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Electrolyte Composition of Histamine Stimulated Gastric Juice from Intact Stomachs of Unanesthetized Dogs.* (27363)

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The change in electrolyte composition of gastric juice after histamine stimulation has been the subject of several reports. Hollander and associates have documented the inverse correlation between $[Na^+]$ and $[H^+]$ in both the content of Heidenhain pouches in dogs and in gastric aspirates of human subjects(1-4). These investigators, however, were unable to correlate $[K^+]$ with $[H^+]$, $[Na^+]$, or with the rate of flow of gastric juice. Some workers have maintained K^+ to be secreted at a fixed concentration from vagotomized gastric pouches of dogs(5), while others have found a positive correlation between $[K^+]$ and rate of flow in the first hour after a single subcutaneous injection of histamine in man(6). A highly significant positive correlation between total outputs of K^+ and H^+ after a slow i.v. infusion of histamine in cats has been reported by Blair, *et al.* (7). More recently Blair and Yassin have found a reduced output of Na^+ and the absence of a linear correlation between total outputs of Na^+ and H^+ following histamine stimulation of gastric secretion in these animals(8). In an attempt to clarify the confusion of the changes in composition of gastric juice after histamine stimulation we have correlated $[Na^+]$ and $[K^+]$ with $[H^+]$, $[K^+]$ with rate of flow, and Na^+, K^+, H^+ and Cl^- outputs with output of water.

Methods. Gastric content was collected for 3 hours from gastric and duodenal fistulas in 5 unanesthetized dogs during an intravenous infusion of 1.8 μg/kg/min of histamine base, a dose which produces a maximal acid response(9). (For details of method of collection see ref. 10.) Each 15-minute collection was filtered through 2 layers of grade 50 absorbent gauze, and free and total acidity were determined by microtitration(11). $[Na^+]$ and $[K^+]$ were determined by flame photometry using the direct reading method, while a coulometric method(12) was used to measure $[Cl^-]$. Concentrations thus obtained were multiplied by the volume of the 15-minute samples to obtain outputs of electrolytes.

Results. The well established inverse correlation between $[Na^+]$ and $[H^+]$ appears in Fig. 1. A similar, but much less dramatic, inverse correlation was found between $[K^+]$ and $[H^+]$ (Fig. 2). During the first hour of histamine infusion an inverse correlation also was observed between $[K^+]$ and rate of flow (Fig. 3), but a positive correlation between these two variables was noted after the beginning of the second hour (Fig. 4), during which time, in all experiments, the volume-rate of secretion remained relatively constant (Table I). When these same data were plotted as rate of output of each ion against rate of water secretion, the positive correla-

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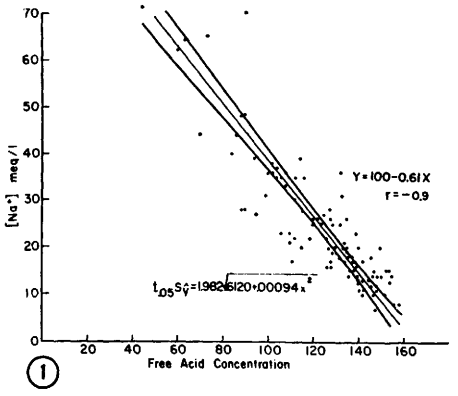
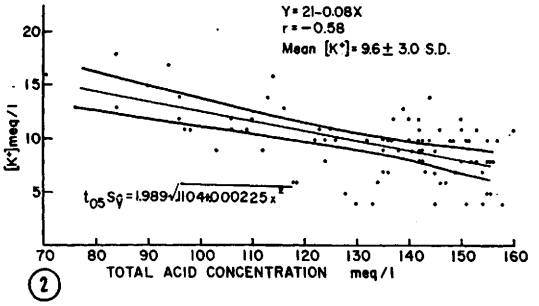
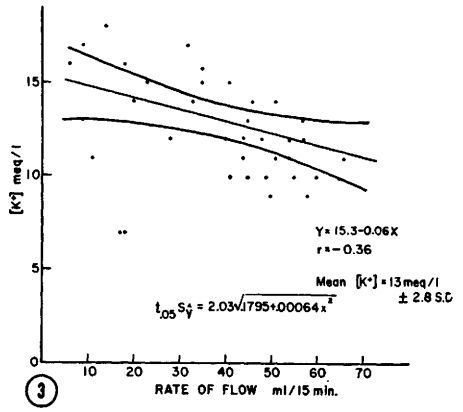
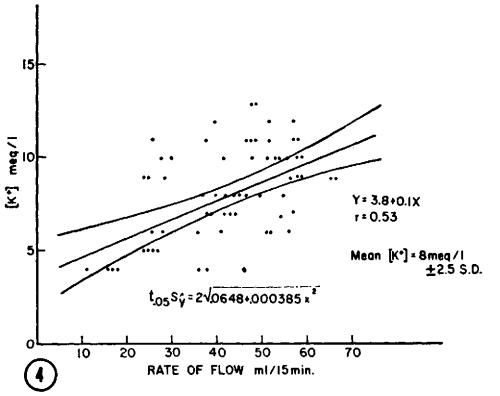
tions of Fig. 5 were obtained. The positive correlations between K^+, H^+, and Cl^- outputs and water output were exceptionally high in samples of gastric juice collected during both periods of histamine stimulation. For these 3 ions the null hypothesis that the 2 sample values of r in each graph of Fig. 5 were drawn from the same population was found acceptable for all 3 cases. It was not so for Na^+ output *vs* water output, and no comparison









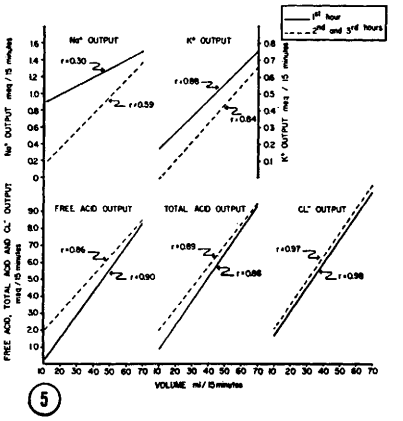


FIG. 1. Regression of $[Na^+]$ on free acid concentration in gastric juice during 3 hr of histamine infusion. Curved lines indicate 95% confidence limits of sample stand. error of Y.

FIG. 2. Regression of $[K^+]$ on total acid concentration in gastric juice during 3 hr of histamine infusion. Curved lines indicate 95% confidence limits of sample stand. error of Y.

FIG. 3. Regression of $[K^+]$ on rate of flow of gastric juice during first hr of histamine infusion. Curved lines indicate 95% confidence limits of sample stand. error of Y.

FIG. 4. Regression of $[K^+]$ on rate of flow of gastric juice during second and third hours of histamine infusion. Curved lines indicate 95% confidence limits of sample stand. error of Y.

FIG. 5. Regressions of Na^+, K^+, H^+, Cl^- outputs on rate of flow of gastric juice during (a) first hr, and (b) second and third hr of histamine infusion.

Na^+ output:	(a) $Y = .826 + .010X$,	(b) $Y = -.043 + .020X$.
K^+ output:	(a) $Y = .077 + .010X$,	(b) $Y = -.123 + .011X$.
Free acid output:	(a) $Y = 1.012 + .134X$,	(b) $Y = .963 + .108X$.
Total acid output:	(a) $Y = -.523 + .143X$,	(b) $Y = .822 + .125X$.
Cl^- output:	(a) $Y = .428 + .141X$,	(b) $Y = .732 + .141X$.

TABLE I. Volume and Electrolyte Response of Gastric Juice in Dogs to Maximal Histamine Stimulation.

	Pre-infusion			1st half hr			2nd half hr			2nd hr			3rd hr			Post-infusion		
Volume, ml/15 min.	8	± 5.5*	(42)†	31	±17.3	(21)	46	±12.6	(22)	48	±11.4	(44)	40	±11.6	(44)	14	±8.2	(9)
Total acid output, meq/15 min.	.49	± .31	(23)	3.42	± 2.47	(22)	6.77	± 2.59	(23)	6.95	± 1.64	(45)	5.59	± 1.51	(44)	2.01	± .82	(7)
Chloride conc., meq/l	139	± 8.5	(15)	148	± 10.3	(8)	150	± 10.0	(8)	156	± 9.1	(16)	160	± 6.0	(16)	156	±6.0	(3)
Sodium conc., meq/l	62	±17.1	(19)	51	±23.5	(16)	27	±13.0	(18)	19	± 7.3	(36)	20	± 6.1	(33)	28	±9.1	(3)
Potassium conc., meq/l	15	± 4.7	(24)	14	± 2.4	(17)	11	± 1.7	(18)	9	± 2.2	(36)	7	± 2.2	(33)	8	±1.7	(4)

* Stand. dev.
† No. of samples.

could be made in this case since a value of r = 0.3 in the first hour was not significantly different from r = 0.

Discussion. Twenty-nine years ago Hollander found neutral chloride negatively related to $[H^+]$(13), and later(1) called attention to the striking similarity of the regressions of $[Na^+]$ on $[H^+]$ and neutral chloride on $[H^+]$. The many studies since 1932 favor the hypothesis that Na^+ is absent from pure parietal secretion and its concentration in the alkaline component is no less than that in blood serum(1). On the other hand, agreement has been lacking on the exact relation of K^+ and H^+(1,5,7). Hollander has considered that H^+-efflux is exocrine in nature but K^+-efflux is of a wholly different character, associated with other kinds of cells in addition to parietal cells(14). If this is true, our correlation between $[K^+]$ and total acid concentration (Fig. 2) may be spurious.

The relation between time of collection of gastric juice samples and initiation of the histamine infusion has appeared to be important. Thus, mean $[K^+]$ was higher during the first hour than during the second and third hours of infusion (Fig. 3,4). Furthermore, the regression of $[K^+]$ on the rate of flow changed from a negative slope in the first hour to a positive slope in the second and third hours. Hollander has postulated that the secretion of water and K^+-efflux are mutually independent processes. Our data do not exclude this possibility, and caution should therefore be used in interpreting the high positive correlation between output of K^+ and output of water (Fig. 5). It should be noted that volume rate enters into the variates of both axes and this can produce spurious correlations.

I.V. infusion rates of histamine necessary to produce a maximal secretion of acid were found by Marks *et al.*(15) to agree well with rates reported by previous investigators, including Hanson, *et al.*(9). The maximal histamine response obtained in our experiments by using the infusion rate suggested by Hanson, *et al.* produces outputs of total acid (Fig. 5) similar to those obtained by Marks, *et al.* According to these latter investigators, the maximal histamine response does not

necessarily represent the maximal secretory capacity of the stomach.

Summary. Analyses of gastric contents collected during a 3-hour infusion of histamine (maximal stimulation) in unanesthetized, gastric fistula dogs revealed statistically significant negative correlations between $[Na^+]$ and $[H^+]$, and between $[K^+]$ and $[H^+]$. K^+ output, H^+ output, and Cl^- output were positively correlated with output of water during this infusion. $[K^+]$ and volume-rate of secretion were inversely correlated during the first hour of infusion and positively correlated during the second and third hours.

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Failure of Vaccination with Killed Brucellae to Modify Monocyte-Bacterium Interactions.* (27364)

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Despite the claims of a few investigators (1,2), it is generally agreed that exposure of brucella-susceptible hosts to killed brucellae fails to provide any significant and lasting protection against subsequent exposure to live, virulent organisms(3-6). Efficient protection against challenge with virulent organisms apparently results only from the temporary or prolonged establishment of living organisms within the host, and for this reason the use of an attenuated strain of *Brucella abortus* such as strain 19, or of a streptomycin-dependent strain of *Br. melitensis*(7), both of which fail to lead to clinical manifestations, has been advocated. The causes for the failure of organisms, killed in a variety of ways, to elicit efficient protection have remained obscure and difficult to understand, since killed brucellae certainly do lead to production of humoral changes (*i.e.*, formation of agglutinating antibodies) that are usually indicative of an immune state.

Many investigators have stressed the importance of cellular mechanisms in relation to immunity against diseases produced by intracellular parasites such as brucellae, and there have been various studies on interactions *in vitro* between mononuclear phagocytes (monocytes) from different hosts and brucellae of different virulence(8-11). Thus it was shown that monocytes from normal,

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