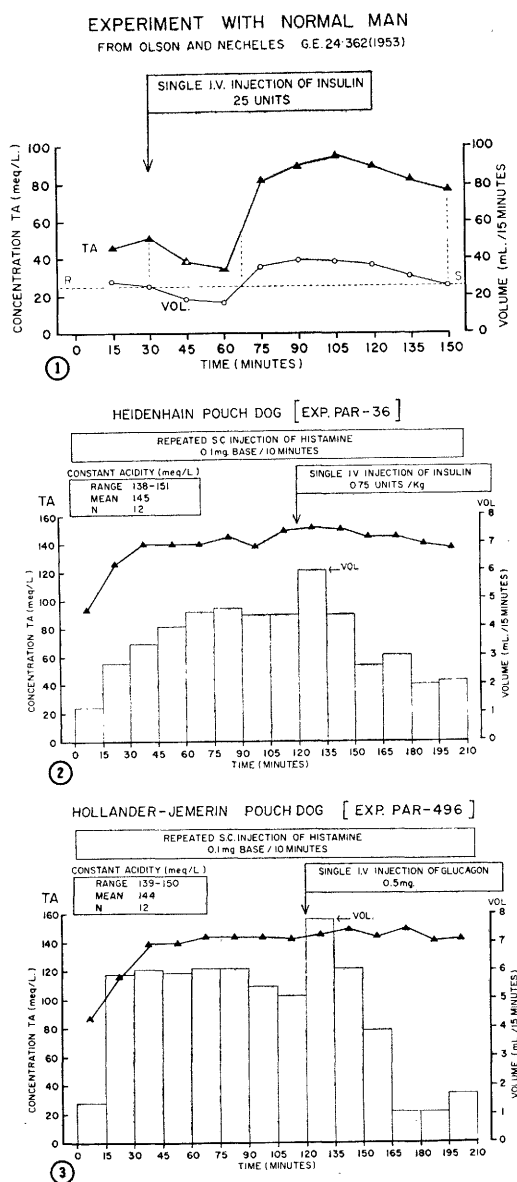


FIG. 1-3.

jection at this point was followed by a rise in rate for a single 15 minute sample, and then a rather steady fall for the remainder of the experiment—from a peak of 6 ml/15 minutes to a low of 2.0 ml/15 minutes. In spite of this 3-fold variation in volume-rate, the acidity remained at a plateau for 3 hours, varying only within the limits of 138 and 151 meq/l—a range of $\pm 4.5\%$ about its mean. Such prolonged constancy of acidity was observed

in 11 experiments in which the insulin-induced decrease in secretory rate persisted 90 minutes or more.

The same phenomenon has been observed in several similar experiments in which the secretion induced by repeated 10-minute injections of histamine was inhibited by a single intravenous injection of glucagon, Lilly; (0.5 mg/kg) in dogs with vagal pouches of our own variety.[§] In the illustrative experiment presented in Fig. 3, the total acidity curve remains constant in the interval 139-150 meq/l (a range of $\pm 3.8\%$ around the mean) for 3 hours, during which volume-rate varied from 7.8 to 1.1 ml/15 minutes.

Conclusion. We have now extended the variety of evidence regarding the constancy of gastric acidity—in refutation of the old concept of a curvilinear correlation between it and volume-rate of secretion—to include 2 additional types of stimulation-inhibition process. With these new findings, the list of experimental conditions for which this has been observed in pouch dogs now includes the following: (1) A single subcutaneous injection of histamine, at both high and low dosage levels, in Pavlov pouches. (2) Ingestion of food, which may be presumed to involve vagal as well as humoral stimulation. (3) Gastric hypersecretion during lactation. (4) Inhibition, by a single subcutaneous injection of atropine, of gastric secretion induced by small doses of histamine injected subcutaneously every 10 minutes, in Heidenhain pouches. (5) Stimulation and inhibition of secretion by a single intravenous injection of insulin.

‡ The authors wish to express their thanks to Dr. Tsung-Min Lin of the Lilly Research Laboratories, for the glucagon used in these experiments.

§ Attention is called to our observation that completely vagotomized (Heidenhain) pouches failed to manifest such inhibition of histamine-induced secretion. This will be discussed in a subsequent report.

superimposed on the response to repeated 10-minute injections of histamine in Hollander-Jemerin pouches. (6) Similar inhibition of histamine-induced secretion by a single intravenous injection of glucagon, on these fully vagal pouches. In spite of this and other recent additions to the mass of evidence supporting the two-component hypothesis to explain observed variations in gastric acidity, it must be remembered that there exist several kinds of observations which are seemingly in conflict with it; experimental efforts to clarify these discrepancies between theory and fact are being continued.

Summary. This report deals with the absence of correlation of acidity and volume-rate of flow of gastric secretion from fully vagal (Hollander-Jemerin) and completely vagotomized (Heidenhain) stomach pouches. Variations in rate of secretion were induced by the inhibitory action of a single intravenous dose of insulin (both types of pouch) or of glucagon (vagal pouch only) on flow of juice induced by stimulation with histamine in repeated 10-minute subcutaneous doses. In both types of experiment it was possible to demonstrate a good degree of constancy of acidity in spite of considerable variations in volume-rate. This brings to 6 the number of experimental situations in which such constancy has been observed.

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Received June 29, 1960. P.S.E.B.M., 1960, v105.