The Composition and Mechanism of Formation of Gastric Acid Secretion

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ONE OF THE MOST IMPORTANT PROBLEMS confronting the clinical physiologist today is how the stomach makes its hydrochloric acid. Nowhere else in the body does a physiological fluid regularly attain a pH less than 3.0, let alone a value between 0.8 and 0.9 of a pH unit. Formation of such a solution requires the liberation of a strong acid, at concentration of about 0.17 N. This process has always fascinated me because of the simplicity of the chemical entity involved, but my interest in the problem derives from utilitarian clinical considerations as well.

Some fifteen years ago, Dr. Alvarez of the Mayo Clinic said that the unequivocal cure of gastrointestinal ulceration awaits a medical procedure based on the complete elimination of acid formation in the stomach, and in order to attain this it is necessary that we learn how to "throw a monkey wrench" into the machinery of the acid-forming cells. This in turn requires an understanding of the cellular mechanism itself, and it is this fundamental cytological process that I am about to discuss—not because I am prepared to offer a monkey wrench for clinical purposes, but because I think we have already gained considerable insight into the machinery we aim to disrupt.

The first suggestion regarding the chemical reaction by which acid is formed in the gastric mucosa was offered by Maly (*24*) in 1877—more than fifty years after Prout (*26*) reported his proof that this acid is HCl. Maly believed that a double decomposition takes place between NaCl and primary sodium phosphate, but he did not state how the two products of the reaction were separated and a reversal of this double decomposition prevented. To compensate for this deficiency, Bergeim (*1*) in 1914 suggested that the NaCl be viewed as reacting with the corresponding calcium acid phosphate, since the resulting secondary phosphate of calcium will precipitate out of solution. Even this mechanism will not bear too close a scrutiny, however. Then, twenty-five years after Maly, Bunge (*3*) suggested that carbonic acid, rather than the H_2PO_4 radical, might be the source of the acidic hydrogen. This possibility remained dormant until 1939, when Davenport (*5*) discovered that the carbonic anhydrase activity of gastric mucosa is enormous—as in the erythrocyte. As a result of this observation, he and Fisher (*7*) revived the Bunge theory and proposed that the entire reaction might be speeded up under the influence of this enzyme—an idea which received considerable support from other investigators. However, quantitative evidence concerning the relative inhibitory actions of thiocyanate ion, sulfanilamide, and thiophene-2-sulfonamide on carbonic anhydrase activity and on the production of gastric HCl *in vivo* proved to be inconsistent with the theory, and in 1946 Davenport was led to retract his hypothesis (*6*)[1]. Instead of H_2CO_3, a number of insoluble weak organic acids have been proposed from time to time as the interactant which liberates HCl from NaCl. These include edestin or some other protein—as suggested by Robertson (*28*) in 1924 on the basis of some very early work of Osborne's; a "lecithalbumin" found in hog mucosa by Rassers (*27*) in 1928; and certain undefined substances which give rise to a phase boundary phenomenon propounded by Clowes (*4*) in 1916, and by Beutner and Caplan (*2*) in 1932.

Many writers have supported a physicochemical reaction based on the Doman equilibrium, but—as I pointed out some years ago (*19*)—this hypothesis demands an impossibly high chloride ion concentration of 7 million molar in the parietal cytoplasm. There is also a process described by A. P. Mathews (*25*) in 1925, whereby intracellular deamination results in the secretion of NH_4Cl by the parietal cell; the salt then undergoes hydrolysis in the neck of the gland, with reabsorption of NH_4OH as ammonia and consequent liberation of HCl into the lumen of the stomach. Our interest in this hypothesis has recently been revived by the excellent work of D. Glick (*8*), wherein he has demonstrated a correlation between the urease activity of minute specimens of the mucosa from successive levels of the gastric gland and the density of parietal cells at these different levels. Since urease is effective in producing ammonia from

[1] In spite of this retraction, the essence of the carbonic anhydrase theory has been retained by several subsequent investigators, e.g.: DAVIES, R. E. and EDELMAN, J. *Biochem. J.*, 1948, **43**, lvii. PATTERSON, W. B. and STETTEN, DEW., JR. *Science*, 1949, **109**, 256.

urea, Glick is now justified in pursuing the hypothesis that this enzyme is an integral part of the intracellular acid-producing mechanism by a process of the kind suggested by Mathews. As another variant of this theory, Hanke (*10*) suggested the cellular extrusion of an organic chloride with a chloroesterase which hydrolyzes the chloride to HCl and a reabsorbable alcohol. Hanke was never able to find such an enzyme in the gastric mucosa and ultimately retracted this hypothesis (*11*).

And finally there is a physicochemical mechanism based on a membrane hydrolysis of NaCl which I proposed some years ago (*12, 19*), and by means of which I attempted to cope with certain aspects of the problem neglected by these other investigators. Before I describe this system, however, I want to tell you some of the accumulated experimental evidence on which this hypothesis now rests.

As one reexamines the various hypotheses concerning acid production by the parietal cell, it becomes evident that they all suffer from two major deficiencies: (1) no physicochemical mechanism is offered to explain how the HCl can be removed from the interior of the cell, which contains buffered cytoplasm at a pH, presumably, in the neighborhood of 7.4; and (2) the presence or absence of other chemical constituents of the parietal secretion is completely neglected. These two considerations are closely interdependent, and in order to include them in any explanation of parietal cell activity it is essential that we know the chemical composition of the pure parietal secretion as it emerges from the cell. To determine this directly in the mammal, by a micropipetting technique like that employed in studying the kidney tubule, is impossible because the inner diameter of the gastric tubule is usually less than 10 microns. Orogastric intubation of unoperated men or dogs is obviously of no avail, because the gastric juice so collected is always contaminated with saliva and the mixed buffer-containing secretions which are regularly regurgitated from the duodenum. Even the gastric juice derived from a Pavlov or other type of gastric pouch, though uncontaminated by these extragastric secretions, is a mixture of several different secretions from the diverse glandular elements of the stomach mucosa itself. In addition to the acid parietal secretion, this mixture comprises: the alkaline mucus from the columnar cells on or near the surface of the mucosa; another alkaline fluid, designated mucoid or dilution secretion, which may originate in the neck chief cells; and finally pepsin secretion from the zymogen or body chief cells. Thus, it is patently impossible to collect pure parietal secretion even from an isolated stomach pouch, not to speak of the intact viscus itself.

And so it became necessary for us to attack the problem indirectly, by studying how the quantitative composition of gastric juice varies with changes in certain pertinent physiological conditions. To describe our experimental procedures very briefly, we prepare our Pavlov pouches in the usual manner from the gastric corpus, as depicted by the original Pavlov diagrams. The Heidenhain pouch is similar to this, except that it is entirely separated from the main stomach and therefore completely deprived of its vagal innervation, whereas the Pavlov pouch continues to receive some of its original vagal innervation through the isthmus.

In the course of our own work (*22*), we discovered that Pavlov and his students had an entirely erroneous idea of the distribution of the gastric vagi in the dog. They believed that only the anterior gastric vagus runs along the lesser curvature, as in man, but that the posterior trunk courses along the greater curvature. Actually, dog and man are alike in that the two trunks run parallel along the lesser curvature. Consequently, in preparing the usual Pavlov pouch, most of the branches of these nerves are cut across and only a small fraction of the preoperative innervation to the mucosa of the pouch area is retained—instead of the full supply as had been generally believed for many years before. As a result, we devised a different type of accessory stomach which avoids transection of the vagal branches in the seromuscular layer and therefore retains practically all of its original supply of parasympathetic innervation (*21*).

Whatever the type of operation, however, the mouth of the pouch is delivered and fixed through a stab wound to the left of the midline, and the skin surrounding the stoma frequently remains uneroded for long periods, provided the dog is dressed meticulously two or three times a day and is generally well cared for otherwise. In the experiment, the animal is supported in a saddle, and a special collecting device is attached to the abdomen with the rubber catheter inserted into the mouth of the pouch. For certain purposes which I shall describe later, the presence of this catheter inside the pouch in undesirable, and so we perform the operation in such a way that the stoma can be kept closed by sphincteric action of the abdominal muscle fibers (*20*). Gastric juice secreted in such a pouch is usually retained for considerable periods of time, even when the animal is left with the dressing on. To draw off the retained fluid, a narrow catheter is inserted, but left there only long enough to aspirate the contents with the aid of a syringe. Using this retention or discontinuous collection technique, the catheter is in contact with the mucosa for only a fraction of a minute, whereas by the older, continuous drainage method, it is held in

position throughout the experiment, which usually lasts for several hours.

Now, what is the chemical composition of gastric juice from such accessory stomach pouches? Of course it contains free and combined hydrochloric acid, pepsin, two different mucins, and even small amounts of other organic compounds. Besides these, however, there are significant amounts of other ionic substances—notably sodium, potassium, calcium, bicarbonate, and phosphate. The quantitative composition of pure pouch juice varies extensively, and this variation is particularly marked as regards the acid component. Thus our first efforts aimed to find out whether there was any regularity about these variations, and we started with the fundamental relation between acidity and rate of secretion. Using the continuous collection technique, with the dog in the stand and food as a stimulus, we confirmed the observation of previous investigators that the curves for these two variables, plotted against time of collection after feeding, are roughly parallel (*20*). This was observed with meat alone and with a synthetic nutritionally balanced diet devised years ago by Karr and Cowgill for dog nutrition experiments. This same parallelism was encountered in fasting dogs when histamine was used as the stimulus (Fig. 1—Exp. B 20), provided the dosage was such as to induce a secretory rate of about the same magnitude as in the feeding experiments. More recently we have found this to be true also for other stimuli like meat extract, pilocarpine, mecholyl, and insulin hypoglycemia.

Both Pavlov and Rosemann knew of this correlation between acidity and rate of secretion, but their interpretations of it were radically different (*14*). Rosemann believed that the relation is inherent in the activity of the parietal cell itself, whereas Pavlov believed that the parietal fluid is ejected by the cell at a constant concentration of acid, independent of the rate of secretion, and that all the variations in acidity below this maximum result from neutralization by mucus. Under well-controlled conditions, a healthy nonirritated pouch may be expected to secrete mucus at a fairly steady rate. Hence, when the rate of parietal secretion is high the proportion of admixed mucus will be low and so will the extent of neutralization. When, on the contrary, the rate of acid secretion is relatively low, the proportion of mucus in the mixed juice will be greater and the acidity correspondingly lower. Neither of these investigators had ever been able to confirm Rosemann's theory, nor had any of their subsequent supporters, and so we attempted to obtain crucial evidence on the subject.

To this end we sought changes in the character of the acidity-time curves which might be associated with a marked change in rate of secretion, such as is obtained with maximal dosages of histamine. The results of these studies confirmed Pavlov most beautifully; when the dosage was increased eightfold, the maximum rate of secretion was more than doubled,

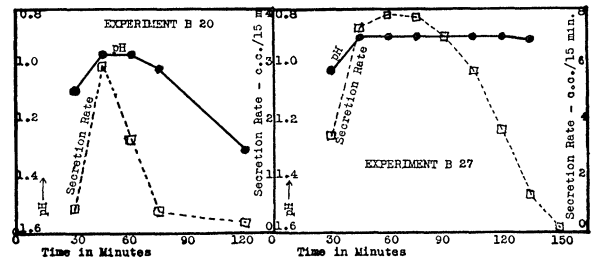

FIG. 1. Continuous collection experiments with histamine as stimulus. Experiment B 20 was performed on a dog with a low secretory rate stimulated by 0.05 mg of histamine per kg; experiment B 27, on a dog with a high secretory rate stimulated by 0.4 mg of histamine per kg.

but the parallelism between rate and acidity disappeared. Instead, the acidity curves rose promptly to plateau values (Fig. 1—Exp. B 27) around pH 0.91 and remained there throughout the experiment, until the rate of flow had again dropped to the postprandial level or lower.

Furthermore, it happens that one of our Pavlov pouch dogs developed a real hypersecretion immediately following parturition—and this did not diminish significantly until her puppies were weaned (*13*). The hypersecretion was probably continuous throughout the 24-hour cycle, and the daily output during the period of lactation was more than ten times that observed during the control periods. A similar though less marked effect was subsequently obtained with another one of our pouch dogs. In spite of this huge increase in secretory activity, however, the total acidity for 66 samples of this hypersecretory pouch juice from the first animal averaged 157 ± 7 mM—corresponding to a pH of 0.89 ± 0.01. The agreement between these data and those from the histamine experiments is striking.

Another confirmation for the Pavlov theory of constant acidity could be obtained if we were able to reduce the flow of mucus secretion markedly in postprandial and similar experiments where the rate of acid secretion is low. Starting with this idea, we reasoned that the mucus may be evoked by mechanical stimulation of the surface epithelium with the collecting catheter, and that additional neutralizing action may sometimes come from a transudate or exudate associated with mild degrees of inflammation or trauma. In order to minimize these two effects, we devised the sphincter-pouch technique that I mentioned previously, for collecting juice without the aid of the collector. Then, when the postprandial and low histamine experiments were repeated by this new tech-

nique, and special attention was given to avoid trauma to the mucosal lining of the pouch, and the pouch was freed of retained mucus by washing out with the first portion of juice secreted in each experiment, we obtained results wholly in accord with our expectation. The acidity rose promptly to values well above those obtained in the corresponding continuous collection experiments, and usually it was in the range of the plateau values obtained with high histamine dosage and spontaneous hypersecretion, i.e., pH 0.91 ± 0.02.

This limiting value seemed to be characteristic of the pure parietal secretion, but actually specimens having pH's of this magnitude still contain small, but significant amounts of the alkaline component of the gastric juice. To demonstrate this, let us see how some of the other chemical components of this pure gastric secretion are related quantitatively to the acidity. In any one experiment, the time curves for total chloride concentration and titrimetric acidity are parallel, in much the same way that the acidity and volume-rate curves are parallel (*15*). Such variations in total chloride also were in accord with Pavlov's theory, but they directly contradicted the reports of Rosemann and others that the total chloride concentration is constant, regardless of the acidity.

The positive correlation between total chloride and total acidity is even more clearly evident from a statistical analysis of the data obtained in a group of 19 experiments. Plotting these variables directly against each other, we obtained a good straight line (Fig. 2) in the acidity range above 100 mM, irrespective of whether the specimens of pouch juice were collected continuously with the dog in the collecting stand, or intermittently by the sphincter retention technique.

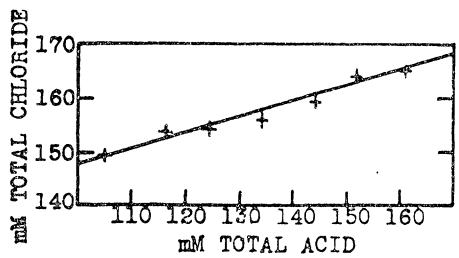

FIG. 2. Total chloride as a function of acidity; mean curve for 121 specimens obtained in 19 continuous collection experiments.

We next calculated the neutral chloride—that is, the combined alkali and alkaline earth chlorides—as the difference between acid and total chloride concentrations, and plotted these values against the total acidity. Again we obtained a straight line (Fig. 3)—of mathematical necessity because of the previous total chloride-acidity relations—but this time the correlation was negative, i.e., the higher the acidity the lower the neutral chloride value. In this particular set of data for 31 specimens of gastric secretion obtained in a series of retention experiments with a single dog, the correlation coefficient is – 0.98. This exceedingly high value probably reflects the selected

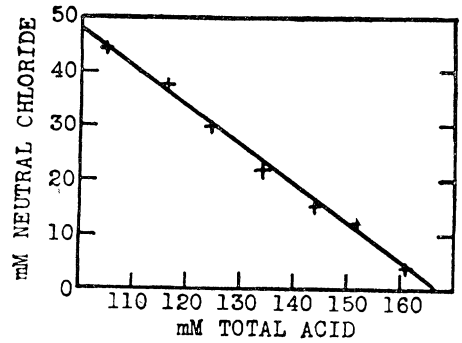

FIG. 3. Neutral chloride as a function of acidity; mean curve for 121 specimens obtained in 19 continuous collection experiments.

character of the specimens, which results from the refinement of experimental technique. The correlation coefficient for the other set of 121 specimens obtained in 19 continuous drainage experiments is somewhat lower, – 0.84, but still high enough to demonstrate the validity of this rectilinear relation between neutral chloride and total acidity. Of six such sets of data subjected to correlation analysis, four gave coefficients between 0.97 and 0.99 (*18*). The lowest neutral chloride value actually obtained in these experiments was 3 mM, with a corresponding acidity of 162 mM. The specimen of secretion giving these values was one of the purest we ever encountered, and did not contain a single flake of insoluble mucin.

Now, let us consider the acidity intercept of the graphs for these two variables. This statistic is defined by the point where an extension of the straight line graph crosses the horizontal or acidity axis, and it corresponds to the acidity of a hypothetical specimen of gastric juice which has a neutral chloride concentration of zero. From the data for this particular experiment, the intercept is 167 mM; for all 6 sets of data which we studied statistically, the intercept varied in the range 157–169, with a weighted mean of 165 mM. Similar graphs, of varying statistical reliability, have been obtained for total nitrogen, total solids, ash, and organic solids, but I shall not take time to present the evidence in detail. Suffice it to say that if we accept the validity of this extrapolation technique, the hypothetical pure gastric juice of zero neutral chloride content has the following composition: a total acidity in the neighborhood of 165 to 170 mM; practically the same concentration of free hydrochloric acid, and therefore a combined acidity of zero; a total chloride concentration identical with the total acidity, in con-

formity with the absence of neutral chloride. Everything else is virtually absent—inorganic phosphate, organic phosphorus, both inorganic ash and organic solids, and those several components indicated by the Biuret, Hopkins-Cole, and Molisch tests. The specific gravity is estimated to be 1.001, and the freezing point depression slightly over 0.6° C, very slightly hypertonic (*16*).

I recognize that mathematical extrapolation of physiological data is in general a highly precarious procedure, but since in most of the present instances the experimental data approach close to the intercept values, the range of extrapolation is very short and I believe that we may accept this mathematical technique with considerable confidence. An effort to refute our results has been made by Liu, Yuan, and Lim, by treating the data mathematically in a different way (*23*). However, some of their inferences have already been disproved by Gray and by ourselves, and the remainder still await confirmation. Also, Gray (*9*) has reported evidence to indicate that the parietal secretion is free of sodium but contains potassium at a constant concentration averaging slightly above 7 mM. This is in conflict with our finding of neutral chloride concentrations as low as 3–5 mM in several specimens which we analyzed, and the discrepancy still awaits clarification.

All of the foregoing evidence, therefore, leads to the conclusion that the fluid normally secreted by the parietal cells is a very slightly hypertonic solution of virtually pure HCl, having a titrimetric acidity around 0.17 N and a pH around 0.87. It contains extremely little if any ash or organic solids of any kind, and its composition is practically independent of its rate of formation, the intensity of the stimulus, and probably even the character of the stimulating agent. The combined acidity, neutral chloride, inorganic phosphate, and various organic substances invariably encountered in mixed gastric juice all derive from nonacid buffer-containing secretions: pepsin, mucus, the hypothetical mucoid or dilution secretion, and even small amounts of transudate which enters the pouch from the interstitial spaces. It is this mixture of nonacid buffer-containing fluids that I have designated the "nonacid component" of the gastric juice (*17*).

Now let us return to our main problem of how the acid secretion is made, and particularly how it is separated from the other solutes in the cytoplasm. If the secretion contains only HCl, and that at a nearly isotonic concentration, there is only one answer to this question that I can see (*19*). I believe we must accept the parietal cell as the source of this secretion, if only because of the evidence of Linderstrom-Lang and his associates. Then, somewhere in this cell, there must be a membrane which is permeable to water, hydrogen ion, and the halide ions, but to essentially nothing else. I say halides generically rather than chloride ion alone, because bromide and iodide, when injected into the blood stream as sodium salts, also appear in the gastric juice as HBr and HI in place of part of the HCl. The existence of such a uniquely specific membrane is not difficult to conceive of, in the light of what we already know about semipermeable membranes in general. It may constitute part of the outer cell membrane or the walls of the intracellular canaliculi, which several microscopists believe to be artifacts but which have been accepted by others on reasonably good evidence.

Such a membrane must exist in order for the cell to effect a complete separation of hydrogen ion from all the metal cations. So far as I know, the other theories about HCl formation make no attempt to explain this quantitative separation, although it is one of the most important steps in the process. The several theories that postulate the secretion of a neutral chloride which undergoes hydrolysis *after* it leaves the cell predicate a reabsorption of ammonium hydroxide or of an alcohol of high molecular weight in the neck of the gastric gland, but not of the HCl. If such a differential reabsorption is possible, then I suppose sodium ion and the other cations can also be reabsorbed under these circumstances. But how can the H ion, which possesses the highest ionic mobility known in aqueous solution, not be able to penetrate a membrane at all when the other cations, which possess considerably lower mobilities, are able to penetrate it completely? I think this premise of postsecretory hydrolysis is contrary to all current physicochemical thinking on the subject.

Let us therefore postulate the existence—as part of the parietal cell—of a membrane which is permeable only to water, H ion, and chloride or related ions. Then, consider what happens when some intracellular change takes place which energizes the cell to excrete water (Fig. 4). Some of this water moves out from the cytoplasm, through the cell membrane, and into the interstitial spaces. In so doing it takes with it the by-products of cellular activity and metabolism, along with the usual electrolytes, because the outer membrane of the parietal cell may be expected to resemble that of any other cell in this respect. But some of the water must also be forced out through the specifically permeable membrane of the intracellular canaliculus. In order to keep the osmotic work at a minimum—an invariable thermodynamic requirement in such a situation—the latter water will be accompanied by whatever solute is able to penetrate this membrane, that is H ion and Cl ion. So even though the hydrogen ion concentration of the cytoplasm is ex-

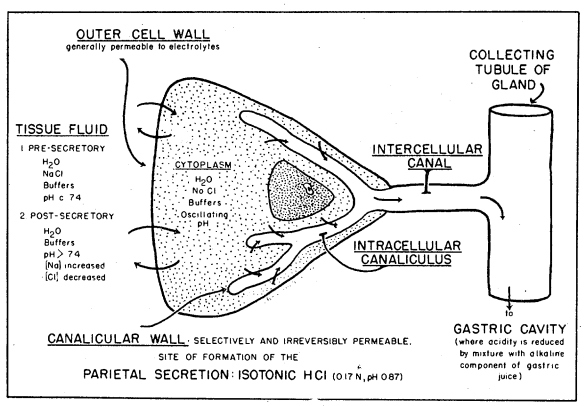

FIG. 4. Schematic representation of the process of HCl formation in the parietal cell of the stomach. The chemical reaction at the wall of the intracellular canaliculus may be written as follows, where B represents the usual cations:

$$BCl + H_2O \longrightarrow HCl + BOH$$

$$BOH + \begin{cases} H_2CO_3 \\ BH_2PO_4 \\ \text{etc.} \end{cases} \longrightarrow H_2O + \begin{cases} BHCO_3 \\ B_2HPO_4 \\ \text{etc.} \end{cases}$$

The over-all energy requirement of the process may be divided into the following components: 1) chemical work (in the cytoplasm and interstitial fluid); 2) electrical work (at the canalicular wall); 3) mechanical work (from the intracellular canaliculus to the open end of the gland tubule); 4) osmotic work (at the canalicular wall). Since the parietal secretion is essentially isotonic with the parietal cytoplasm, the osmotic work is zero.

ceedingly low, some of it will be transported across the membrane, into the lumen of the canaliculus in the form of HCl. Since these ionic movements will leave OH ion and Na ion behind, this reaction is in essence a hydrolysis effected by means of a membrane of highly specialized character, i.e., a membrane hydrolysis.

The HCl solution, passing through the membrane, may be an isotonic or a hypotonic solution, which subsequently undergoes concentration in the collecting tubule of the gland until it reaches osmotic equilibrium with the adjacent interstitial fluid. But the latter process would require two specifically permeable membranes instead of one, and a dual expenditure of energy—first to concentrate the isotonic cytoplasm by removal of a hypotonic HCl solution, and second to concentrate the latter by reabsorption of water. Hence it seems more likely that the HCl will tend to come out of the cell in the first place at a concentration which is isotonic with the parietal cytoplasm, and so keep the osmotic work of this process equal to zero and simultaneously obviate a secondary concentrating process in the collecting tubule. This isotonic concentration of HCl would be about 155 mM, except that probably the intracellular fluid is itself slightly hypertonic with respect to the blood stream, for reasons that I cannot go into here. Hence we may expect to find a value somewhat above 155 mM, which explains the limiting value of 165–170 mM actually found in animal experiments, and the slightly hypertonic freezing point depression. In short, granted the premise of a specifically permeable membrane, the logic of the situation seems to necessitate the secretion of a virtually pure HCl solution, free of all other cytoplasmic components, and possessing a constant concentration somewhat greater than 155 mM.

According to this picture, the acid is formed in or immediately adjacent to the canalicular wall, and its anion derives directly from the sodium and other chlorides of the cytoplasm. The immediate source of H ion appears to be the water, so that the reaction for this process may be written as a membrane hydrolysis of, for example, NaCl to HCl and NaOH. But the instant such alkali is liberated it will be neutralized by the several buffer systems present in cytoplasm. Some of the carbonic acid will shift to base bicarbonate, and a small amount of the latter will shift to carbonate; primary phosphate will be converted to secondary phosphate; and some of the intracellular proteins may be converted to alkali proteinate. The addition of NaOH to these buffer systems may possibly shift the intracellular pH a little to the alkaline side; if so, this will soon be readjusted by the excretion of the alkalinized buffers into the interstitial spaces, along with the products of cell metabolism. The excess NaOH, of course, will ultimately be excreted by the kidneys, after it has been balanced by reabsorption of the HCl in the small intestine.

Thus the membrane hydrolysis theory actually incorporates the theories of Maly, Bergeim, Bunge, and Robertson as essential but subordinate aspects of the over-all process. Even Davenport's carbonic anhydrase may play a role, in spite of his recent negation of it; the discrepancies between the magnitudes of certain inhibitory actions on enzyme activity and acid production may have no significance because the catalyzed formation of carbonic acid is only one of a group of reactions which are secondary to the primary actions of water transport and membrane hydrolysis. How we can bring Glick's ammonia-urease system into the picture, I cannot see as yet, but it will not surprise me at all if this should prove to be one of the mélange of intracellular reactions.

It is noteworthy that there is no evidence for a storage of concentrated neutral chlorides inside the cell. The movement of chloride ion from the blood stream and interstitial fluid to the parietal secretion appears to occur with great rapidity. As judged by the appearance of intravenously injected sodium iodide or radioactive chloride in the gastric juice, reported by other investigators, this entire passage from arteries to lumen of the stomach may require less than two minutes for its initiation. Evidently the cells are not susceptible to fatigue for any significant length of

time. As long as there is an adequate supply of water and chloride, and an adequate removal of waste products, acid production will continue even though other tissues in the body may give evidence of salt depletion. This has been demonstrated by other workers, with animals kept on restricted salt intake for prolonged periods of time.

One might speculate at length about the cellular mechanics and energy requirement of the process of HCl formation, but as yet we have little evidence to work with. Although the osmotic work is zero, energy is certainly being expended in other forms—chemical work for hydrolysis and other reactions within the cytoplasm, electrical for transporting the solution across the canalicular wall, and mechanical for driving fluid out of the cell and through the intercellular canal and tubule of the gland proper. There is already some evidence that the energy can be supplied by glucose, but steps in the conversion are still a mystery. The entire process may be viewed as starting with the movement of water. Then fluid may be forced out because of local changes in hydrostatic pressure, or a pulsatory contraction of some specialized part of the cell, or even an intermittent reversible imbibition of an intracellular macromolecule, but these ideas are all pure fantasy at the present time.

And so I give you a picture of what may be happening in the parietal cell when it manufactures hydrochloric acid. I offer this, however, not as a statement of all that unquestionably occurs, but rather as a hypothesis for further investigation, and one which should be fruitful of many new approaches to the problem. The fact that this mechanism leads of necessity to many of the other theories which have already been advanced, and incorporates them as parts of itself by logical necessity, makes me hopeful of its essential validity. We are probably still far removed from knowing what kind of monkey wrench can be tossed into the parietal machinery for the therapy of ulcer disease, but I hope that this picture of its mechanism will make some contribution toward a simple medical solution of this most vexing clinical problem.

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