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SOME PROPERTIES OF AN ALIMENTARY OSMORECEPTOR MECHANISM

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The rate at which a test meal leaves the stomach is influenced by the volume of the meal and by its constituents. Fat and concentrated solutions of sugar, of acid and of salt slow gastric emptying (Shay, 1944). It has been shown that receptive areas mediating these effects lie in the duodenum and jejunum (Marbaix, 1898). It is possible that chemical stimuli may also influence gastric emptying by acting on receptors in the gastric mucosa, but the threshold of some of the duodenal receptors appears at this time to be lower than that of the hypothetical gastric receptors, which may thus have significance only in extreme situations (Keeton, 1925; Luckardt, Phillips & Carlson, 1919). In addition, there are probably cephalic receptors which influence gastric emptying. Because it is common experience that flavours may be nauseating, it may be supposed that the appreciation of the taste of a test meal can influence its rate of onward progress.

From studies in man there has grown up a general idea that solutions hyperosmotic relative to plasma, or hypertonic relative to the red cell, delay gastric emptying; the stomach has been represented as an organ which holds and dilutes hyperosmotic meals, so protecting the small intestine from this form of osmotic injury. For example, Apperly (1926) writes: 'the stomach retains its contents until a suitable osmotic pressure roughly isotonic with plasma is reached'. The results of Hunt, Macdonald & Spurrell (1951) did not support this idea of retention; serial test meal studies showed that even for solutions containing 200 g sucrose/l., which is considerably hyperosmotic relative to plasma, the maximal rate of emptying of the meal was early in the digestive period before gastric contributions had diluted the meal. Nevertheless, such high concentrations of sucrose did slow the process of gastric emptying at every stage.

Ideas concerning the influence of the constituents of test meals on gastric emptying in man have been based largely on fractional test meals and radiological studies. The fractional test meal gives information about the total time required for one particular constituent of the meal to leave the stomach, the 'emptying time'; but this is a somewhat insensitive index of the progress of gastric emptying, which is exponential during the greater part of its course (Marbaix, 1898; Salamanca & Picazo, 1943; Hunt & Spurrell, 1951; Hawkins, Margolin & Thompson, 1953; Thornton, Bean & Hodges, 1955). Radiological studies are more revealing but cannot be repeated frequently on the same subject, nor are the results easily expressed quantitatively.

As an alternative to these methods, single withdrawals of the total gastric contents at a fixed time after giving standard meals were made in students and in patients with peptic ulcer to study the influence on gastric emptying of varying the concentration of sucrose in test meals (Hunt, 1954). It was found that the volume of the gastric contents was greater at 30 min with test meals containing 35g sucrose/l. than it was with test meals containing no sucrose. Thus a test meal of distilled water emptied more quickly than one with an osmotic pressure roughly one-third that of plasma. A meal with a higher concentration of sucrose to give an osmotic pressure equal to that of plasma emptied even more slowly. In these experiments the stomach was clearly not shielding the intestine from osmotic stress as conceived at its simplest, for hypo-osmotic as well as hyperosmotic solutions might be considered to provide stress. As the simplest concept relating the osmotic pressure of test meals and gastric emptying did not provide an adequate explanation of the results in this instance, the present experiments were made to explore in a more general way the relationship between the concentration of some representative solutes in test meals and gastric emptying. By such experiments it was hoped to obtain information about the receptive mechanism involved.

METHODS

After washing out the stomach with 250 ml. of tap water at about 8 a.m. test meals of 750 ml. of distilled water at 37° C containing varying concentrations of solutes were given to fasting volunteer medical students. Salivary aspiration was usually maintained until 10–30 min later, when the gastric contents were recovered through a tube. In some instances phenol red was added to the test meal as a marker, and when this was done the stomach was washed out with tap water and the value for the volume of gastric contents represented by the phenol red so recovered was added to the volume of the gastric contents recovered directly. In the majority of experiments in which the test meal contained no phenol red, the stomach was washed out with 250 ml. of phenol red solution, and the residual volume was determined from the dilution of the dye. In some experiments the meals were given by stomach tube, the rate of inflow being about 750 ml./min; when this was done, the tube was left down until the gastric contents were recovered. In the other experiments it was withdrawn after the initial washout and re-inserted later. The methods used have been published (Hunt & Spurrell, 1951; Hunt, 1951).

RESULTS

The influence of phenol red on gastric emptying of swallowed test meals

As some of the experiments referred to in this paper were performed with solutions containing 60 mg phenol red/l. simply as a marker, it was first necessary to determine whether or not it significantly influenced emptying. In Table 1 are set out the results for twelve subjects of forty-eight experiments designed to examine this point. It may be seen that when the test meal contained no sucrose in six subjects out of seven the phenol red had an

TABLE 1. The influence of phenol red on the volume of the gastric contents after fixed periods for swallowed test meals

Subject	Composition of meal	Duration (min)	Mean volume of gastric contents (ml.) No phenol red A	Mean volume of gastric contents (ml.) Phenol red 60 mg/l. B	A − B
H.D.W.P.	Water	20	482 (4)	410 (1)	+72
P.A.R.	Water	20	328 (3)	340 (1)	−12
L.V.H.	Water	20	361 (3)	350 (1)	+11
J.N.H.	Water	20	302 (5)	272 (2)	+30
M.B.R.M.	Water	30	170 (1)	160 (1)	+10
I.D.G.	Water	30	184 (1)	165 (1)	+19
H.D.W.P.	Water	30	337 (2)	310 (1)	+27
J. L. McN.	35 g sucrose/l.	20	445 (1)	410 (1)	+35
M.J.R.	35 g sucrose/l.	20	350 (1)	385 (1)	−35
J.J.	35 g sucrose/l.	20	350 (1)	385 (1)	−35
A.G.	35 g sucrose/l.	20	423 (2)	445 (1)	−22
I.C.R.	35 g sucrose/l.	20	208 (2)	275 (1)	−67
H.D.W.P.	35 g sucrose/l.	20	435 (2)	380 (1)	+55
P.A.R.	35 g sucrose/l.	20	383 (2)	500 (1)	−117
J.N.H.	35 g sucrose/l.	20	340 (2)	370 (1)	−30

The concentration of phenol red was about 60 mg/l. Figures in parentheses give the number of results contributing to the means.

apparent slight hastening effect on emptying ($P = 0{\cdot}1$): on the other hand, in the presence of sucrose the phenol red apparently delayed emptying in six subjects out of eight ($P = 0{\cdot}2$). It may be concluded that phenol red probably had no material influence on gastric emptying under these conditions.

The influence of instilling meals into the stomach on gastric emptying

During the course of the experiments described in this paper meals were either swallowed in the ordinary way or given by stomach-tube in order to avoid stimulating 'precardial' receptors i.e. those between the lips and the cardia, with the solutes introduced into the test meals as deliberate variables.

It therefore seemed desirable to determine whether giving a bland meal by stomach-tube altered the subsequent gastric emptying as compared with the emptying of a similar meal swallowed in the ordinary way. It may be seen from Table 2, which shows the results of 103 experiments in 6 subjects, that test meals of water and salines left the stomach more rapidly when they were given by tube than when they were swallowed.

TABLE 2. The influence of instilling meals into the stomach on the volume of the gastric contents after fixed periods

Subject	Composition of meal	Duration (min)	Mean volume of gastric contents (ml.) Swallowed A	Down tube B	A − B
L.H.	Water	15	510 (2)	443 (6)	+67
H.D.W.P.	Water	15	658 (3)	584 (6)	+74
I.D.G.	Water	10	361 (3)	350 (5)	+11
M.B.R.M.	Water	10	554 (1)	473 (3)	+81
J.N.H.	Water	15	407 (3)	356 (5)	+51
L.V.H.	Water	15	498 (3)	466 (5)	+32
L.H.	NaCl 100 m-equiv/l.	15	280 (1)	206 (4)	+74
H.D.W.P.	NaCl 100 m-equiv/l.	15	475 (2)	422 (5)	+53
I.D.G.	NaCl 100 m-equiv/l.	10	120 (1)	87 (1)	+33
M.B.R.M.	NaCl 100 m-equiv/l.	10	330 (1)	256 (3)	+74
J.N.H.	NaCl 100 m-equiv/l.	15	244 (2)	229 (7)	+15
L.V.H.	NaCl 100 m-equiv/l.	15	272 (1)	211 (6)	+61
L.H.	NaCl 160 m-equiv/l.	15	268 (2)	296 (3)	−28
H.D.W.P.	NaCl 160 m-equiv/l.	15	512 (2)	493 (4)	+19
I.D.G.	NaCl 160 m-equiv/l.	10	154 (1)	121 (1)	+33
M.B.R.M.	NaCl 160 m-equiv/l.	10	531 (1)	353 (2)	+178
J.N.H.	NaCl 160 m-equiv/l.	15	320 (3)	274 (5)	+46

Figures in parentheses give the number of results contributing to the means.

The results of Tables 1 and 2 refer to the volume of the gastric contents, that is meal with secretion added. It is conceivable that the differences between volumes of gastric contents shown in the tables are really the result of alterations in secretion rather than in emptying. It would therefore have been apparently preferable to have based comparisons on the volumes of meal remaining in the stomach rather than on volumes of gastric contents. However, this has not been done because an occasional *increase* in the concentration of phenol red in a swallowed test meal whilst it was in the stomach has been observed, suggesting that some water may be absorbed from the gastric contents when they are hypo-osmotic relative to plasma. This has previously been reported by Penner, Hollander & Post (1940). The amount of marker remaining is therefore not always a completely reliable index of the volume of the original test meal which remains in the stomach when the meals are of a lower osmotic pressure than that of the plasma. If the larger volumes of the gastric contents when the meals were swallowed were the result of greater secretion in these circumstances, it would be expected that the gastric contents after swallowing the meal would be more acid than after giving the meal down the tube. Study of the concentrations of acid in the recovered gastric contents showed that the differences between the volumes of the recovered gastric contents could not be accounted for in this way, since there was virtually no difference between the means of the concentration of acid in the recovered gastric contents after meals given down the tube and after meals swallowed. Thus the data of Tables 1 and 2 may be interpreted in terms of gastric emptying.

The influence of sucrose on gastric emptying in experiments of 20 min duration

The data of Table 3 show that in eight subjects out of nine the volume of the gastric contents was greater 20 min after taking test meals containing 35 g sucrose/l. than it was after meals of distilled water. These data confirm similar earlier experiments in which the digestive period was 30 min (Hunt, 1954).

TABLE 3. The influence of sucrose on the volume of gastric contents 20 min after taking a 750 ml. test meal

Subject	Mean volume of gastric contents (ml.) Water A	Water + 35 g sucrose B	B − A
J.L.McN.	388	428	+40
M.J.R.	232	368	+136
J.J.	342	368	+26
A.G.	388	430	+42
I.C.R.	88	230	+142
H.D.W.P.	459	418	−41
P.A.R.	331	421	+90
L.V.H.	345	475	+130
J.N.H.	302	350	+48

The influence of sodium chloride on the gastric emptying of swallowed test meals

Eight subjects were given twenty-six meals of distilled water and twenty-six meals containing 100 m-equiv or 160 m-equiv NaCl/l. to swallow. The results are shown in Table 4. It may be seen that in every instance the volume of the gastric contents was less 20 min after a meal of saline containing 100 m-equiv NaCl/l. than it was after a meal of distilled water, or of saline containing 160 m-equiv NaCl/l. This finding was surprising since the solution containing 160 m-equiv NaCl/l. is nearly isotonic for red cells and might therefore be expected to offer a minimal osmotic stress to the intestinal mucosa. However, these meals were taken by mouth, and it is a fact that meals containing 160 m-equiv NaCl/l. are slightly unpalatable. It was therefore decided to determine the gastric response to such meals when they were given by stomach tube.

TABLE 4. The influence of sodium chloride in test meals on the volume of the gastric contents 20 min after taking a 750 ml. test meal by mouth

	Mean volumes of gastric contents (ml.)				
Subject	Water A	Water + 100 m-equiv NaCl/l. B	A - B	Water + 160 m-equiv NaCl/l. C	B - C
J.L.McN.	388 (2)	343 (3)	+45	—	—
M.J.R.	232 (2)	188 (2)	+44	260 (1)	-72
J.J.	342 (4)	210 (1)	+132	260 (2)	-50
A.G.	388 (3)	147 (2)	+241	275 (1)	-128
H.D.W.P.	482 (4)	450 (2)	+32	450 (1)	0
P.A.R.	328 (3)	300 (3)	+28	290 (1)	+10
L.V.H.	361 (3)	145 (2)	+116	180 (1)	-35
J.N.H.	302 (5)	142 (2)	+160	265 (2)	-123

Figures in parentheses give the number of results contributing to the means.

The influence of sodium chloride on the gastric emptying of instilled test meals

Table 5 shows the results obtained in 113 experiments on six subjects who received by tube test meals of distilled water and saline solutions containing 50, 100, 160, 250 or 350 m-equiv NaCl/l. In every subject the volume of the recovered gastric contents was least with meals containing 100 m-equiv NaCl/l.

In addition to the mean volumes of the gastric contents Table 5 shows the coefficients of variation $\left(\frac{\text{standard deviation} \times 100}{\text{mean}}\right)$, of the individual values about the means. It is apparent that the coefficients are in general considerably smaller for the meals of distilled water than they are for the saline meals. In one or other of his results for saline meals every subject shows at least a doubling of the coefficient of variation as compared with the meals of water. It is relevant to the experiments which follow to note that the differences in emptying rates between distilled water and meals containing solutes are apparent even when the duration of the test is only 10 min. Because meals swallowed and meals given by tube are similarly influenced by the addition of salt it appears that saline solutions exert their main effects via receptors distal to the cardia.

The influence of HCl *on gastric emptying*

The results of 102 tests to determine the influence on gastric emptying of 10 m-equiv HCl/l. of test meals are shown in Table 6. It may be seen that in tests lasting 20 min, when the meal was taken by mouth 10 m-equiv HCl/l.

was effective in slowing emptying in all eight subjects: whereas when a similar meal was given by tube three subjects did not show slowing of emptying as compared with water. A similar comparison of the emptying rates of water and dilute acid given by tube, in tests of slightly shorter duration but of greater number per subject, again failed to show that the addition of hydrochloric acid had any reliable influence in slowing emptying when the

TABLE 5. The influence of sodium chloride in test meals instilled into the stomach on the mean volume of the gastric contents after fixed periods

Subjects ...	L.H.	H.D.W.P.	I.D.G.	M.B.R.M.	J.N.H.	L.V.H.
Duration ...	15 min	15 min	10 min	10 min	15 min	15 min
Water						
Mean volume gastric contents (ml.)	443	584	350	473	356	466
Coeff. of variation (%)	11	8	16	11	14	21
S.E. of mean	±21	±17	±25	±31	±23	±44
No. of results	6	6	5	3	5	5
50 m-equiv NaCl/l.						
Mean volume gastric contents (ml.)	224	449	207	323	246	384
Coeff. of variation (%)	61	33	30	17	7	32
S.E. of mean	±80	±60	±43	±32	±8	±61
No. of results	3	6	2	3	5	4
100 m-equiv NaCl/l.						
Mean volume gastric contents (ml.)	206	422	87	256	229	211
Coeff. of variation (%)	37	13	—	27	36	13
S.E. of mean	±38	±24	—	±41	±31	±27
No. of results	4	5	1	3	7	6
160 m-equiv NaCl/l.						
Mean volume gastric contents (ml.)	296	493	121	353	274	268
Coeff. of variation (%)	11	13	—	35	31	49
S.E. of mean	±19	±33	—	±87	±38	±65
No. of results	3	4	1	2	5	4
250 m-equiv NaCl/l.						
Mean volume gastric contents (ml.)	340	554	172	—	419	530
No. of results	1	1	1	—	2	1
350 m-equiv NaCl/l.						
Mean volume gastric contents (ml.)	488	650	345	438	576	470
No. of results	1	2	1	2	2	1

subject was not allowed to taste the meal (which has a peculiarly unpleasant quality when 750 ml. are drunk). These results are significant in the light of the data of Table 5, which show that even the tests of 10 min duration are sufficiently long to allow differences in rates of emptying to show themselves. The data of Table 6 show that 10 m-equiv HCl/l. of test meal do not slow gastric emptying by stimulating 'postcardial' receptors. The data of Wilhelmj, Neigus & Hill (1933) for dogs show that solutions containing 20 m-equiv H^+/l. slow gastric emptying by stimulating receptors distal to the pylorus.

TABLE 6. The influence of 10 m-equiv hydrochloric acid/l. in test meals, swallowed and instilled, on the volume of the gastric contents after fixed periods

			Mean volume of gastric contents (ml.)			
Subject	Duration of test (min)	Method of ingestion	Water A	10 m-equiv HCl/l. B	A − B	S.E. of (A − B)
J.L. McN.	20	Swallowed	388 (2)	550	−162	—
M.J.R.	20	Swallowed	232 (2)	300 (1)	−68	—
J.J.	20	Swallowed	342 (4)	450 (1)	−108	—
A.G.	20	Swallowed	388 (3)	530 (1)	−142	—
I.C.R.	20	Swallowed	88 (2)	300 (1)	−212	—
H.D.W.P.	20	Swallowed	482 (4)	550 (1)	−68	—
L.V.H.	20	Swallowed	361 (3)	370 (1)	−9	—
J.N.H.	20	Swallowed	302 (5)	410 (1)	−108	—
J.L. McN.	20	Instilled	400 (1)	395 (2)	+5	—
M.J.R.	20	Instilled	118 (2)	200 (1)	−82	—
J.J.	20	Instilled	380 (2)	328 (2)	+52	—
A.G.	20	Instilled	390 (1)	418 (2)	−28	—
I.C.R.	20	Instilled	7 (1)	190 (2)	−183	—
H.D.W.P.	20	Instilled	375 (1)	540 (1)	−165	—
L.V.H.	20	Instilled	450 (1)	400 (1)	+50	—
J.N.H.	20	Instilled	283 (2)	400 (1)	−117	—
L.H.	15	Instilled	443 (6)	412 (3)	+31	±25
H.D.W.P.	15	Instilled	584 (6)	573 (2)	+11	±46
I.D.G.	10	Instilled	350 (5)	414 (3)	−64	±43
M.B.R.M.	10	Instilled	473 (3)	512 (2)	−39	±31
J.N.H.	15	Instilled	356 (5)	373 (4)	−17	+25
L.V.H.	15	Instilled	466 (5)	406 (2)	+60	±46

Figures in parentheses give the number of results contributing to the means.

A comparison of the influence on gastric emptying of sodium and potassium in test meals

Having found that test meals containing 100 m-equiv NaCl/l. emptied more rapidly than distilled water, it was natural to try to determine whether Na^+ or Cl^- was the important factor in this action. Table 7 shows the results of sixty-nine experiments on eleven subjects in which test meals containing 100 m-equiv of NaCl, $NaHCO_3$, Na_2SO_4, KCl, $KHCO_3$ or K_2SO_4 per litre were given by tube and recovered after 10 and 15 min. Inspection shows that the meals containing potassium salts emptied considerably more slowly than those containing sodium salts. However, the anions Cl^-, HCO_3^-, and SO_4^{2-} also had their effect. The solutions containing bicarbonate ions emptied more rapidly than those containing chloride ions. The mean decrease in the volume of the gastric contents produced by the change from chloride to bicarbonate was 27 % (S.E. of mean ±5·3) when the cation was sodium and 6·7 % (S.E. of mean ± 3·4) when the cation was potassium. This effect of the bicarbonate ion cannot be ascribed to the neutralization of the hydrogen ions produced by the stomach with the consequent abolition of the slowing action of H^+ acting from the duodenum. Reference to Table 6 will show that even 10 m-equiv H^+/l. of test meal had no consistent effect on gastric emptying when the meal was instilled down a tube. Since the acidity of the gastric contents in these subjects only rarely exceeded 10 m-equiv/l. at the end of the 15 min period of the test meal, the difference between the rates of emptying of the meals containing Cl^- and HCO_3^- must very probably be attributed to some direct action of these anions on the receptor mechanism. In addition, it may be seen from Table 7 that solutions containing 100 m-equiv Na_2SO_4/l. emptied more slowly than solutions containing 100 m-equiv NaCl/l., the mean increase in the volume of the gastric contents being 29% (S.E. of mean $\pm$ 7·4). The significance of this comparison is not as clear as that of the comparison of Cl^- and HCO_3^- since the divalency of the SO_4^{2-} imposes a change in the concentration of anion particles as compared with the NaCl control. However,

TABLE 7. The volume of the gastric contents 15 min after instilling into the stomach test meals of 750 ml. containing 100 m-equiv of various sodium and potassium salts/litre

	Mean volume of gastric contents (ml.)					
Subject	NaCl	$NaHCO_3$	Na_2SO_4	KCl	$KHCO_3$	K_2SO_4
J.A.M.	315 (2)	199 (2)	414	637 (2)	551 (2)	—
J.N.H.	175 (2)	127 (3)	291	611 (2)	558 (2)	—
P.J.W.	424 (2)	285 (2)	462 (2)	637	622	—
J.J.	398	277	466 (2)	577	557	—
I.D.G.*	146	102	—	—	—	—
M.B.R.M.*	—	232	400	627	—	—
E.S.K.	382	191	409	621	505	506
J.M.S.	147	164	293	628	661	652
B.W.J.	166 (2)	147	247	489	417	381
M.S.D.	370	259	461	484	536	630
G.G.W.	232	147	314	430	359	456

Figures in parentheses give the number of results contributing to the means.

* Indicates that the duration of the test was 10 min.

the relatively small effect of reducing the concentration of NaCl from 100 to 50 m-equiv/l., in the experiment the results of which are given in Table 5, suggests that the sulphate ion may have some action on the 'postcardial' receptor mechanism which regulates gastric emptying. It is to be expected that the ions which slow gastric emptying when added to test meals which already empty slowly will not show their action as convincingly as when they are added to meals which empty rapidly. It is therefore not surprising that the emptying of meals containing 100 m-equiv K_2SO_4/l. was not consistently slower than that of meals containing 100 m-equiv KCl/l., since the KCl meals themselves leave the stomach slowly. In general, these experiments show that at the concentrations of 100 m-equiv/l. the receptor mechanism readily distinguishes between Na^+ and K^+, and between HCO_3^- and Cl^-. It seems possible that the receptor mechanism distinguishes between Cl^- and SO_4^{2-}, but this point has not been rigidly tested.

The influence of variation of the concentration of sodium bicarbonate in instilled test meals on gastric emptying

Having in mind the relation between the concentration of NaCl and the rate of emptying shown in Table 5, it was decided to explore the relation between the rate of emptying and the concentration of $NaHCO_3$; in particular because 100 m-equiv/l. of this solute gave a higher rate of emptying than a corresponding solution of NaCl in the experiments, the results of which are shown in Table 7. It seemed, therefore, that the minimal operation of the receptor mechanism which slows gastric emptying might be obtained with $NaHCO_3$.

To determine the concentration which would give the most rapid emptying demanded that the concentrations of $NaHCO_3$ be varied by smaller steps than those used in the experiments reported in Table 5. In addition, the results shown in Table 5 lead to the expectation that the variation between the results of repetitions of the same experiment in each subject would be relatively large when the test meals contained concentrations of solutes giving rapid rates of emptying. These points made it desirable to attempt some form of synthesis of data obtained from a number of subjects so as to minimize the expected unreliability of the results of single experiments.

Because there is a considerable intersubject variation in the rate of emptying it is desirable to use different digestive periods for different subjects in order that a workable volume of gastric contents shall remain at the time of withdrawal. The results of the sixty-three experiments made in five subjects to examine the relationship between the concentration of $NaHCO_3$ and the rate of gastric emptying are shown in Fig. 1. In order to minimize the intersubject variation each experimentally determined volume of the gastric contents with solutions containing $NaHCO_3$ has been expressed as a percentage of the mean volume of water remaining in the stomach of each subject after the particular digestive period chosen for him. Close inspection of Fig. 1 shows that, in spite of this effort to minimize the intersubject variation, the results for different subjects do differ, and these differences cannot be wholly ascribed to some subjects having 10 min digestive periods whilst others have 15 min periods. It is clear that adding between 60 and 100 m-equiv of $NaHCO_3$/l. of meal reduced the volume of the gastric contents remaining by about 50% as compared with that remaining when water alone was given. It is also clear that solutions containing higher concentrations of $NaHCO_3$ than 100 m-equiv/l. emptied more slowly than those containing between 60 and 100 m-equiv/l., but even when the meal contained 200 m-equiv $NaHCO_3$/l. the emptying rate was still faster than that for water. Thus in general the relation between the concentration of $NaHCO_3$ in the meal and its rate of emptying is much the same as that for NaCl shown in Table 5.

The influence of urea in test meals on gastric emptying

The difference between the action of sodium and potassium on gastric emptying might depend upon the receptor mechanism being permeable to sodium but not to potassium. If this were so it might be expected that any particle to which the receptor cells were permeable would act similarly to sodium. This speculation led to experiments in which urea, a molecule which permeates most mammalian membranes readily, was added to the test meal.

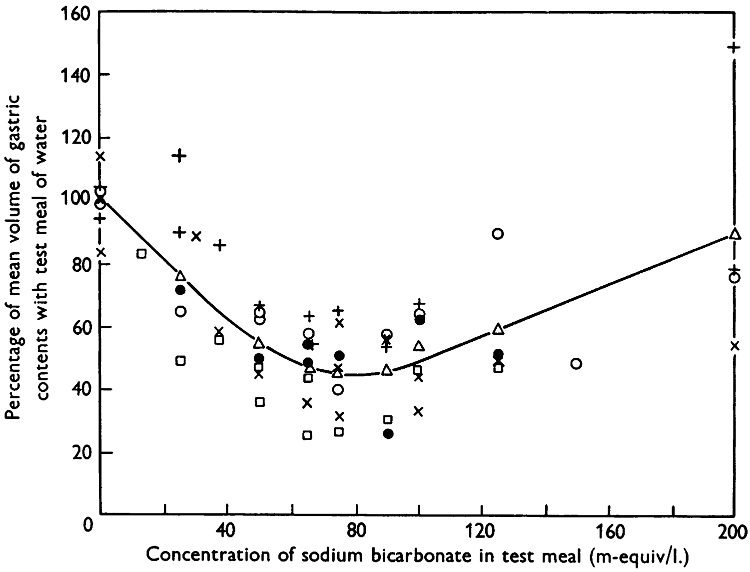

Fig. 1. The influence of the concentration of sodium bicarbonate in 750 ml. test meals on the volume of the gastric contents remaining after a fixed interval. ×, J.N.H. 10 min; ○, J.M.J. 15 min; ●, A.V. 10 min; +, R.J.S.M. 15 min; □, G.M.P. 15 min; △, mean.

Table 8 shows that the addition of varying amounts of urea to test meals taken by mouth did not systematically change the emptying of the test meal as compared with that of a meal of water. However, the experimental data given in Table 6 indicate that unpleasant flavours may activate 'pre-cardial' receptors which slow gastric emptying. The flavour of the meal containing urea was certainly unattractive to some of the subjects so that it might well have acted in this way. With this in mind the experiments were repeated with meals containing 12 g urea/l. of osmotic pressure comparable to 100 m-equiv NaCl/l, but given by stomach tube. It may be seen from the second part of Table 8 that the test meal containing urea when given down a tube emptied more rapidly than distilled water in all ten subjects.

TABLE 8. The influence of urea in test meals on the volume of the gastric contents after fixed periods

Subject	Time (min)	Volume of the gastric contents (ml.) Water A	6 g/l. B	A − B	12 g/l. C	A − C	20 g/l. D	A − D
Meals swallowed:								
J.N.H.	20	302	295 (2)	+7	303 (3)	−1	360 (1)	−57
J.L.McN.	20	388	—	—	370 (1)	+18	—	—
M.J.R.	20	232	—	—	270 (1)	−38	—	—
J.J.	20	342	—	—	360 (1)	−18	—	—
A.G.	20	388	—	—	350 (1)	+38	—	—
I.C.R.	20	88	—	—	105 (1)	−17	—	—
H.D.W.P.	20	482	400 (1)	+82	327 (3)	+155	400 (1)	+82
P.A.R.	20	328	270 (1)	+58	355 (2)	−27	330 (1)	−2
L.V.H.	20	361	375 (1)	−14	400 (1)	−39	310 (1)	+51
Meals down tube:								
L.H.	25	443	—	—	407 (1)	+36	—	—
H.D.W.P.	25	584	—	—	453 (1)	+131	—	—
I.D.G.	10	350	—	—	255 (1)	+95	—	—
J.N.H.	15	356	—	—	262 (1)	+94	—	—
L.V.H.	15	558	—	—	525 (1)	+33	—	—
J.M.J.	15	600	—	—	394 (1)	+206	—	—
J.C.B.	15	505	—	—	483 (1)	+22	—	—
E.S.K.	15	347	—	—	342 (1)	+5	—	—
C.J.R.	15	189	—	—	135 (1)	+54	—	—
G.G.W.	15	194	—	—	127 (1)	+64	—	—

The influence on gastric emptying of sorbitol in test meals

Having found that test meals containing urea left the stomach more rapidly than those of distilled water, another non-ionized solute which possibly diffuses into cells was tested for its effect on gastric emptying. Sorbitol (suggested by Dr R. B. Fisher) was added to test meals given to four subjects. The results, expressed in the same manner as those of Fig. 1, are shown in Fig. 2. It is clear from these data that if sorbitol at concentrations of 5–10 g/l. has any effect at all in accelerating gastric emptying it is very small and not likely to be revealed by any reasonable number of repetitions of the experiments whose results are shown in Fig. 2.

However, a detailed test of the hypothesis that test meals containing 10 g sorbitol/l. leave the stomach more rapidly than those of distilled water has been made in a single subject who was remarkable at this time for the consistent behaviour of his stomach. Experiments were made on successive days, the sorbitol being included in the meal on alternate days. The data are set out in Table 9 in the order in which they were obtained. The volume of the gastric contents for meals containing sorbitol has been subtracted from the volume of the gastric contents of the previous day with the test meal of water. It appears from this experiment that meals containing 10 g sorbitol/l. of meal empty more rapidly than meals of distilled water ($P = 0{\cdot}001$).

A comparison of the effect of change of concentration of sodium bicarbonate, of sodium chloride and of urea upon gastric emptying of instilled test meals

Having established in a general way the relation between the rate of gastric emptying and the concentration of some solutes in test meals it was decided to make a more detailed study of the effects on the rate of emptying of the various solutes at different concentrations. Because of the large number of experiments required, this investigation has been made in one subject only with meals of one duration only. Nevertheless, a consideration of the data in Tables 1–8 suggests that differences between subjects are quantitative

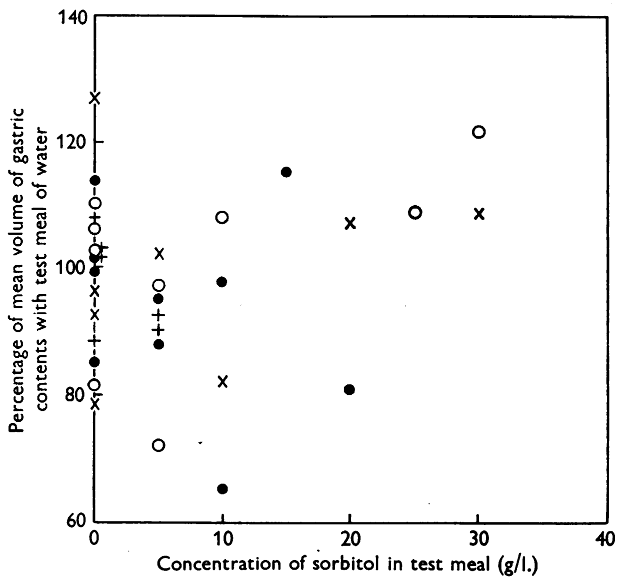

Fig. 2. The influence of the concentration of sorbitol in 750 ml. test meals on the volume of the gastric contents remaining after a fixed interval. ×, J.N.H. 10 min; ○, J.M.J. 15 min; ●, A.V. 10 min; +, R.J.S.M. 15 min.

TABLE 9. The influence of 10 g sorbitol/l. of test meal on the volume of the gastric contents remaining after 20 min

Subject H.D.W.P.

Volume of gastric contents (ml.) Water A	Water + 10 g sorbitol/l. B	A − B
441	364	77
411	367	44
493	434	59
422	371	51
	Mean	58
	S.E. mean ±	7·1

rather than qualitative so that generalizations from a single subject may be acceptable for the moment.

The results of twenty-three experiments with urea, twenty-nine experiments with sodium bicarbonate and twenty experiments with sodium chloride are set out in Figs. 3–5. The general relationship between concentration of the solute and its influence on emptying is similar in the three

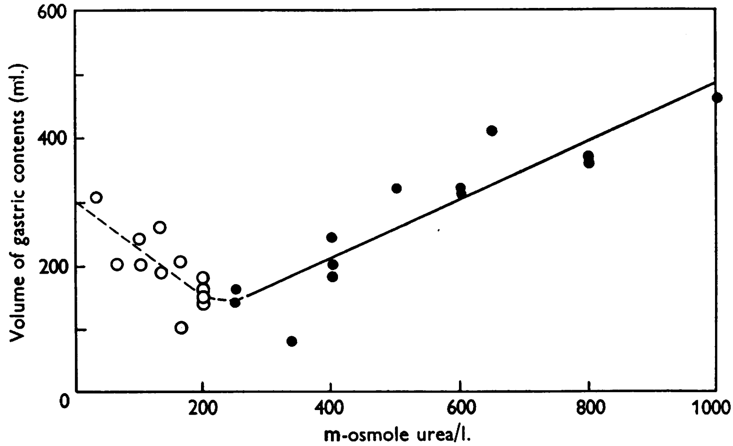

Fig. 3. The influence of the concentration of urea on the volume of the gastric contents 20 min after taking a 750 ml. test meal. Subject J.N.H. The solid line is fitted statistically to the solid points. The broken line is fitted by eye to the open circles.

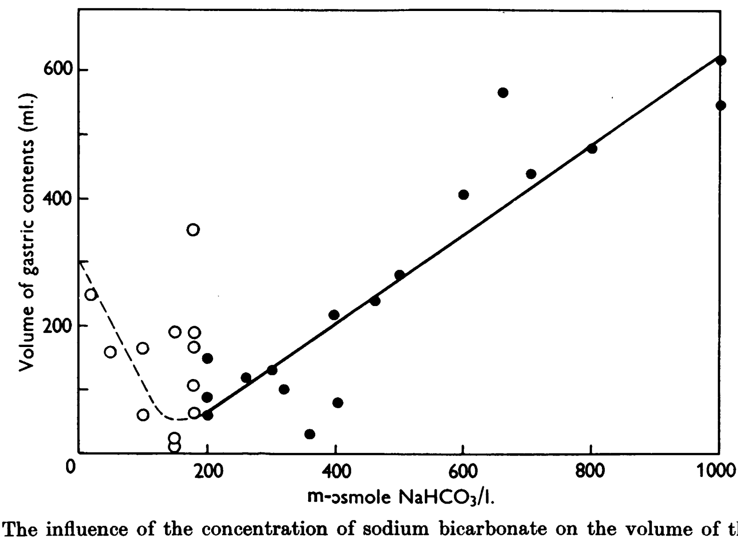

Fig. 4. The influence of the concentration of sodium bicarbonate on the volume of the gastric contents 20 min after taking a 750 ml. test meal. Subject J.N.H. The solid line is fitted statistically to the solid points. The broken line is fitted by eye to the open circles.

figures in that there is a maximal rate of emptying at a concentration of about 200 m-osmole/l., whilst at higher concentrations the rate of emptying is slowed. A more detailed examination of these data is given in the discussion.

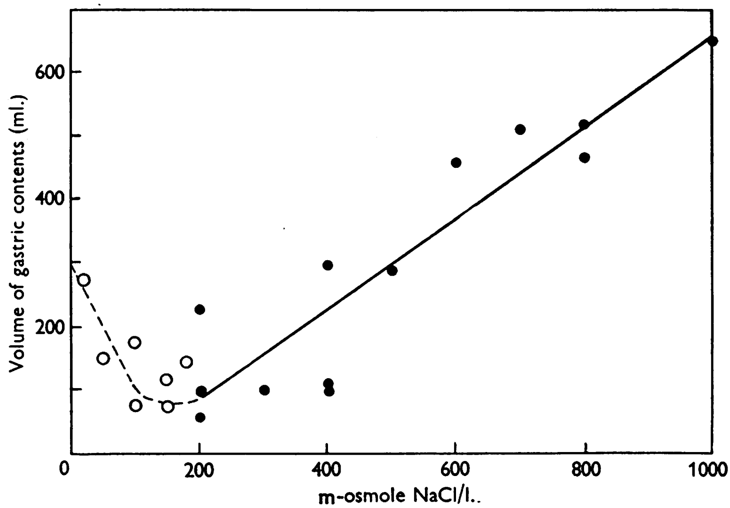

Fig. 5. The influence of the concentration of sodium chloride on the volume of the gastric contents 20 min after taking a 750 ml. test meal. Subject J.N.H. The solid line is fitted statistically to the solid points. The broken line is fitted by eye to the open circles.

A comparison of the effects on gastric emptying of various concentrations of potassium chloride, of sorbitol and of glucose in test meals

To extend the investigation of solutes which mainly retard gastric emptying as compared with that of distilled water, experiments were made with meals containing potassium chloride as a typical ionized solute, glucose, a sugar particularly likely to suffer active transport, and sorbitol, an alcohol with a molecular weight almost equal to glucose and unlikely to be metabolized in the body. Inspection of the data presented in Figs. 6–8 shows that at the lower concentrations of these solutes, expressed in m-osmole/l., they are about equipotent in slowing gastric emptying but that at 500 m-osmole/l. potassium chloride appears to be consistently more potent than glucose and sorbitol.

DISCUSSION

The technique

Giving a meal of fixed volume containing varying concentrations of a solute and aspirating the gastric contents after a fixed interval is a very simple method of studying gastric emptying, but some precautions are probably necessary to obtain reliable results. The stomach should be washed out before

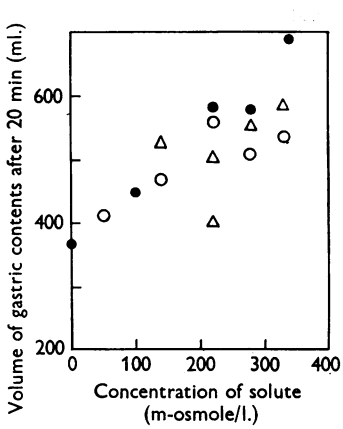

Fig. 6

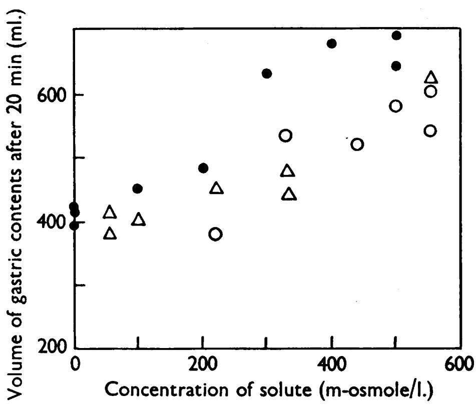

Fig. 7

Fig. 6. The influence of the concentration of glucose, sorbitol and potassium chloride in test meals on the volume of the gastric contents 20 min after taking a 750 ml. test meal. Subject H.D.W.P. ○, Glucose; △, sorbitol; ●, KCl.

Fig. 7. The influence of the concentration of glucose, sorbitol and potassium chloride in test meals on the volume of the gastric contents 15 min after taking a 750 ml. test meal. Subject M.B.R.M. ○, Glucose; △, sorbitol; ●, KCl.

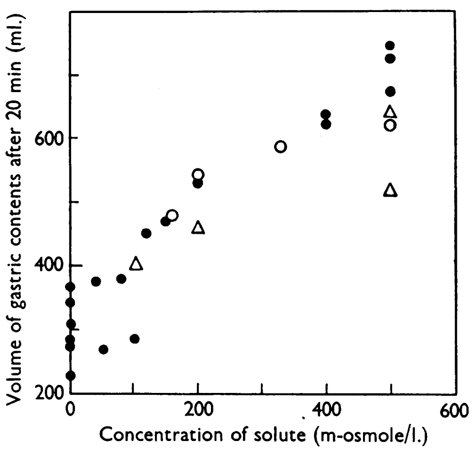

Fig. 8. The influence of the concentration of glucose, sorbitol and potassium chloride in test meals on the volume of the gastric contents 20 min after taking a 750 ml. test meal. Subject J.N.H. ○, Glucose; △, sorbitol; ●, KCl.

giving the meal so that variations in the amount of resting secretion mixing with the meal are minimized. When the flavour of the meal is unpleasant the meal should be given down a tube and the tube should not be withdrawn if the unpleasant flavour is strong. The more the emptying is slowed by the addition of solutes the more reproducible do the results become. There are probably a number of other factors which influence the results, but their effect can be minimized by practising a very strict routine from day to day and by using a large volume of test meal.

The effect of instilling the meal into the stomach

Whether the meal is water or saline, instilling the meal down a tube results in faster gastric emptying as compared with a meal swallowed in the ordinary way. This effect may be attributable to the shorter duration of inflow of instilled meals into the stomach, 1 min as compared with about 2 min, or it may be the result of the abolition of the receptive relaxation of the stomach (Cannon & Lieb, 1911), which follows a swallow and persists whilst swallowing continues. The majority of subjects take about 2 min to drink 750 ml., and it is possible that a reduction in intragastric pressure for this period is sufficient to account for the small reduction of the rate of emptying for the swallowed meal as compared with the instilled meal. However, the effect is a small one and does not give reason to doubt that mechanisms discovered by experiments with instilled meals will also operate with meals swallowed in the ordinary way. The need to instil meals of unpleasant flavour if 'postcardial' receptors are to be investigated is clearly shown by the experimental data of Table 6. The marked slowing effect of stimulation of 'precardial' receptors by 10 m-equiv HCl/l. of test meal was entirely abolished by instilling the meal down a tube. In this series of experiments the slowing of emptying by 'precardial' receptors was an important finding, because such stimulation presumably accounted for the variability of the results in the first experiments with urea.

The properties of the osmoreceptor mechanism

As the concentration of potassium chloride or glucose in an instilled test meal of water is raised from zero, the rate of emptying of the meal from the stomach becomes progressively slower. On the other hand, as the concentration of sodium bicarbonate or urea in a test meal is raised, the rate of emptying of the meal increases at first but becomes progressively slower after a certain concentration is surpassed. Fig. 9, which extends this statement, gives a quantitative synopsis of all the data of this study. It is actually based on data drawn from Figs. 3–5 and 8, and refers only to one subject, but it is substantiated by qualitatively similar data given in the tables for many other subjects. The small distinction between the values for the minimal volumes of gastric contents remaining for meals containing sodium chloride and sodium bicarbonate is supported by the data of Table 7 based on ten subjects. The distinction between the values of the minimal volumes of the gastric contents with meals containing sodium salts and urea is sufficiently clear from a comparison of Figs. 3–5. The slopes of the lines in Fig. 9 for meals containing sorbitol, glucose and potassium chloride are based on the data of Fig. 8.

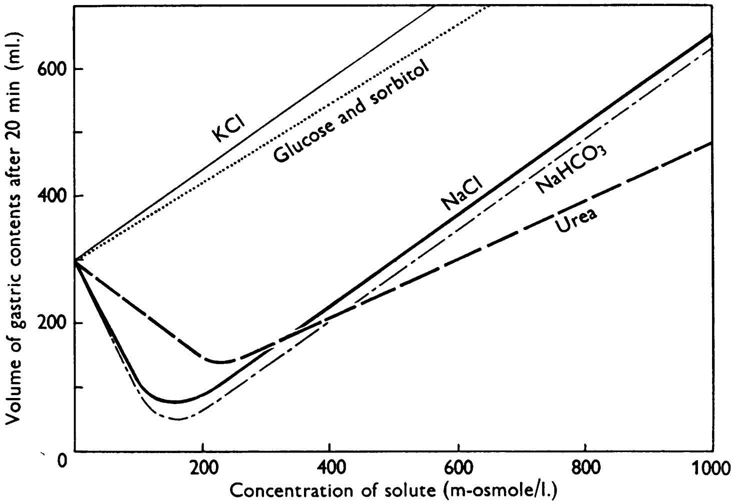

Fig. 9. The influence of the concentration of several solutes in test meals on the volume of the gastric contents 20 min after taking a 750 ml. test meal. Subject J.N.H.

TABLE 10. The equations of the lines shown in Fig. 9 relating the volumes of the gastric contents 20 min after taking a 750 ml. test meal containing varying concentrations of solutes and the concentrations of NaCl, $NaHCO_3$, KCl and urea (m-osmole/l.) in the meals.

$$x = a + by,$$

where x = volume of gastric contents (ml.), y = concentration of solute (m-osmole/l.)

Solute	a	b	S.E. of b	m
NaCl	−52	0·706	±0·090	200
$NaHCO_3$	−78	0·707	±0·075	200
KCl	+308	0·848	±0·068	0
Urea	+27	0·454	±0·058	250

m = minimal concentration of solute to which the equations relate.

Finally, inspection of the data set out in Table 10 leaves no reasonable doubt that the lines relating volume of gastric contents at a fixed time and the concentration of the solute for meals containing potassium chloride at concentrations 0–500 m-osmole/l. and sodium chloride and sodium bicarbonate at 300–1000 m-osmole/l. are virtually parallel, in contra-distinction to the comparable line for meals containing urea, which differs from the others in that its slope is less. Some of the facts expressed in Fig. 9 are not new, in particular those relating to sodium chloride, sodium bicarbonate and glucose which confirm in more detail the findings of Apperly (1926), Shay (1944) and van Liere & Sleeth (1940). However, the increased detail provided by these new experiments makes it worth while to attempt to account for the facts by a hypothesis.

A hypothesis to account for the properties of the alimentary osmoreceptor mechanism

Although the characteristics of the alimentary mechanism revealed by the present experiments may depend upon the activity of more than one kind of receptor, as does a qualitatively similar mechanism in the tongue of the cat (Liljestrand & Zotterman, 1954), it is possible to explain the results on the assumption that only one type of receptor is involved. This receptor is assumed to have the sole function of slowing gastric emptying so that maximal rate of emptying corresponds to minimal receptor activity. The degree of stimulation of the osmoreceptor is postulated to be a function of the amount of work done by the mechanism in separating from the luminal contents a fixed volume of a solution of constant osmotic concentration, possibly equal to that of plasma. The actual detection of the work might depend upon the accumulation of some metabolite or, alternatively, on distortion of the receptor resulting from the inadequacy of a fixed amount of available work to maintain constant the spatial relationships of the receptor. The receptor mechanism is assumed to be drawing water and solutes from solutions corresponding to those which were instilled into the stomach. This is not the real state of affairs since the stomach and the duodenum add their secretions to the test meals, but by considering only the results of meals of large volume and short duration the influence of the added secretions is minimized.

If the osmoreceptor mechanism is to secrete a solution of constant osmotic pressure it requires water and solute from the intestine. The supply of solute will be limited by making available either no solute or only those to which the mechanism is postulated to be virtually impermeable, e.g. KCl, and to a less extent glucose and sorbitol. But an increase in the concentration of any solute in the intestinal lumen will correspondingly lower the effective concentration of water, thus increasing the work of obtaining water. Thus the slope of the line relating the volume of the gastric contents and the concentration of KCl in Fig. 9 is assumed to represent, as a first approximation, the relation between work of obtaining water as the concentration of water is lowered by increasing concentrations of KCl and the inhibitory effect on gastric emptying.

For solutions containing solutes to which the osmoreceptor is assumed to be permeable to varying degrees, such as NaCl, $NaHCO_3$ and urea, the greater the concentration of solute the less the work of obtaining it from the solution. On the other hand, even increasing the concentration of a solute which penetrates the receptor will also correspondingly lower the ambient concentration of water, thus increasing the work of obtaining water. The concentration of urea which gives the maximal rate of emptying as shown in Fig. 9 presumably corresponds to a compromise between the concentration for minimal work in obtaining solute at high concentrations of solute and the concentration for minimal work in obtaining water at zero concentrations of solute. It is noteworthy that once the concentration corresponding to minimal inhibition is passed the slope of the line for urea in Fig. 9 is significantly less than that for potassium chloride. The smaller slope for urea can be accounted for by supposing that up to 1 molar the diffusion of urea is a function of its concentration, so that the difference between the slope of the line for solutions containing non-penetrating solutes such as potassium chloride and that for solutions containing penetrating solutes such as urea corresponds to the reduced amount of work of obtaining urea as the concentration rises.

The lines relating strength of KCl, of NaCl and of $NaHCO_3$ solutions at concentrations greater than 300 m-osmole/l. to the volume of the gastric contents after a fixed period are virtually parallel to each other. Thus above a concentration of 300 m-osmole/l. the osmoreceptor behaves towards NaCl as it does towards KCl, which has been postulated not to penetrate the receptor. This discrepancy in the hypothesis could be overcome if it were supposed that sodium is subject to facilitated transfer with an upper limit to the amount which can be transferred. Once maximal transfer has been achieved the mechanism behaves towards increasing concentrations of NaCl as it does towards increasing concentrations of any particles to which it is impermeable.

There remain a few minor points to be considered. The receptor mechanism seems to accept both ionized and un-ionized particles since sodium and urea reduce the retarding effect of distilled water. This property is not confined to urea but has been shown for sorbitol in one subject and for glycerol in another (unpublished). This lack of chemical discrimination justifies the use of the term osmoreception.

It has been postulated that the receptor is completely impermeable to potassium, but it has been noted that solutions of $KHCO_3$ empty more rapidly than solutions of KCl. It would be difficult to explain how the substitution of bicarbonate ions for chloride ions could reduce the work of obtaining this solute since the potassium is postulated not to penetrate. However, the alimentary luminal contents must presumably contain some sodium added in the stomach and duodenum so that the inward migration of the bicarbonate ion might occur in electrical equilibrium with sodium ion. This would be in accord with the finding that the bicarbonate ion present in test meals as $KHCO_3$ was much less effective in reducing the inhibition of emptying than bicarbonate ion as $NaHCO_3$.

The upper limit in the gut of the osmoreceptor mechanism can be inferred from the observations of Shay & Gershon-Cohen (1934) that radio-opaque hyperosmotic meals penetrating no further than the duodenal bulb completely inhibited gastric peristalsis and stopped emptying. It would seem from experience with test meals containing sorbitol and glucose that the actual volume in the intestine may have little influence on gastric emptying in the presence of hyperosmotic solutions, for glucose has never purged whereas hyperosmotic solutions of sorbitol, which presumably reduce the absorption of water, usually purge vigorously, yet both solutions are equally effective in delaying emptying. Solutions of NaCl and of $NaHCO_3$ at concentrations which give minimal inhibition of emptying, and at higher concentrations, frequently purge in those subjects whose stomachs empty rapidly.

This tentative hypothesis appears to account for the experimental findings and at the same time it is open to several further tests. For example, it would be expected that if the movement of water were restricted by adding sugar to the meal, the concentration of penetrating solute which would give minimal inhibition would be less than that required in the absence of limitation of water movement by non-penetrating solute. This expectation has been satisfied in a number of experiments in several subjects, but the effect is small and the relation between the concentration of penetrating solute giving minimal inhibition and the concentration of the non-penetrating solute has not been established fully. When these data are available, it might be possible to state the hypothesis in quantitative terms.

SUMMARY

1. Studies of gastric emptying in man were made by giving 750 ml. test meals and determining the volume of the gastric contents after fixed intervals.

2. Phenol red (60 mg/l.) added as a marker to test meals had no material effect on gastric emptying.

3. Bland test meals instilled into the stomach through a tube emptied more rapidly than similar meals swallowed in the ordinary way.

4. Sucrose (35 g/l.) slowed the gastric emptying of test meals of water.

5. As the concentration of NaCl in swallowed and instilled test meals was increased from zero to 100 m-equiv/l. the rate of emptying of the test meal increased. Increasing the concentration of NaCl from 160 to 350 m-equiv/l. progressively slowed emptying. The results with salines containing 100 m-equiv NaCl/l. were more variable than those with test meals of distilled water.

6. 'Precardial' receptors responded to 10 m-equiv HCl/l. of test meal by slowing gastric emptying, but this concentration of acid in test meals had no action on gastric emptying when the test meal did not come into contact with 'precardial' receptors.

7. As the concentration of potassium chloride or glucose in an instilled

test meal of water was progressively raised from zero the rate of emptying of the meal from the stomach became progressively slower. On the other hand, as the concentration of sodium bicarbonate, of sodium chloride and of urea was raised, the rate of emptying of an instilled meal increased at first but became progressively slower after certain concentrations were surpassed.

8. The most prominent effect of increasing the concentration of sorbitol in test meals was to slow gastric emptying as the concentration was raised: but in one subject test meals containing 10 g sorbitol/l. emptied more rapidly than test meals of distilled water.

9. A hypothesis to explain these results in terms of a simple osmoreceptor is outlined.

It is a pleasure to acknowledge my debt to the many students who acted as the subjects for this study, to Mr V. Bennett who did much of the technical work, to Prof. W. R. Spurrell for his criticism, and to the Worshipful Society of Apothecaries who defrayed part of the expenses of the investigation under the terms of the Gillson Scholarship.

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