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THE INORGANIC COMPONENTS OF GASTRIC SECRETION

By R. B. FISHER and J. N. HUNT

From the Department of Biochemistry, University of Oxford and Department of Physiology, Guy's Hospital, S.E. 1

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Many attempts have been made to account quantitatively for the observed variations in composition of gastric juice, the most recent being those made by Hollander (1938), Gray, Bucher & Harman (1941) and Gray & Bucher (1941). Almost all the work in this field has been done on dogs, and has tacitly assumed (*a*) that the acid parietal cell secretion is of constant composition, so far as HCl and neutral chloride are concerned, and (*b*) that the remainder of the secretions, referred to as non-parietal, are not only constant in composition with respect to bicarbonate and chloride, but are also secreted at constant rates.

In connexion with other work we have been faced with the necessity to find some specification of gastric secretory activity in man in terms of acid, neutral chloride, and volume secreted. We have taken the extensive data of Ihre (1938) on gastric secretion in selected young men in response to histamine or insulin administration as a basis for testing possible theoretical relations between amounts of acid, neutral chloride, and total volume of juice secreted.

Basic assumptions. In this work we have started with less restrictive assumptions than those referred to above. The primary assumptions here are: (1) that the parietal secretion contains HCl and neutral chloride in constant concentrations; (2) that the mixed non-parietal secretions contain neutral chloride and bicarbonate in constant concentrations.

No assumptions are made about the constancy or otherwise of the rate of secretion of either parietal or non-parietal secretions. There is, however, a further tacit assumption, common to this work and to earlier work on dogs, that no changes in composition occur in the mixed gastric juice whilst it remains in the stomach. Ihre's data are based on samples continuously withdrawn from the stomach, which reduces to a minimum the opportunity for the exchange of ions across the gastric mucosa.

Theoretical relations between composition and volume

Denoting the concentrations of acid, neutral chloride, and bicarbonate in the component secretions and the amounts of acid and neutral chloride in the mixed juice as follows:

Parietal secretion	Non-parietal secretions	Mixed juice
h = conc. of acid	b = conc. of bicarbonate	A = amount of acid m.equiv.
p = conc. of neutral chloride	c = conc. of neutral chloride	N = amount of neutral chloride m.equiv.

and putting

x = volume of parietal secretion in period of observation,

y = volume of non-parietal secretion in period of observation,

V = volume of mixed juice secretion in period of observation,

we have
$$V = x + y, \tag{i}$$
$$A = hx - by, \tag{ii}$$
and
$$N = px + cy + by, \tag{iii}$$
provided the juice is acid.

These three equations constitute the fundamental relations, and the further development is largely a matter of algebraic modification of them.

Solving equations (ii) and (iii) for x and y gives

$$x = \frac{bA + cA + bN}{bh + ch + bp}, \quad y = \frac{hN - pA}{bh + ch + bp},$$

whence
$$V(= x + y) = \frac{h + c - p}{bh + ch + bp} A + \frac{b + h}{bh + ch + bp} N. \tag{iv}$$

Since the coefficients of A and N in (iv) are functions of quantities assumed to be constant, this equation can be written more compactly as

$$V = K_1 A + K_2 N, \tag{v}$$

which expresses the general form of the relation between volume, total acid, and total neutral chloride content of gastric juice which follows from the assumptions made.

Tests of fit of the fundamental theory to observation

Two tests of the fit of equation (v) to Ihre's published data are possible.

(1) The most general first-order relation between the three observable variables V, A and N is of the form

$$V = k_1 A + k_2 N + k_3, \tag{vi}$$

but the particular first order relation required by the theory requires that k_3 should be zero. The best fit of Ihre's two series of observations on normal subjects (twenty-four observations on secretion in response to histamine, twenty-four observations on secretion in response to insulin, both on the same set of subjects, each series giving totals for three consecutive 20 min. periods) to the most general type of relation of the form of equation (vi) was computed, and the magnitude and error of estimation of k_3 was obtained for each series. The values obtained were: histamine secretion, $k_3 = 5{\cdot}86 \pm 3{\cdot}13$ ml./hr; insulin secretion, $k_3 = 4{\cdot}34 \pm 2{\cdot}30$ ml./hr.

Neither of these estimates is significantly different from zero. Their significance is best judged by noting that they represent those portions (in ml./hr.) of the total volume secreted per hour which cannot be accounted for on the assumption that the mixed juice is a mixture of two components of constant composition. Since the mean rates of secretion in the two series are 102 and 132 ml./hr. respectively, it is clear that the k_3 terms are not only not statistically significantly different from zero but also quite trivial in relative magnitude.

(2) The second test is to plot for all observations the volumes estimated by the best fit relation of the theoretical form ($V = k_1A + k_2N$) against the observed volume. Should the theoretical relation be only a rough approximation to the true relation, such a plot should disclose this: if, on the other hand, the calculated volume corresponds equally closely to the observed volume over the whole range of observed volumes, the observations can be taken to be systematically consistent with the theory.

As a prelude to this test the best-fit relations of the form $V = k_1A + k_2N$ were computed for both series. The values of the constants for the two series were found not to differ significantly (Table 1), despite the difference in the manner

TABLE 1. Values of the constants obtained by fitting the equation $V = k_1A + k_2N$ to Ihre's (1938) observations on normal male subjects

	k_1	k_2
Histamine juice	$5{\cdot}63 \pm 0{\cdot}24$	$8{\cdot}16 \pm 0{\cdot}74$
Insulin juice	$5{\cdot}98 \pm 0{\cdot}12$	$6{\cdot}52 \pm 0{\cdot}43$
Differences	$0{\cdot}35 \pm 0{\cdot}29$	$1{\cdot}64 \pm 0{\cdot}83$

(Twenty-four observations in each series.)

of exciting secretion. The data for the two series were pooled, in view of the similarity of the equations, and Fig. 1 shows the correspondence of volumes calculated from this pooled relation and the observed volumes. Both series show a uniform correspondence of estimated with observed volumes over the whole range of observed volumes available (50–204 ml./hr.).

On the basis of these two tests it is reasonable to conclude that Ihre's observations are in conformity with the theory set out here. The theory is not proved, but the available observations can be accounted for in terms of it.

Composition of components of gastric secretion

'*Extrapolation methods.*' Much of the work on dogs referred to in the introduction to this paper was directed to attempts to determine the composition of the parietal secretion. In particular, earlier workers have found that, by plotting free-acid concentration against the reciprocal of the volume, a straight line is obtained. The acid concentration obtained by extrapolating this line to $1/V = 0$ has been taken as the free-acid concentration in the parietal component.

Such a relationship can be derived from the theory set out here on the basis of an additional assumption, namely, that the rate of secretion of the non-parietal component is constant.

Put the volume of non-parietal component secreted in the period of observation at a constant value y, and substitute $V-y$ for x in equations (ii) and (iii), obtaining:

$$A=hV-(b+h)y, \tag{vii}$$

$$N=pV+(c+b-p)y, \tag{viii}$$

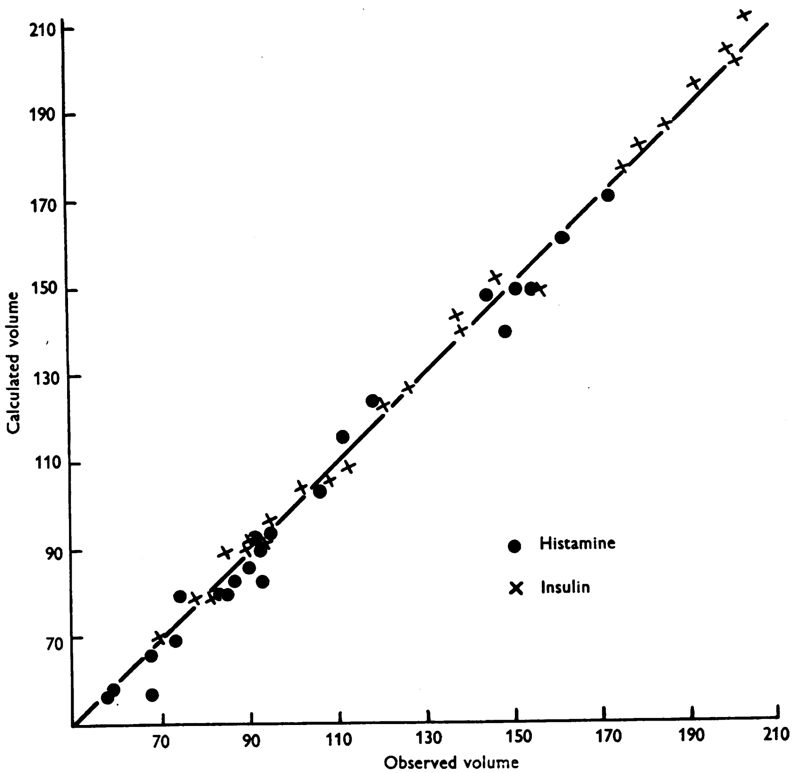

Fig. 1. The correspondence of calculated to observed volume. The abscissa is the volume observed, and the ordinate the volume calculated from the equation $V=5{\cdot}79\,A+7{\cdot}41\,N$, the pooled relation for all observations on normal subjects.

or, on dividing both these equations through by V,

$$A/V=h-(b+h)y\,.\,1/V, \tag{ix}$$

and

$$N/V=p+(c+b-p)y\,.\,1/V. \tag{x}$$

These equations give linear relations such that the values of A/V and N/V corresponding to $1/V=0$ are respectively the concentrations of acid and neutral chloride in the parietal component.

But if it should be the case that the non-parietal component is secreted at a rate which shows any systematic relation to rate of parietal secretion, this convenient relation would no longer hold. Suppose, for instance, that the rate of non-parietal secretion is related to the rate of gastric juice secretion in a manner approximating to $y = rV + s$, where r may be either positive or negative, and both r and s are constants. Then equations (ix) and (x) become:

$$A/V = (h - rb - rh) - (b + h)s \,.\, 1/V, \tag{xi}$$

and

$$N/V = (p + rc + rb - rp) + (c + b - p)s \,.\, 1/V. \tag{xii}$$

Equations (xi) and (xii) are still straight lines, but the values of A/V and N/V corresponding to $1/V = 0$ are no longer equal to the concentrations of free acid and neutral chloride in the parietal component: they differ from these concentrations by amounts dependent on the unknown constant r, and on the values assumed for the concentrations of the other constituents of the two secretions.

Since there seems to be no sound basis on which to found an assumption either of constancy of rate of non-parietal secretion or of any particular relation between the rates of secretion of the parietal and non-parietal components in intact animals, results obtained by this kind of extrapolation procedure are not of great utility in man.

The isosmotic assumption. The two constants of equation (v), experimental values of which are given in Table 1, are the only quantitative measures of composition of the components that can be obtained from the experimental data on acid, neutral chloride and volume. They provide two relations between the four unknown parameters of the component secretions h, p, b and c. Two other relations between these four are needed in order to solve for the four. One assumption, providing an additional relation, is that the two secretions are isosmotic, i.e. that $h + p = b + c$. This is in conformity with the observations of Ivy & Oyama (1921), Gilman & Cowgill (1933), Lifson, Visscher & Varco (1943) and Gray & Bucher (1941). In order to obtain the requisite two additional relations one must assume a definite value, I, for the sum of the concentrations of the constituents, so that

$$h + p = I, \tag{xiii}$$

$$b + c = I. \tag{xiv}$$

Combining these with

$$k_1 = \frac{b + c - p}{bh + ch + bp}, \tag{xv}$$

and

$$k_2 = \frac{b + h}{bh + ch + bp} \tag{xvi}$$

(which are the equations of the experimentally measurable constants of equation (v) with their theoretical forms set out in equation (iv)), it is possible to write expressions for h, p, b, and c in terms of the k's and of an assumed value of I. These expressions are:

$$\left.\begin{array}{ll} h = (k_2 I - 1)/(k_2 - k_1), & p = (1 - k_1 I)/(k_2 - k_1), \\ b = (k_2 I - 1)/k_1, & c = (1 + k_1 I - k_2 I)/k_1. \end{array}\right\} \tag{xvii}$$

Using a series of arbitrarily selected values of I, and the experimentally determined pooled values of k_1 and k_2, the values obtained for h, p, b and c are those listed in Table 2.

TABLE 2. Estimates of concentrations of constituents of components of human gastric juice corresponding to different values of I. All concentrations in m.equiv./l.

I	h	b	p	c
160	114·6	32·2	45·4	127·8
162	123·7	34·7	38·3	127·3
164	132·9	37·3	31·1	126·7
166	142·0	39·9	24·0	126·1
168	151·1	42·4	16·9	125·6
170	160·2	45·0	9·8	125·0
172	169·4	47·5	2·6	124·5
174	178·5	50·1	—	123·9

(These values are based on $k_1 = 5{\cdot}79$, $k_2 = 7{\cdot}41$, the estimates derived from the pooled observations on normal subjects.)

Quantitative consequences of the isosmotic hypothesis. It would appear that I must be less than 174 m.equiv./l., if the isosmotic hypothesis is valid, since this value of I gives a value of h which exceeds 174. The value of I for which $h = I$ is $1/k_1$, corresponding to $I = 172{\cdot}7$ m.equiv./l. for the present data.

Dr Ihre has kindly placed at our disposal the individual values for the separate 20 min. periods on which his published figures are based, and these permit of somewhat more precise estimation of the probable value of I. For instance, the highest concentration of acid to be expected in a sample of gastric juice will be less than h, unless the juice is pure parietal component, but 18 of Ihre's 238 individual values have acid concentrations exceeding 140 m.equiv./l., the highest value being 151. This suggests that h is probably rather in excess of 151 m.equiv./l., corresponding to I in excess of 168 (Table 2). On the other hand, the total Cl^- of mixed juice will be expected to reach the value of I only when the juice is pure parietal secretion, and in only four instances out of 238 was the observed total Cl^- in excess of 170 m.equiv./l. Combining these observations, I is probably greater than 170, though probably not much greater, and must be less than 172·7 m.equiv./l.

There is one other possible way of fixing the probable value of I. In Ihre's data the minimum concentration of neutral chloride recorded is 16 m.equiv./l. There are thus no observations which demand the assumption that the parietal component contains no metallic cations. From the work of Gray & Bucher (1941) it appears that the parietal component, at least in dogs, contains 7 m.equiv./l of potassium. They arrived at this value from the results of an analysis of gastric juice collected from the stomachs of vagotomized dogs after the injection of histamine. In spite of variations in the rate of secretion and of the proportion of parietal component to non-parietal component the concentration of potassium remained constant at 7 m.equiv./l. They thus came to the conclusion that the concentration of potassium was the same in both components. In man it is difficult to collect gastric juice without contamination with saliva, which contains at least 16 m.equiv./l. of potassium. It is therefore not surprising to find that the recorded concentrations of potassium in human gastric contents vary. But the lowest concentration recorded might be expected to give some indication of the concentration in the parietal component if Gray & Bucher's work in dogs is applicable to man. The lowest recorded concentration that has come to light is 10 m.equiv./l. reported by Katsch, Baltzer & Brink (1934). This estimate is confirmed by the observations of Kozawa, Fukushima, Umeno, Kurihara, Takata & Horiuchi (1933). These authors investigated gastric content, not continuously aspirated gastric juice. If those of their samples in which the Cl^- concentration is less than 125 m.equiv./l. are excluded, since they were probably contaminated by extra-gastric fluids, the mean K content of the remaining samples is $12 \pm 0{\cdot}6$ m.equiv./l. If it be assumed that the value of p, the neutral chloride concentration in parietal secretion, can be equated with the minimal K concentration in gastric juice, then both these series of observations correspond to values of I in the region of 170 m.equiv./l. (See Table 2 for the relation between p and I.) It would seem then that if the isosmotic hypothesis is valid for man, the estimates for Ihre's group of subjects give approximately:

Isosmotic conc. of Cl^-	170	m.equiv./l.
Parietal H^+ concentration	160	,,
Parietal neutral Cl^- conc.	10	,,
Non-parietal neutral Cl^- conc.	125	,,
Non-parietal HCO_3^- conc.	45	,,

It is particularly suggestive that three different criteria, the maximum observed acid concentration, the maximum observed total Cl^- concentration and the minimum observed potassium concentration should all indicate approximately the same value of I. However, as will be shown later, this does not mean that the estimates of h, p, b and c are correspondingly closely determined.

Application to other groups of subjects

The group of Ihre's subjects providing the data used to test the theoretical relations developed here was a selected group of young male students. The quantitative deductions above concerning the composition of the components of human gastric juice may therefore not be of general application.

Some check on this can be made by using a transformation of the fundamental equation developed in this paper. If the concise form, equation (v), is divided through by V, we have

$$1 = k_1 A/V + k_2 N/V,$$

or

$$A/V = 1/k_1 - (k_2/k_1)(N/V), \qquad \text{(xviii)}$$

which is a linear relation between acid concentration and neutral chloride concentration, the parameters of which are functions of the composition of the component secretions. Both the slope and intercept of this line are functions of all four of h, p, b and c, so that both the slope and intercept should be altered by any appreciable variation in the composition of either parietal or non-parietal secretion. Thus a plot of A/V, i.e. concentration of acid, against N/V, i.e. concentration of neutral chloride, either for a group of subjects or for a group of observations on a single subject should provide a visual test of fit or divergence from the relation found here for Ihre's subjects.

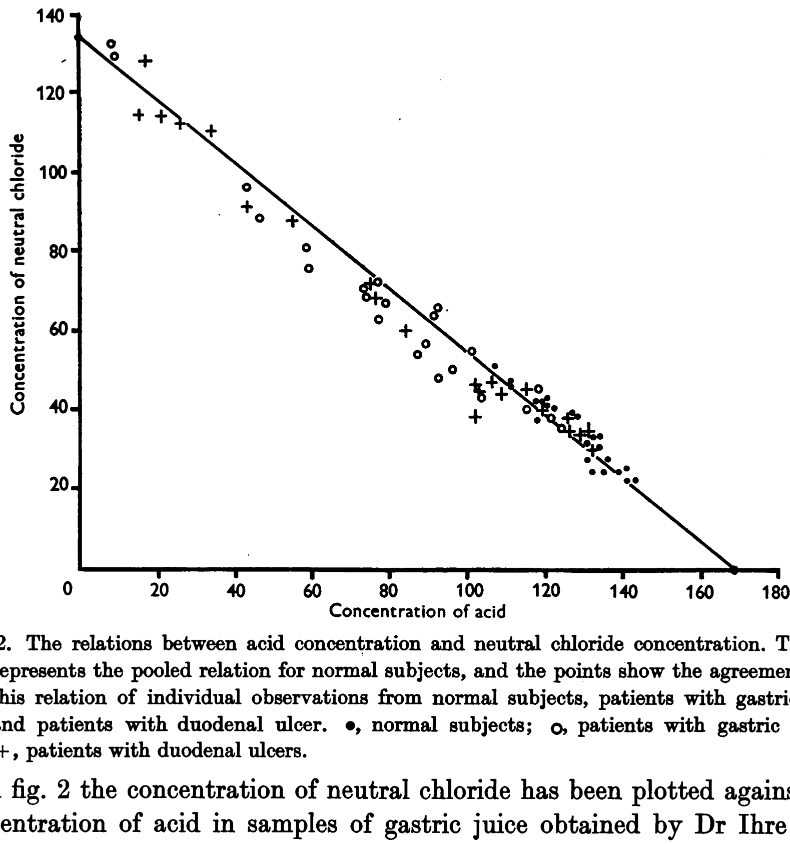

Fig. 2. The relations between acid concentration and neutral chloride concentration. The line represents the pooled relation for normal subjects, and the points show the agreement with this relation of individual observations from normal subjects, patients with gastric ulcer and patients with duodenal ulcer. •, normal subjects; o, patients with gastric ulcers; +, patients with duodenal ulcers.

In fig. 2 the concentration of neutral chloride has been plotted against the concentration of acid in samples of gastric juice obtained by Dr Ihre from twenty-four normal subjects, and forty patients with peptic ulcers, after stimulation with insulin. It may be seen that all the points fit well on to the line which was computed for normal subjects. This fit is all the more remarkable since the composition of the pathological juices differs widely from that of the normal juices, and since there is in the pathological group no selection of subjects by age or by copiousness of secretion. Thus the quantitative relationships set up for a selected group of normal young subjects are also true of patients with peptic ulcers with a mean age of 40.

This point has been investigated further and it has been shown that the best fit planes through the origin describing the (V, A, N) relations of Ihre's series of normal subjects, gastric ulcer patients and duodenal ulcer patients are statistically indistinguishable.

Thus the relationships described earlier would seem to be generally valid, not merely applicable to a selected group of young males. We may therefore suppose that all the observations from normal and peptic ulcer patients may be reclassified into those on histamine juice and those on insulin juice, and the two series of seventy observations may be used to test more rigorously for differences between secretions elicited by the two means. The (V, A, N) relations for these two series were computed, and the constants found to differ significantly from one another (Table 3). The values of h, p, b and c, corresponding to different

TABLE 3. Values of the constants obtained by fitting the equation $V=k_1A+k_2N$ to Ihre's (1938) observations on all subjects combined (normal males, patients with gastric ulcers and patients with duodenal ulcers)

	k_1	k_2
Histamine juice	$5{\cdot}44 \pm 0{\cdot}12$	$9{\cdot}12 \pm 0{\cdot}26$
Insulin juice	$5{\cdot}77 \pm 0{\cdot}08$	$7{\cdot}66 \pm 0{\cdot}16$
Differences	$0{\cdot}33 \pm 0{\cdot}128$	$1{\cdot}46 \pm 0{\cdot}307$

(Seventy observations in each series.)

TABLE 4. Estimates of concentrations of constituents of components of human gastric juice, corresponding to different values of I, based on the separate equations for histamine-excited and insulin-excited juice, the constants of which are given in Table 3. All concentrations in m.equiv./l.

	Histamine juices				Insulin juices			
I	h	p	b	c	h	p	b	c
164	134·8	29·2	91·0	73·0	136·0	28·0	44·4	119·6
166	139·8	26·2	94·4	71·6	144·2	21·8	47·0	119·0
168	144·7	23·3	97·7	70·3	152·3	15·7	49·7	118·3
170	149·7	20·3	101·1	68·9	160·4	9·6	52·3	117·7
172	154·6	17·4	104·4	67·6	168·5	3·5	55·0	117·0
174	159·6	14·4	107·8	66·2	(176·7)	(—)	(57·6)	(116·4)

values of I were, therefore, computed for these new equations and are given in Table 4. It will be seen that the estimates of composition of the parietal secretion (h and p) do not differ greatly for the two kinds of juice, but that the estimates of non-parietal composition (b and c) differ considerably. It is difficult to evaluate the errors of estimation of these quantities, but it seems that the standard errors of the estimates of h and p must be in the neighbourhood of ± 10 m.equiv./l., whilst the standard errors of the estimates of b and c are probably somewhat in excess of ± 5 m.equiv./l. Thus, the parietal component composition is probably not significantly different in the two instances, whereas the composition of the non-parietal secretions probably does depend significantly on the nature of the agent exciting secretion.

The second point to be tested with the larger number of observations is the validity of the equation $V=k_1A+k_2N$. Best-fit planes of the form $V=k_1A+k_2N+k_3$ were fitted to the pooled histamine observations and to the pooled insulin observations. The values of k_3 obtained were $-1{\cdot}70 \pm 1{\cdot}83$ and $+0{\cdot}07 \pm 2{\cdot}26$ respectively for the two series of seventy observations. Thus there is no conflict with the theoretical requirement of $k_3 = 0$.

Utility of the quantitative relations described

Although there seems to be ground for supposing that the theoretical relations set out in this paper describe adequately the relations between volume, total acidity, the neutral chloride content of gastric secretion, it appears that these relations will not, of themselves, yield estimates of the composition of parietal and non-parietal secretions. The further assumptions of (*a*) the isosmotic relation between the component secretions, and (*b*) of an arbitrary isosmotic concentration must first be made, and then the estimates of the composition of the component secretions prove to involve errors of estimation which are too great to leave to the estimates any appreciable physiological interest.

Having regard to the remarkable pains which Ihre took to collect pure gastric juice, this probably means that this type of study cannot yield useful information concerning the composition of the component secretions. He avoided contamination by swallowed saliva, by using a saliva-aspirator in the mouth, and by not beginning his experiments until the collecting tube had been in place for more than 1 hr., by which time the secretion of saliva had fallen to low levels. Contamination by duodenal contents was avoided by aspirating the duodenal contents. It is only when the gastric juice is collected with these precautions that the plot of concentration of acid against concentration of neutral chloride will give a line comparable with Ihre's. When the results are vitiated by salivary contamination the points would be expected to lie below the line for Ihre's data. Further, the significance of salivary contamination would be expected to be greater when the rate of secretion of gastric juice is low, which is tantamount to saying when the concentration of acid is low. In connexion with other work, histamine tests were performed by one of us (J.N.H.) on twenty-one normal subjects. Gastric juice was aspirated continuously in these tests, and there was effective salivary aspiration. However, the tests were begun shortly after passing the stomach tube and not after 1 hr. as in Ihre's experiments. No attempt at continuous duodenal aspiration was made. Fig. 3 shows the results of these tests plotted in the same way as in Fig. 2. It may be seen that the expected trend of the results away from the line for Ihre's normal subjects is shown in spite of continuous salivary aspiration from the mouths of these trained subjects.

The relation described has proved useful, however, in gastric emptying studies to estimate the total volume of secretion added to the gastric contents, and it may be used with a modicum of confidence to estimate the probable volume of a component secretion, given a reasonable reliable estimate of the isosmotic concentration, I. Referring back to equations (ii) and (iii), the expression for y, the volume of non-parietal secretion, may be combined with the equation (xvii), relating h, p, b and c to k_1, k_2 and I to yield the following expression

$$y = k_1\{(k_1 I - 1)/(k_2 I - 1)\}A + N.$$

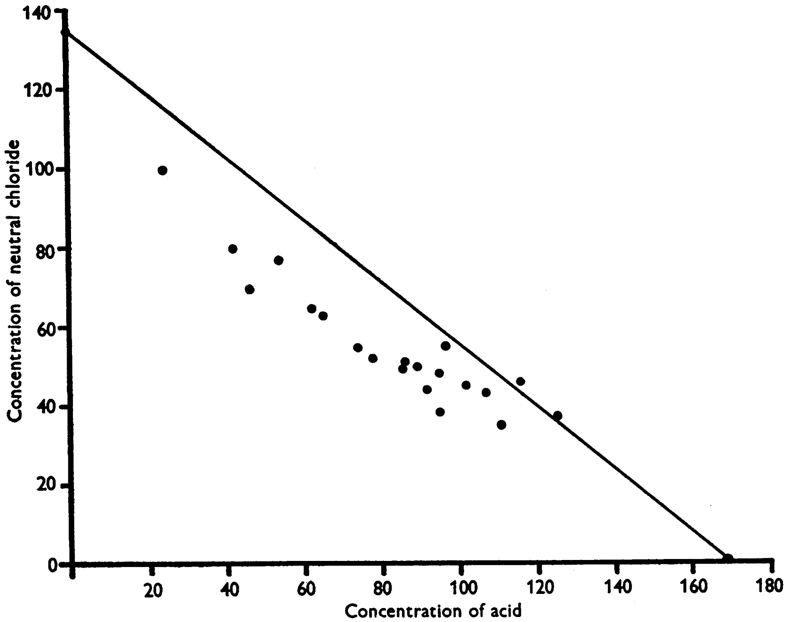

Fig. 3. The effect of omission of precautions on the relation between acid concentration and neutral chloride concentration. The points represent a series of observations by one of us (J.N.H.) on normal subjects stimulated with histamine. Salivary aspiration was used, but there was no duodenal suction and no waiting period before commencing collection of juice.

The estimate of y obtained is clearly dependent on the value of I assumed, but over the range of probable values of I this dependence is fairly small. Thus for $k_1 = 5{\cdot}44$, $k_2 = 9{\cdot}12$ (histamine juice) we have

$$y_{168} = 5{\cdot}44(N - 0{\cdot}162A), \quad y_{172} = 5{\cdot}44(N - 0{\cdot}113A).$$

That is, in this range, when A has a maximum value of around 30 m.equiv./hr., an error of 4 m.equiv./l. in the estimate of I will cause a maximum error in the estimation of y of about 8 ml./hr. Thus, if we take I as about 170 m.equiv./l., and write

$$y = 5{\cdot}44(N - 0{\cdot}14A),$$

then, for a sample of juice for which $A = 30$ and $N = 10$ m.equiv./hr., and $y = 31{\cdot}5$ ml., the error in the estimate of y due to inaccurate estimation of I is almost certainly within 10%. The absolute error similarly introduced into the estimation of the volume of parietal secretion will of course be the same, but the percentage error will be much smaller.

SUMMARY

1. The theoretical consequences of the assumption that the gastric juice is a mixture of two components of constant composition are developed.

2. It is shown that Ihre's (1938) extensive series of observations on human subjects fit the equations developed.

3. The relation of the equations developed to the various graphical methods for the determination of the composition of the component gastric secretions is demonstrated, and it is shown that an additional arbitrary assumption is involved in any such method.

4. Using the additional arbitrary assumptions: (*a*) that the component secretions have the same osmotic pressure, and (*b*) that the common cation concentration is 170 m.equiv./l., it is estimated that it is most probable that human 'parietal' secretion contains 160 m.equiv./l. of hydrion and 10 m.equiv./l. of neutral chloride.

5. It seems probable that the 'non-parietal' secretion elicited by histamine is of different composition from that elicited by insulin.

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