Upsala J Med Sci 85: 295–301, 1980

Gastric Primary Acidity. A Speculation about a Speculation

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Pavlov suggested that although the acidity of gastric juice collected from the stomach showed different values, its strength at the moment of secretion was constant, the "primary acidity". The nature of the subsequent changes in acidity, the "acidity regulation", was a matter of debate for many years, the mucus or a hypothetical bicarbonate secretion being suggested as the cause of the event. In 1933 Teorell (15) published his "diffusion hypothesis". He found that HCl instilled in a resting cat's stomach decreased in H-ion concentration without a change in volume. He explained the observation as a diffusion process in which hydrogen ions left the stomach lumen while sodium entered. Chloride, having a very small concentration gradient between the gastric content and the plasma, showed minor changes. In 1947 Teorell (17) formulated his hypothesis mathematically and in 1948 it was experimentally confirmed by Öbrink (14). Several experiments have since strengthend the hypothesis but the discovery by Flemström (5, 6, 9) that the surface-epithelial cells do actively transport bicarbonate points to a much steeper concentration gradient for the hydrogen ions than previously thought, as only the mucus layer has to be passed before the hydrogen ions become neutralized. The bicarbonate itself from the surface-epithelial cells does not normally penetrate into the bulk solution (1).

The diffusion hypothesis predicts an exchange of hydrogen ions for sodium in amounts that are related to their mobilities. That excludes a one to one exchange which has so often been wrongly expected. Fig. 1 shows the relation in a Heidenhain pouch dog.

As a consequence of the diffusion hypothesis Teorell could devise an experiment to determine the strength of the primary acidity. He simply prevented the back diffusion of the hydrogen ions by trapping them in an isotonic glycine buffer. He then determined the volume increment and titrated the buffer-acid mixture back to its original pH. By dividing the amount of

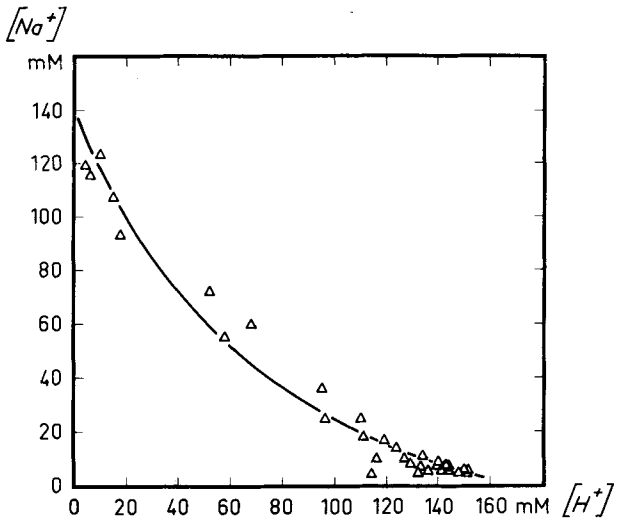

Fig. 1. The relation between $[H^+]$ and $[Na^+]$ in a Heidenhain pouch dog.

hydrogen ions being secreted into the buffer by the volume increment, the strength of the secreted acid was determined. The first experiments were performed in anaestetized cats and showed remarkably high values (16). In 1948 Teorell together with Linde & Öbrink (12) made a thourough investigation of the hydrogen ion primary concentration in a Heidenhain pouch dog. The results are shown in fig. 2, where both the primary and the secondary acidities are presented. The lower curve describes the dependence of the normally obtained acidity on the volume secretion rate, whereas the upper curve gives the calculated values from the glycine experiments - the primary acidity. It is evident that this acidity is high and constant except for low secretory rates. This was, however, expected from the technique used for the following reason, which is depicted in fig. 3. Normally both H^+ and Cl^- are thought to be

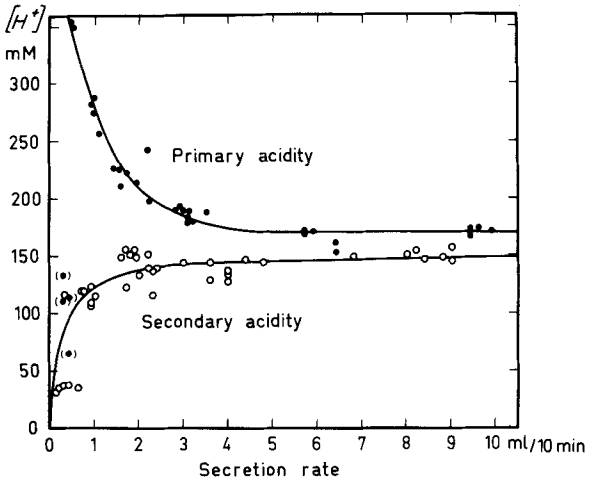

Fig. 2. The acidity of gastric juice obtained from a denervated gastric pouch in a dog (lower curve) in relation to the volume secretion rate. When caught in a glycine buffer the primary acidity is obtained (upper curve).

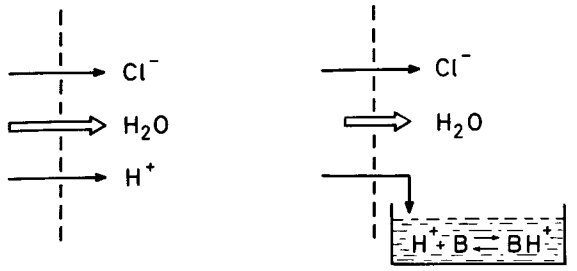

Fig. 3. Explanation for the apparent high primary acid at low secretion rates in glycine experiments (see text).

$$\frac{\text{moles } H^+}{\Delta V} = PA$$

secreted into the lumen and thereby creating an osmotic dragging force. When an isotonic buffer has been instilled - which by itself does not influence the water movement - the H^+-ions will be caught in the buffer and thus deprived of its osmotic effect. The fewer the H-ions the more complete is the capture. The amount of water dragged in relation to the number of H^+ and Cl^--ions secreted will thus decrease and result in a calculated higher primary acidity. It is thus quite conceivable that the true primary acidity is constant and has a value close to isotonicity.

It has ever since repeatedly been asked whether this primary acidity has any physiological significance or if it is only a result of a mathematical game. Does a primary acidity really exist? If the volume flow is a result of an osmotic drag where would the primary acidity be generated? Probably right at the site of formation, but theoretically then one could argue that the concentration should be infinetely high before water had enterd to form a bulk of acid. From a practical point of view these considerations are not terribly important.

New knowledge about the mechanism of the acid formation in the stomach offers, however, new aspects to the concept of primary acidity. The previously used membrane concept as a model of the gastric mucosa was mainly treated as a black box. Today we know were in the parietal cell the acid is formed and what subcellular structures are involved. For reviews see (2, 7). The parietal cells consist of a very large amount of smoth endoplasmatic reticulum which in a resting parietal cell forms a tubular-vesicular system (fig. 4a). Upon stimulation the cells undergo a morphological transformation so that intracellular cannaliculi or secretory tubules with a large number of microvilli

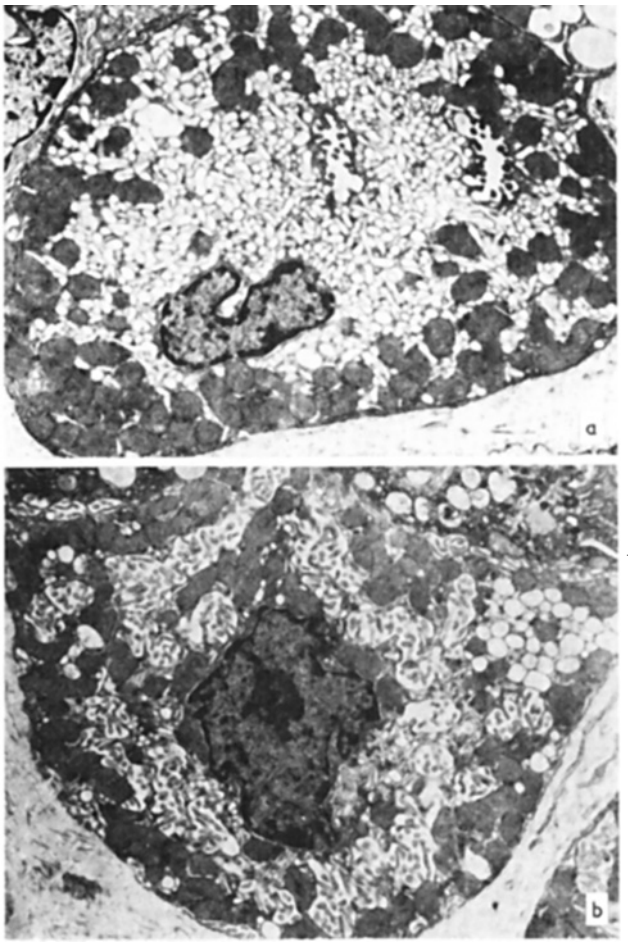

Fig. 4. Electronmicroscopic pictures of parietal cells. a) resting (note the numerous tubulo-vesicles). b) secreting (note the secretory cannaliculi with numerous microvilli). (By the courtesy of H. Helander, Umeå, Sweden)

are formed (fig. 4b). In the department where Teorell used to work a new technique with isolated gastric glands has been developed (3) (fig. 5). These glands are too small to allow a direct titration of acid. Indirect methods have therefore been adopted and amongst them the accumulation of the weak base aminopyrin (pKa 5.0). When acid is formed aminopyrin will accumulate in the glands as compared to the nutrient solution, which is kept at a neutral pH. In this way it has been possible to study the effects of the usual secretagogues on the isolated glands. It turned out, however, that also in non-stimulated glands aminopyrin accumulated to a certain degree. The interpretation of these findings was obviously that acid had already been formed in the tubular-vesicular system within the resting parietal cells. A stimulation by secretagogues, like histamine, would therefore have the main effect to connect the vesicles with the lumen of the gland and thus allow the acid a free flow out from the gland. Thus it seems possible that acid is formed already in a resting cell within a closed compartment, the vesicle.

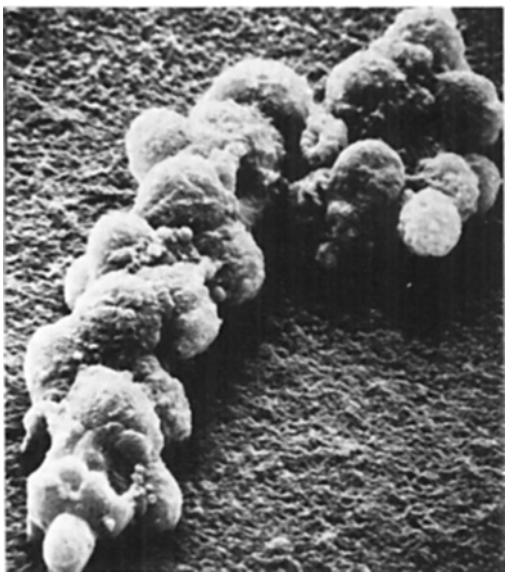

Fig. 5. A scanning electronmicrograph of an isolated gastric gland from rabbit.

It is further known that the vesicular membranes contain a K^+-activated ATPas which acts by exchaning potassium from the inside of the vesicle for hydrogen ions taken from the cytoplasm (8). The energy for this exchange transport is derived from a hydrolysis of ATP. Such an effect can even be shown in vitro in a microsomal preparation of glandular membranes (10, 4). Simply an addition of ATP results in a pH-rise in the nutrient medium indicating an inflow of hydrogen ions into the vesicles.

In this closed system a proton gradient will thus be formed with a high concentration inside the vesicles compared to the cytoplasm. In the cytoplasm we have the reaction

$$ATP + H_2O \rightleftarrows ADP + P_i$$

At equilibrium this gives

$$\frac{[ATP]}{[ADP]\,[P_i]} = k$$

which usually is known as the "phosphorylation potential". According to the chemi-osmotic theory of Mitchell (13) a proton gradient in the mitochondria is the source of energy for the ATP formation. This reaction can be driven backwards, i.e. a hydrolysis of ATP can create a proton gradient, and it is possible that this backward reaction takes place in the vesicles of the parietal cells.

In a resting cell where the vesicles are closed and densely packed they will

probably not have great possibilities to expand. As long as H^+-ions moving into the vesicles can drag water the proton gradient would not rise, but when the vesicle volume is filled and no more water could enter the H^+-gradient would tend to rise, but only to a limit where it balances the "phosphorylation potential". At this balance point the reaction would stop, no more ATP would be used and the need for oxygen disappear. The system would give a picture of secretory rest. If, however, a communication were created between the vesicles and the lumen the proton transport would start again.

This hypothesis demands that the proton gradient would depend on the ATP/ADP ratio or more correctly on the so called "energy charge" (11) which is equal to

$$\frac{0.5\ ADP + ATP}{AMP + ADP + ATP}$$

This has been shown to be remarkably constant around 0.85. At the balance point we would have to expect a constant acidity which probably is the primary acidity. We know that this primary acidity is almost isotonic with blood, which may indicate that the "energy charge" of the ATP system may be the responsible factor for the level of solute concentration in the animal body which we normally call isotonicity.

In conclusion it may be suggested that the concept of primary acidity which to begin with only was an operational term now seems to be a physiological reality of functional interest.

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Received October 20, 1980.

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