A Gastric Acid Secretion Model

Anthony M. de Beus,* Thomas L. Fabry,‡ and H. Michael Lacker§

‡Henry D. Janowitz Division of Gastroenterology, Department of Medicine, *Mount Sinai School of Medicine, New York, New York 10029; §Department of Mathematics, New Jersey Institute of Technology, Cullimore Hall, Newark, New Jersey 01702 USA

ABSTRACT A theory of gastric acid production and self-protection is formulated mathematically and examined for clinical and experimental correlations, implications, and predictions using analytic and numerical techniques. In our model, gastric acid secretion in the stomach, as represented by an archetypal gastron, consists of two chambers, circulatory and luminal, connected by two different regions of ion exchange. The capillary circulation of the gastric mucosa is arranged in arterial-venous arcades which pass from the gastric glands up to the surface epithelial lining of the lumen; therefore the upstream region of the capillary chamber communicates with oxyntic cells, while the downstream region communicates with epithelial cells. Both cell types abut the gastric lumen. Ion currents across the upstream region are calculated from a steady-state oxyntic cell model with active ion transport, while the downstream ion fluxes are (facilitated) diffusion driven or secondarily active. Water transport is considered iso-osmotic. The steady-state model is solved in closed form for low gastric lumen pH. A wide variety of previously performed static and dynamic experiments on ion and CO_2 transport in the gastric lumen and gastric blood supply are for the first time correlated with each other for an (at least) semiquantitative test of current concepts of gastric acid secretion and for the purpose of model verification. Agreement with the data is reported with a few outstanding and instructive exceptions. Model predictions and implications are also discussed.

GLOSSARY

$a(B_b(x),C_b(x),B_L,C_L)$	a 1:1 bicarbonate-chloride antiport exchanger function, since it is implicitly a function of x because of the x dependence of $B_b(x)$ and $C_b(x)$. It is also referred to as $\tilde{a}(x)$.
C	the stomach compliance
D_e	the diffusion coefficient between the capillary bed and the stomach lumen
D_m	CO_2 diffusion coefficient between the parietal cell and the stomach lumen
D_s	CO_2 diffusion coefficient between the parietal cell and the capillary bed
e_1	the basolateral HCO_3^-/Cl^- antiport flux depicted in Fig. 1
e_2	the basolateral H^+/Na^+ antiport flux depicted in Fig. 1
ϕ	the membrane voltage. Superscripts indicate respective membranes in Fig. 1.
$g_{Cl^{(1)}}$	the chloride flux through conductive channels in membrane (1) of Fig. 1, i.e., the apical membrane
$g_{K^{(1)}}$	the potassium flux through conductive channels in membrane (1) of Fig. 1, i.e., the apical membrane
$g_{K^{(2)}}$	the potassium flux through conductive channels in membrane (2) of Fig. 1, i.e., the basolateral membrane
H_0, B_0, N_0, C_0, K_0	the proton, bicarbonate, carbon dioxide, chloride, and potassium concentrations in chamber I, at $x = 0$; i.e., the arterial concentrations. These are parameters of the model.
H_b,B_b,N_b,C_b,K_b	the proton, bicarbonate, carbon dioxide, chloride, and potassium concentrations in the capillary, upstream and downstream. These are all functions of x, the distance along the capillary.
H_d,B_d,N_d,C_d,K_d,S_d	the proton, bicarbonate, carbon dioxide, chloride, potassium, and sodium concentrations of the noncirculatory fluid entering the stomach. These are parameters of the model.
H_L,B_L,N_L,C_L,K_L,S_L	the proton, bicarbonate, carbon dioxide, chloride, potassium, and sodium concentrations in the stomach lumen. These are not functions of x, the distance along the capillary, since the stomach lumen is assumed to be well-mixed.
H_p,B_p,N_p,C_p,K_p,S_p	the proton, bicarbonate, carbon dioxide, chloride, potassium, and sodium concentrations in the parietal/oxyntic cell: all functions of x, the distance along the capillary.
L_e	the length of the (downstream) epithelial cell region
L_p	the length of the (upstream) parietal/oxyntic cell region
M_p	metabolic production of carbon dioxide in the parietal cell, a parameter of the model.
ô	the osmotic strength in any region.
p_1	the pump rate of the 1:1 H^+/K^+ exchange pump on the apical (mucosal) side of the parietal cell, a fixed parameter of the model.
p_2	the pump rate of the 3:2 Na^+/K^+ exchange pump on the basolateral (serosal) side of the parietal cell, a fixed parameter of the model.
$Q[H,B,N]$	a volumetric reversible reaction produces one mole of proton and one mole of bicarbonate for each mole of carbon dioxide

Received for publication 23 November 1992 and in final form 18 March 1993.

0006-3495/93/07/362/17 $2.00

	and mole of water, catalyzed by carbonic anhydrase. It is a function of the three substances indicated in the brackets.
q_a	the barrier parameter of $a(x)$
Q_b	the volumetric flow rate of blood in the capillary bed, a parameter of ther model.
Q_d	the volumetric flux into the stomach, a parameter
Q_v	the pyloric volumetric flux out of the stomach
R	the pyloric fluid resistance (see text)
s	the apical K^+/Cl^- symport flux depicted in Fig. 1
T	the total transfer of bicarbonate for chloride across the surface epithelial cell (SEC) layer
V	the volume of fluid in the stomach lumen
x	the distance along the arterial-venous capillary arcade
X_i	the concentration of species i (dilute solutions assumed)
z_i	the valence of species i

INTRODUCTION

Gastric secretion of acid proceeds from the activity of about a million oxyntic cells (parietal cells) found in the tubular gastric pits of the fundus and body of the stomach (Guyton, 1966). The generation and maintenance of a concentration gradient of 10^6 between the pH 1 of the stomach lumen on the mucosal side of the gastric epithelium contrasted with the pH 7 of the nutrient blood vessels supplying the serosal side of the mucosa have provided experimental and theoretical physiologists a subject for investigation for more than a century. Current concepts of HCl secretion have evolved from four earlier theories (Hunt and Wan, 1967): 1) the Rosemann view, 2) the two-component hypothesis of Pavlov and Hollander, 3) the Na^+-H^+ exchange model of Teorell, and 4) the Hirschowitz "gastron." Hunt and Wan (1967) assert, but do not show, that a synthesis of these models can account for the observed ionic concentrations of gastric juice in resting and acid secreting states in whole animal preparations.

This work presents a mathematical model incorporating the current concepts of acid generation and its coupling to gastric self-protection via the microcirculatory alkaline tide. Our model incorporates several ideas related to the four early theories presented above as well as data concerning the microcirculation and the mucus layer. It is a departure from previous work in this area in that it integrates information about ion exchange between the gastric epithelium, its microvasculature, and the stomach lumen, predicts secretory flow, and incorporates a secondarily active epithelial cell bicarbonate secretion, unlike the classic Pavlov-Hollander model, for example. Predicted ion concentrations in the capillary bed and lumen of the stomach are derived analytically in various special cases and numerically for the general model. The results are then discussed against the backround of known clinical and experimental gastric knowledge.

The efficacy of the mucus layer and the bicarbonate flow in gastric protection has been much debated (Flemström and Turnberg, 1984). Engel et al. (1984) analyzed the bicarbonate-proton reaction layer in the mucus and concluded that it was not sufficient for neutralization at the surface epithelial apical membrane. However, their data from Heidenhain pouches estimates the bicarbonate output of the epithelium in the absence of acid secretion, thereby not accounting for the alkaline flow from the "upstream" oxyntic cells. Bicarbonate transport across the epithelium from the microvasculature (mediated by the movement of Cl^-) has been described by the work of many investigators, e.g. (Flemström, 1987; Flemström and Turnberg, 1984; Hollander and Tarnawski, 1989; Hirst, 1989; Flemström and Garner, 1989). The alkaline flow hypothesis suggests that supplying excess bicarbonate to the nutrient side of an otherwise compromised gastric epithelium in the presence of carbonic anhydrase, the enzyme which catalyzes the neutralization reaction normally present at the apical surface of the gastric epithelial cells (Flemström and Garner, 1989), would prevent ulcers, which was shown in vivo (Starlinger et al., 1981; see also Silen, 1980).

Clinically, the manner in which acid generation is coupled to self-protection has important implications in understanding different gastrointestinal states. In the Zollinger-Ellison syndrome acid hypersecretion is caused by excess oxyntic cell stimulation due to elevated gastrin levels; despite the 5-fold increase in acid production very few ulcers are seen in the fundus and body of the stomach, where the majority of gastric glands containing the acid secreting oxyntic cells are found. Instead, ulcers are found in the duodenum. Surprisingly, gastric ulcers in the body and fundus are correlated with low acid secretion or ischemic shock (Meeroff, 1984; Hollander and Tarnawski, 1989; Starlinger et al., 1981). Damage to the mucus layer by prostaglandin inhibitors (such as aspirin and NSAIDs), bile salt reflux, *Helicobacter pylori*, ethanol, and stress have all been implicated in ulcer production (Hollander and Tarnawski, 1989; Meeroff, 1984).

MODEL DESCRIPTION

Ion exchange between the capillary bed of the stomach and the stomach lumen is represented with a two-chamber model. The first chamber, representing the capillary bed underlying the stomach mucosa, is modeled as a convective plug flow chamber (no axial variation in fluid velocity). The second chamber, representing the stomach lumen and gastric pits, is modeled as a well-mixed chamber with steady volumetric inflow (esophageal) and outflow (duodenal). The ion fluxes across the wall between the convective chamber and the gastric pit is based on a steady-state well-mixed chamber model of the parietal/oxyntic cell in the upstream region of the capillary bed, while ion exchange between the stomach lumen and the capillary bed in the downstream region is based on a simplification of the surface epithelial cell. Discussion of the experimental basis of the oxyntic cell model is beyond

the scope of this paper, involving, as it does, a massive body of literature. Indeed, the oxyntic cell by itself provides sufficient complexities warranting a separate investigation which we provide elsewhere (de Beus, 1992). The entire acid generating machinery of the stomach is represented with a single gastric pit/capillary bed/surface epithelial cell combination (a *gastron*) in the same way that the kidney is often modeled as a single nephron. See Fig. 1. The steady-state species conservation equations for the parietal/oxyntic cell, using a well-mixed chamber model, derived on the basis of the scheme in Fig. 1 (e.g., Demarest et al. (1989) or Wolosin (1985)); follow below (see the Glossary for an explanation of symbols):

$$\frac{d(V \times Sp)}{dt} = -3p_2 + e_2 = 0 \quad (1)$$

$$\frac{d(V \times H_p)}{dt} = Q[H_p,B_p,N_p] - e_2 - p_1 = 0 \quad (2)$$

$$\frac{d(V \times B_p)}{dt} = Q[H_p,B_p,N_p] - e_1 = 0 \quad (3)$$

$$\frac{d(V \times N_p)}{dt} = M_p - Q[Hx_p,B_p,N_p] + D_s[N_b - N_p] + D_m[N_L - N_p] = 0 \quad (4)$$

$$\frac{d(V \times C_p)}{dt} = e_1 - s - g_c^{(1)} = 0 \quad (5)$$

$$\frac{d(V \times K_p)}{dt} = 2p_2 - s + p_1 + g_k^{(2)} - g_k^{(1)} = 0 \quad (6)$$

$$\sum z_i \left[\frac{d}{dt}\right]^{(2)} (VX_i) = g_k^{(2)} - p_2 = 0 \quad (7)$$

$$\sum z_i \left[\frac{d}{dt}\right]^{(1)} (VX_i) = g_k^{(1)} - g_c^{(1)} = 0 \quad (8)$$

The final two equations of the set are the open circuit electrical current equations across the apical membrane (membrane "1" in Fig. 1) and basolateral membrane (membrane "2" in Fig. 1). These equations assume the bulk electroneutrality of solutions in each chamber.

The equations were obtained using the principle that the rate of change of the number of particles in any given region of space is equal to the rate of creation of particles in that region and the net flux of particles across the region's borders. More formally, we may use the following paradigm on a differential *control volume*[1] in x: (net flux of moles in) + (moles created by reaction) – (net flux of moles out) – (moles consumed by reaction) = (net rate of increase), where the last term is set to zero in the steady-state. The basolateral fluxes of each ion entering the cell are then set to the ion fluxes exiting the capillary/convective region. The boundary condition at $x = 0$, the beginning of the exchange region, is that the concentration of each ion is set to the normal arterial value. For example, the H_p equation above is derived by considering that the net increase in moles of H_p is equal to the source function $Q[H_p,B_p,N_p]$ minus the flux out across the basolateral membrane, defined as e_2, and the flux out across the apical membrane, defined as p_1. Using the above equations (Eqs. 1–8), it is easy to solve for $g_k^{(2)}$, $g_k^{(1)}$, $g_c^{(1)}$, e_2, e_1, and s in terms of p_1 and p_2 so that each ion flux across either the apical or basolateral membrane is known in terms of p_1 and p_2. Simultaneously solving the above expressions will yield the results that $e_2=3p_2$ and $Q[H_p,B_p,N_p]=p_1+3p_2$. Note that $g_k^{(2)}$, $g_k^{(1)}$, $g_c^{(1)}$, e_2, e_1, s, and Q are not constants, but are functions of the ion concentrations inside and outside the parietal cell and the membrane potential; the fact that their value at steady-state can be known in terms of p_1 and p_2, constants, regardless of outside concentrations is a singular (although not unique) convenience of this particular cell model. It is especially significant that the exact manner of K^+ and Cl^- transport, a major area of uncertainty experimentally, whether conductive channel or carrier, does not affect the overall ion fluxes since these fluxes are entirely determined in the steady-state by the apical H^+/K^+ ATPase pump and the various fairly well-agreed on features of the basolateral membrane. Minor changes such as replacing the basolateral Na^+/H^+ antiport with a Na^+ channel could be incorporated easily without significant impact; relaxing the open circuit condition, on the other hand, would increase the complexity of solution to an unmanageable degree. The specific details of the cell physiology are unimportant in terms of our model if the transparietal ion fluxes are known in terms of constants and if the cell CO_2 is proportional to a known metabolic production of CO_2 in the cell and to the CO_2 outside of the cell.

Knowing the ion fluxes across the wall in terms of p_1 and p_2, the species conservation equations for the blood in the upstream region, abutting the parietal/oxyntic cells and the gastric pit ($0 \le x \le L_p$) then follow.

$$-Q_b \frac{dH_b}{dx} + Q[H_b, B_b, N_b] + e_2 = 0; \qquad e_2 = 3p_2 \quad (9)$$

$$-Q_b \frac{dB_b}{dx} + Q[H_b, B_b, N_b] + e_1 = 0; \qquad e_1 = p_1 + 3p_2 \quad (10)$$

$$-Q_b \frac{dN_b}{dx} - Q[H_b, B_b, N_b] + D_s[N_p - N_b] + 0 \quad (11)$$

$$-Q_b \frac{dC_b}{dx} - e_1 = 0 \quad (12)$$

$$-Q_b \frac{dK_b}{dx} - 2p_1 - g_k^{(2)} + 0 \quad (13)$$

The downstream region, abutting the surface epithelial cells and the stomach lumen, is defined on $L_p \le x \le L_e + L_p$.

[1] A *control volume* is an arbitrary region of space over which physical laws, such as conservation of evergy, mass, or momentum (and sometimes entropy) are applied. Fixed or global control volumes are known as *Eulerian*, while moving or local control volumes are *Lagrangian*.

The boundary conditions are that the concentrations at $x = L_p$ are the same as those at this point for the upstream region to ensure continuity of the concentrations as a function of x. The mass conservation equations for the blood in the downstream region may be written as follows.

$$-Q_b \frac{dH_b}{dx} + Q[H_b, B_b, N_b] = 0 \quad (14)$$

$$-Q_b \frac{dB_b}{dx} + Q[H_b, B_b, N_b] - a[B_b(x), C_b(x), B_L, C_L] = 0 \quad (15)$$

$$-Q_b \frac{dN_b}{dx} - Q[H_b, B_b, N_b] + D_e[N_L - N_b] = 0 \quad (16)$$

$$-Q_b \frac{dC_b}{dx} + a[B_b(x), C_b(x), B_L, C_L] = 0 \quad (17)$$

Note that potassium is not exchanged in this chamber and is therefore a constant; whereas protons react and therefore are a function of x.

The ion fluxes for chloride and bicarbonate are given by a rate law which lumps together the total ion exchange barrier represented by the mucus layer and the epithelial cell. This expression, given below (Eq. 18), is a simple expression of the idea that the bicarbonate secretion by the epithelial cells into the stomach lumen is secondarily active, being driven by the chloride gradient which is indirectly established by the ATPases of the oxyntic cell.

$$\tilde{a}(x)\ a[B_b(x), C_b(x), B_L, C_L] = q_a[B_b(x)C_L - B_L C_b(x)] \quad (18)$$

The flux densities are complementary, since the main mode of transport across the epithelium is by way of an electroneutral chloride-bicarbonate antiporter (e.g., Hirst, 1989; Flemström and Garner, 1989). This functional form can represent a single nonsaturating antiport kinetic function spanning the epithelial layer, or more realistically, some combination of an apical antiport, basolateral antiport, and/or a one-dimensional diffusion barrier across a mucus layer all in series. Appendix A shows that the only change in Eq. 18 upon inclusion of these features is the meaning of the parameter q_a. The total exchange of chloride for bicarbonate is then given by the integral:

$$T = \int_{L_p}^{L_e} \tilde{a}(x)\, dx \quad (19)$$

The same analysis yields conservation laws for the stomach lumen, except here the control volume is the whole lumen rather than an infinitesimal slice along x, leading to integral rather than differential equations, with the following additions and subtractions to eliminate the carbonic anhydrase reaction $Q[H,B,N]$:

$$\frac{d(V[B_L - H_L])}{dt} = Q_d(B_d - H_d) - Q_v(B_L - H_L) + T - p_l L_p = 0 \quad (20)$$

$$\frac{d(V[H_L + N_L])}{dt} = Q_d(N_d + H_d) - Q_v(N_L + H_L) + \int_0^{L_p} (p_l + D_m[N_p - N_L])\, dx + \int_{L_p}^{L_e} D_e[N_b - N_L]\, dx = 0 \quad (21)$$

$$\frac{dV}{dt} = Q_d + \frac{2(p_l + 3p_2)}{\hat{o}_b} - Q_v = 0 \quad (22)$$

$$\frac{d(VC_L)}{dt} = Q_d C_d - Q_v C_L + \int_0^{L_p} [s + g_c^{(1)}]\, dx - T = 0; \quad s + g_c^{(1)} = p_l + 3p_2 \quad (23)$$

$$\frac{d(VK_L)}{dt} = Q_d K_d - Q_v K_L + \int_0^{L_p} [s + g_K^{(1)} - p_l]\, dx = 0; \quad s + g_K^{(1)} = p_l + 3p_2 \quad (24)$$

$$\frac{d(VS_L)}{dt} = Q_d S_d - Q_v S_L = 0 \quad (25)$$

Since it has been shown that the mucosa is freely permeable to water, (Lee et al., 1955; Machen and Forte, 1979), water is assumed to be driven primarily by osmotic forces (Stein, 1986; Thull and Rehm, 1956; Rehm et al., 1970; although Rehm et al., 1970) have shown how, at least in the Teorell model, the difference in free diffusion between HCl and NaCl can account for slight (within 6%) hypo- or hypertonicity of the gastric fluid with respect to the blood plasma. Regardless of mechanism, however, gastric contents are observed to be roughly iso-osmolar with plasma. To derive the term in dV/dt for water entering the stomach lumen, we consider that H_2O is secreted in the pits iso-osmotically with the ions H^+, K^+, and Cl^-; then the flux of water entering the stomach is simply proportional to the total ion flux plus the esophageal inflow term Q_d since the only ionic transport in the lumen itself is 1:1 Cl^-/HCO_s^- exchange, which is osmotically neutral. The osmotic contribution of CO_2 and its

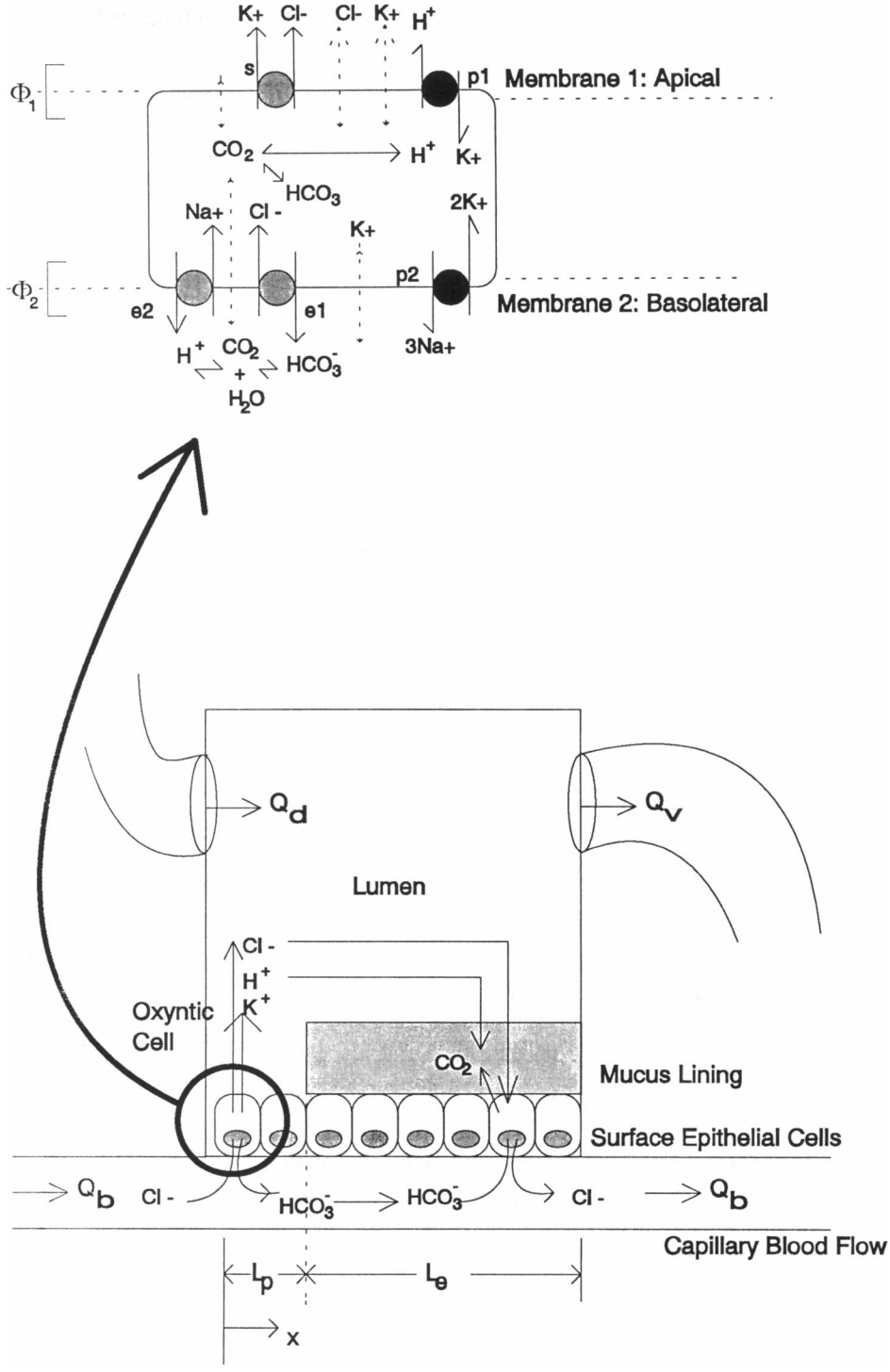

FIGURE 1 Schematics of gastron (*bottom*) and oxyntic cell (*top*).

flux across the epithelium has been considered and is a second order effect.

Following data from Davenport (1966), Malagelada (1977), and Malagelada and Azpiroz (1989) for outflow of fluids, we have chosen a simple resistance (R) and compliance (C) pressure-volume relationship such that $Q_v = V/RC$. (Guyton (1966) proposes $Q_v \propto V$ on the basis of empirical observations between the relation between gastric distension and the increase in antral peristalsis.) Although we have kept RC constant, it might be useful to make R a increasing function of pH to simulate the enterogastric reflex that increases pyloric tonus and decreases antral peristalsis when the pH in the duodenum drops (say, as a result of large $Q_v H_L$). In the gastric pouch $R \to \infty$, forcing $Q_v \to 0$ so that in order to achieve a steady-state solution (including $dK_i/dt = 0$ and $dS_i/dt = 0$) modifications on p_2 are necessary (see Appendix B). In addition, for $dV/dt = 0$, we can (*a*) disregard the volume in our model (let it become infinite); and (*b*) include a correction for the osmotic transepithelial efflux of CO_2 and a normally insignificant hydrostatic perfusion term.

NUMERICAL SOLUTION

Equations 1–25 describe a relationship between the model parameters and the ion and CO_2 concentrations entering the gastron, inside the gastron, and leaving the gastron. Initially, our objective is to find the concentrations of each ion inside the gastron and leaving the gastron (i.e., in the gastric lumen and in the blood and the pyloric volumetric outflow) given the parameters and the concentrations entering the gastron (arterial and nonparietal concentrations and fluxes). We shall call this objective *finding a solution* to Eqs. 1–25. By contrast, another possible procedure would be to assume knowledge of the outgoing and incoming concentrations and to use Eqs. 1–25 to deduce the model parameters; this latter procedure is usually called a backward solution or a curve fit.

In order to check the validity of our numerical method we have obtained analytic solutions to several limiting cases, as shown in Appendix B. It is useful to state at this point those simplifications which are integral to the model and those which are made for the purposes of analytic expedience. Simplifications made for analytic solution include assuming 1) that parietal cell/blood CO_2 concentrations are in equilibrium, 2) that CO_2 diffusion across the stomach wall occurs across the mucus/surface epithelial cell layer, 3) that the pH in the capillary is physiological (pH $>$ 5), and 4) that the pH in the lumen is low (pH $<$ 3). Simplifications integral to the model include 1) the steady-state condition used to evaluate the parietal cell, lumen, and capillary equations, 2) the Henderson-Hasselbach equation's representation of the carbonic anhydrase reaction in equilibrium, 3) the iso-osmotic transport of water, and 4) the open circuit condition.

In our numerical work we have eliminated all of the first category of CO_2 and pH simplifications; in addition, we have extended the model itself by relaxing the steady-state assumption somewhat as well. Specifically we have computed a quasidynamic solution of the lumen concentrations: while dynamic (time-dependent) equations were used in the lumen (i.e., Eqs. 21–25 were not set equal to zero, as shown), the steady-state assumption was still applied to the capillary and the parietal cell. The justification for this extension is that the lumen is a large chamber compared to the capillary and cell chambers so that it is likely that the transient solutions of the other two chambers essentially occur instantaneously measured by the time scale of the lumen transient; i.e., the lumen concentrations respond much more slowly to change than the cell and blood concentrations. It is important to consider nonsteady-state solutions of this system, because the physiology of the stomach demands it. Secretion of acid in the stomach occurs in bursts associated with meals, not as a backround process, as in the kidney.

Numerical integration of Eqs. 21–25 with a known function $Q_v[V,H_L,B_L\ldots]$ (e.g., $Q_v = V/RC$ or $Q_v = 0$ for a gastric pouch) may be performed using an explicit scheme. An initial condition is picked for the luminal concentrations and volume. The right-hand side of Eqs. 21–25 is evaluated at this point (see below), and a new value for the variables $V(H_L + N_L)$, $V(B_L - H_L)$, V, VK_L, VC_L, and VS_L is computed by addition of the previous value plus the right-hand side of the equation (the flux) multiplied by some Δt. These "lumped" variables may be transformed into the concentrations and volume using the quadratic formula and the Henderson-Hasselbach equation, whereupon one may proceed with the next time step in the same manner. To evaluate the right-hand side of Eqs. 21–25 requires a solution for $C_b(x),B_b(x)$ and $N_b(x)$ *given* C_L,B_L,N_L. If we make the assumption of physiological pH in the blood it is relatively simple to obtain closed form solutions for $N_b(x)$, $C_b(x)$, and $B_b(x)$ in terms of N_L, C_L, and B_L without any assumptions about D_e, D_m, D_s, or Q_b. However, at the expense of a little more computer time, it is possible to integrate Eqs. 9–17 using the same sort of explicit scheme in their spatial dependence as used for the time dependence in Eqs. 21–25. Possibly contrary to expectations, this "downwind" differencing does not appear to cause any artifactual oscillations or instabilities, possibly because of the lumping and back transformation of variables made at each step.

COMPARISONS WITH DATA AND DISCUSSION

In the range of applicability (i.e., low pH, reasonable pCO_2, appropriate CO_2 transport limits) there is excellent agreement between the analytic and numerical solutions developed here; furthermore, the closed form solutions to the capillary equations (Eqs. 9–17) using physiological pH were always within 1% of the considerably slower numerical integration of Eqs. 9–17 without this assumption. Finally, note that the epithelial electrical potential, a decreasing function of p_1 experimentally, is irrelevent to the current analysis. In fact, any potential could be predicted given the choice of $g_c^{(1)}$, $g_k^{(1)}$, and $g_k^{(2)}$. The subject of the relationship between the membrane potentials, p_2, and the secretion rate may be entirely left to a detailed oxyntic cell model (de Beus, 1992).

PARAMETER IDENTIFICATION

Previous experimental data was used in two ways: first, model parameters were extracted from various sources, as explained below, and then on the basis of the parameters obtained, model predictions were compared to experimental findings. Therefore, although no "curve-fitting" was performed, our intention being to build our theory and to verify it independently, there is a partial degree of overlap between the experimental data originally used to estimate the parameters and the experimental data used in the present model verification. We have minimized this overlap in several ways: (*a*) whenever possible, parameter data was collected from a wide variety of sources who determined the parameter in different ways, (*b*) some of the experiments used for verification were unrelated to any of the experiments used to obtain parameters. As an example of overlap, the "nonparietal" secretion rate and concentrations were "curve-fit" using the two component Pavlov-Hollander model and therefore are not independent from the steady-state data presented in Fig. 3, but the nonparietal concentration

"fits" are, of course, close to plasma or extracellular fluid concentrations, and therefore have a higher degree of independence. As an example of independence, the blood flow rate was determined almost directly using several different techniques. In between these two extremes lie oxyntic cell secretion rates, which are usually varied as the independent variable, and the CO_2 and water transport terms. Finally, the transient (time-dependent) experiments of Kurtz and Clark (1947) are independent of any previously obtained parameters. The final judgment on the relative independence of the parameters from the verification data is left to the reader.

Doubtlessly, a systematic effort to curve fit our model to the data presented could improve the overall agreement at the cost of changing our study design from a "bottom-up" attempt to understand the physiology from "first principles" to a "top-down" empirical model with many adjustable parameters.

Tables 1-4 present the model parameters and their sources. When several different values appear, the values used in the model corresponding to different cases (saliva contamination, surgical cannulas) are shown in boldface type unless otherwise noted. Table 5 and Figs. 2–8 present model verification studies comparing model predictions versus existing data, while Table 6 presents one of the model's predictions. A few comments on Tables 1–4:

"(DU)" after a value for the oxyntic cell peak rates stands for data relating to patients with duodenal ulcers. We generally varied p_1L_p as the independent parameter in our studies, but the values used which correspond to normal secretion rates Q_v corresponded to the normal values in this Table. The nonparietal secretion rate Q_d is derived from the two-component model as analyzed by Makhlouf et al. (1966) and therefore is somewhat less "independent" than the rest of the model constants from Fig. 2 in the model verification studies. Table 2 presents well-known physical chemical parameters relating to CO_2, while Tables 3 and 4 show representative physiological data. Most experiments are performed in the absence of salivary contamination of the stomach contents.

The oxyntic cell basal Na^+/K^+ rate (ouabain-sensitive) was unobtainable, therefore a rate which roughly reproduced the K^+ lumen concentration in the steady-state was used. Although this was a curve-fit to this particular data, it is still instructive, because it predicts that the oxyntic cell must increase its uptake of K^+ from the blood with its secretion rate. However, the ouabain-sensitive basolateral Na^+/K^+ ATPase pump is usually regarded as being regulated to keep the cell

TABLE 1 Model constants

Symbol	Meaning	Value	Reference
p_1L_p	Oxyntic cell secretion rate (peak rates)	**30 mEq/h**	Hirschowitz (1989)
		50 mEq/h (DU)	
		17 mEq/h	Davenport (1966)
		31–96 mEq/h (DU)	
		22–60 mEq/h	Guyton (1986)
		28 mEq/h	Rune (1966)
		15–40 mEq/h	Emås et al. (1967)
		20 mEq/h	Grossman (1967)
Q_b	Blood flow	70–140 ml/min per 100 g tissue	Cheung et al. (1984)
		17–**244 ml/min**	Guth (1977)
		37–326 ml/min (DU)	
		25 ml/min (left gast. art. dogs)	Hollander et al. (42)
Q_d	Nonparietal secretion rate	0.35 ml/min	Hirst (1989)
		0.31–0.4 ml/min	Makhlouf et al. (1966)
		1.01 ml/min (with saliva)	Guyton (1986) or Davenport (1966)
p_2L_p	Na^+/K^+ ATPase rate	**3% of p_1L_p**	N.A. (see text)
RC	Fluid volume/exit flow rate $V/\rightarrow Q_v$ ratio (resistance × compliance)	**100 min** (humans)	Malgelada (1977)
		37 min (dogs)	Davenport (1966)
		0.5 min (large glass cannula)	Kurtz et al. (1947) (see text)
$D_e(L_e - L_p)$	Lumen-blood diffusion constant	**15 ml/min** (calculated from $t_{1/2}$)	McIver et al. (1926) Stevens (1987)
		13 ml/min	Davenport (1966)
D_sL_p	Oxyntic cell-blood diffusion constant	**840 ml/min**	Milhorn et al. (1968) for alveoli, see text
		infinite	
D_mL_p	Oxyntic cell-lumen diffusion constant	0.001 ml/min	N.A. (see text)
M_pL_p	Oxyntic cell metabolic CO_2 production	Mean **63%**	Miyagi et al. (1966)
		Range 42%–95%	
		62% of $Q_b\Delta HCO_3$ of p_1L_p	Eichenholz et al. (1967)
$q_a(L_e - L_p)$	Cl^-/HCO_3^- exchange coefficient **8.4 × 10^{-4}** mEq/h per (mEq/liter)^2 (calculated from $T + Q_dB_d$; see text)	**2.3 mEq/h**	Flemström (1987)
		0.4 mEq/h	Engel et al. (1984)
		2.5 mEq/h	Hollander et al. (1989)
		0.45 mEq/h	
		1–6 mEq/h	Hirschowitz (1989)

TABLE 2 Physical chemical constants

Symbol	Meaning	Value
κ	$CO_2 + H_2O \rightleftarrows H^+ + HCO_3^-$ equilibrium constant	0.8 μM/liter
α	CO_2 solubility	0.03 mM/mmHg

TABLE 3 Physiological constants (Guyton (1986))

Symbol	Meaning	Value
$\hat{o}_b$ and $\hat{o}_L$ (see text)	Lumen osmotic strength	320 mOsm
H_0	Arterial H^+	$10^{-7.4}$ M
B_0	Arterial HCO_3^-	24 mM
K_0	Arterial K^+	5 mM
C_0	Arterial Cl^-	108 mM
pn_0	Arterial pCO_2	40 mmHg

TABLE 4 Nonparietal secretion/extracellular fluids/salivary admixture (Makhlouf et al., 1966; Guyton, 1986; Alberts et al., 1989; Davenport, 1966; Hunt et al., 1967)

Symbol	Meaning	With saliva	Without saliva
$\hat{o}_d$	Osmotic strength	280 mOsm	280 mOsm
S_d	Na^+ conc.	53 mM	130 mM
H_d	H^+ conc.	$10^{-7.4}$ M	$10^{-7.4}$ M
B_d	HCO_3^- conc.	50 mM	28 mM
K_d	K^+ conc.	20 mM	6 mM
C_d	Cl^- conc.	43 mM	116 mM
pn_d	pCO_2 conc.	19.2 mmHg	34.3 mmHg

Na^+ low; in the context of the oxyntic cell model considered in Fig. 1, the apical H^+/K^+ can be shown to indirectly lower the cell Na^+, therefore if the basolateral Na^+/K^+ pump regulates on the basis of increased Na^+, increased p_1 activity should lead to decreased p_2 activity, contrary to the prediction of this model. Clearly, the increased K^+ uptake is at odds with the Na^+ regulation. Note that if a constant value of p_2 is used, K^+ in the lumen decreases due to dilution.

The CO_2 diffusion constants were obtained in the following manner. The cell/blood exchange was assumed very fast on the basis of physiological requirements for O_2 and the data of Milhorn et al. (1968). Exchange between the lumen and oxyntic cell was assumed to be negligible based on its deep position in the gastric pit. These assumptions correspond to the analytic approximation given in Appendix B. The final diffusion constant from epithelial cell to lumen therefore represents the only CO_2 diffusion constant. Using the method of McIver et al. (1926), data for $t_{1/2}$ from McIver et al. (1926), Stevens et al. (1987) and Davenport (1966) was converted to $D_e(L_e - L_p)$. If D_m had not been assumed to be negligible, then $D_mL_p + D_e(L_e - L_p)$ would have accounted for $t_{1/2}$, and additional information would be necessary to determine the relative contribution of each constant.

The Cl^-/HCO_3^- exchange coefficient can be estimated in the following manner. The alkaline secretion rate of the stomach has been estimated in the presence or absence of H^+ secretion. The alkaline secretion in the model is $Q_dB_d + T$. Since T varies with p_1, the H^+ secretion rate, and since Q_dB_d is fixed, the exchange coefficient was chosen such that the sum $Q_dB_d + T$ corresponded to the observed alkaline secretion rate. In Table 1, 2.3–2.5 mEq/h are the values observed in the presence of acid secretion, 0.4–0.45 mEq/h are the rates observed without acid secretion. Taking the nonparietal Cl^- and HCO_s^- concentrations as the baseline lumen concentrations, $Q_dB_d + T = 0.4$ mEq/h with the tabulated value of $q_a(L_e - L_p)$. With the peak oxyntic rates tabulated, the sum $Q_dB_d + T \approx 2.3$ mEq/h.

MODEL VERIFICATION

Having obtained, in one way or another, the essential model parameters, we now proceeded to apply the model to steady-state and transient data. Table 5 presents correlations between experimental pCO_2 and model predictions. Note that these in vivo experimental results did not exclude salivary secretions.

In addition, Flemström (1987) reports $pCO_2 > 100$ mmHg in secreting states; with salival contamination our model predicts $pCO_2 > 100$ mmHg whenever the H^+ secretion rate $p_1 > 1.7$ mEq/h; without contamination $pCO_2 > 100$ mmHg whenever 1.8 mEq/h $< p_1 <$ 15.4 mEq/h.

Fig. 2 shows the predicted Na^+ and H^+ lumen concentrations with differing gastric fluid flow rates versus data from Hirst (1989), Makhlouf et al. (1966), and Davenport (1966). The fit is good, but perhaps that is not surprising since the nonparietal secretion parameters from Makhlouf et al. (1966) was fit using this data. On the other hand, the rest of our model's parameters do not correspond with those curve fits. For example, the curves in Fig. 2 for H^+ are shifted to the right because of the presence of the additional HCO_s^- secreted by the surface epithelial cell (SEC) exchanger. The predicted Na^+, K^+, and Cl^- lumen concentrations with differing H^+ lumen concentration versus the same data from Hirst (1989), Makhlouf et al. (1966), and Davenport (1966) is shown in Fig. 3. Note the close agreement between the analytic approximation and the numerical solution.

Fig. 4, adapted from Miyagi et al. (1966), shows the "alkaline tide." Clearly a logarithmically shaped curve is indicated by this data, and, in fact, Miyagi et al. (1966) fit such a curve to this data. Unfortunately, the details of this fit were not presented in their paper but it ". . .corresponds *closely* [our italics] to the calculated pH change which would result from the addition of 1 mEq bicarbonate ion to venous blood per each milliequivalent of hydrogen ion secreted into the stomach." Of course, our model uses the same idea with the addition of considering the flow of blood (and consequent arterial replenishment of HCO_s^- and loss of accumulated H^+) as well as the CO_2 arterial-venous drop, which Miyagi et al. (1966) measured experimentally. Nevertheless, the solution to our model generates the nearly linear relationship shown in Fig. 4, as do different CO_2 transport assumptions shown in Fig. 4 as "analytic." Furthermore, the data is clearly incompatible with arterial pH 7.4 and a consequent rise in pH due to an alkaline tide. The fit is therefore only roughly qualitative, but would be much improved if the arterial pH were 7.1–7.2, as suggested by the data (but not given by Miyagi

TABLE 5 Comparison of lumen pCO_2 versus H secretion

State	pCO_2 lumen	Reference	Model pred.	With saliva
Fasting	60–125 mmHg mean 85 mmHg	Rune et al. (1969)	63–92 mmHg at pH 6–7	83–154 mmHg at pH 6–7
After feeding	90–175 mmHg mean 130 mmHg	Rune et al. (1969)	101–105 mmHg at pH 1–2	146–170 mmHg at pH 1–2

TABLE 6 Predictions for a HCl/NaCl constant infusion CO_2 "clamp" experiment using the steady-state analytic model

120 mM HCl/30 mM NaCl or 150 mM NaCl at 3 ml/min	pCO_2 = 0 mmHg	pCO_2 = 760 mmHg
H^+ = 1.8 mEq/h	Venous blood: pH 7.5, pCO_2 33 mmHg	Venous blood: pH 6.9, pCO_2 119 mmHg
H^+ = 24 mEq/h	Venous blood: pH 9.4, pCO_2 0.5 mmHg	Venous blood: pH 7.1, pCO_2 86 mmHg

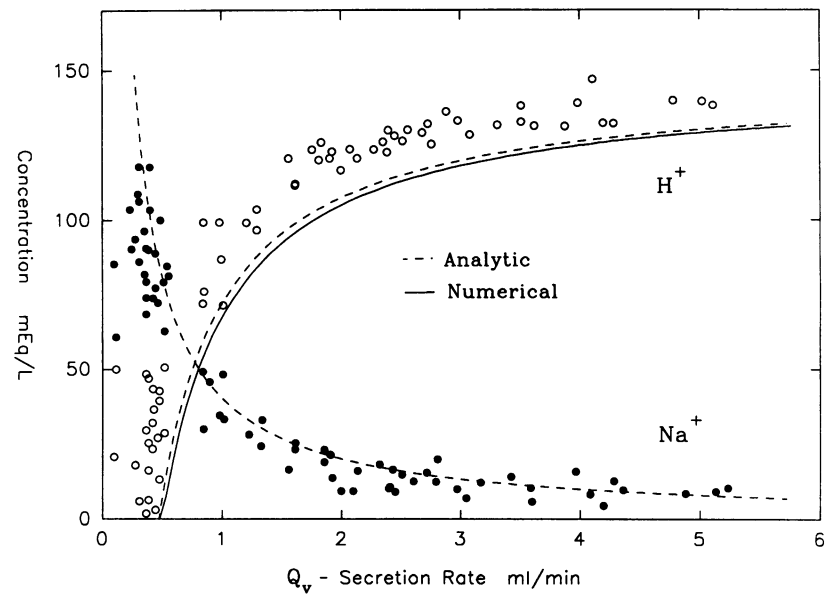

FIGURE 2 Predicted and experimental Na^+ and H^+ versus Q_v.

et al. explicitly). The etiology of the discrepancy between our model and the original figure caption partially quoted above is not clear.

Figs. 5-8 are based on the work of Kurtz and Clark (1947). In these experiments, the CO_2 in the stomach of four dogs was continuously extracted by perfusing with air or pure nitrogen at 6–10 liters/h. A large glass cannula was inserted into the stomach to drain the gastric juices, and the fluid volume and CO_2 accumulated every 30 min was measured. Periodic histamine injections were given to stimulate acid secretion. To simulate this experiment with our model it was necessary to simulate the effective secretion rate (p_1L_p) that was caused by the histamine. The mean secretion rate over each 30-min period was estimated by making p_1L_p proportional to the measured volume per 30 min (as shown in the bottom panel of Figs. 5–8) using the lumen osmotic strength as the constant of proportionality, as before in the estimate of Q_v. It was also necessary to change the exit flow parameter to a small number (1/2 min) to simulate free drainage out the glass cannula since no accumulation of volume in the lumen was noted in the experiment. The results are not particularly sensitive to the exact magnitude of this parameter. To simulate perfusion and collection of the CO_2, we fixed the "Q_v" (the outflow) of CO_2 alone to 8 liters/h. The resulting 8 liters/h × CO_2(lumen) and Q_v were integrated numerically over each 30-min time interval to yield the milliequivalent of CO_2 and fluid volume collected over that time period. However, the data is inconsistent with a baseline secretory rate of q_d = 0.3 ml/min since this would result in at least 10 cc every 30 min. Perhaps evaporation due to their perfusion accounts for this difference; for the purpose of illustration we have subtracted off the baseline volume and CO_2 generated by our model's "nonparietal secretion." Finally, the blood flow rate was roughly scaled to the weight of each dog and the observed gastric fluid volume flow as noted in the figure legends. The agreement is encouraging in light of the number of approximations made in the model and the experimental variability.

MODEL PREDICTIONS

In addition to the comments made previously about K^+ uptake, we offer some other predictions of our model. If we close off the pyloric sphincter so that $Q_v = 0$, we can predict the luminal Cl^- and CO_2, as shown in the Gastric Pouch section of Appendix B. Note that the other ion concentrations

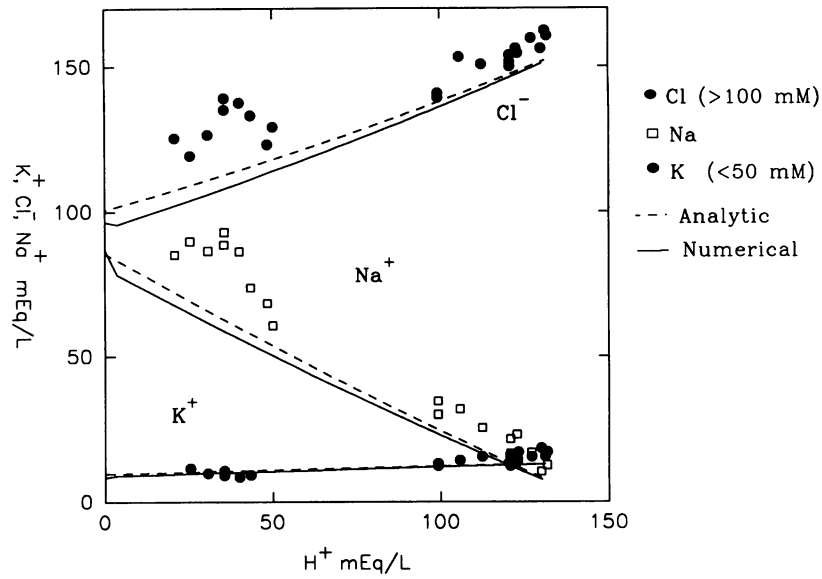

FIGURE 3 Predicted and experimental Na^+, K^+, and Cl^- versus H^+.

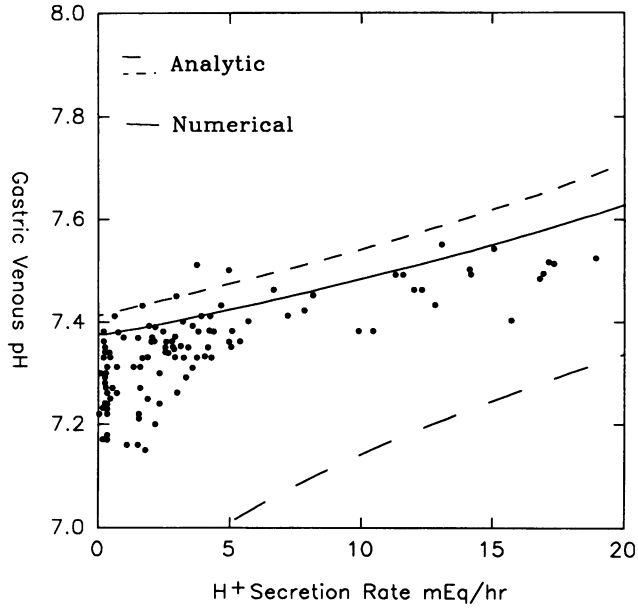

FIGURE 4 Predicted and experimental gastric venous pH versus H^+ secretion rate.

are indeterminate in the steady-state model: in fact, they depend on the starting conditions in the transient solution of the model. This behavior can explain the observation that the cessation of measurable acid secretion does not result in a rise in pH. If the lumen begins at pH 7 with the pylorus relaxed and stimulation occurs the pH drops to 1, as expected. But if the enterogastric reflex (Guyton, 1966) closes the pylorus, our model predicts that a very low level of H^+ secretion will maintain the lumen at pH 1. If the pylorus is closed due to stenosis, or perhaps stress, when the stomach is at pH 7 and secretion begins, our model suggests that levels of secretion normally capable of acidification are no longer capable of lowering the luminal pH. Since part of the stomach's low pH serves a sterilization function, this situation could conceivably result in ulceration due to *Helicobacter pylori* or some other biological agent.

Many other experiments could doubtlessly be simulated, but it is important to measure all of the information necessary to test the model. For example, an interesting experiment by Kivilaakso et al. (1978) was performed on secretory and nonsecretory rabbit gastric pouches in which the intramural (epithelial cell) pH was measured after luminal instillation of 120 mM HCl. Two crucial pieces of information are missing for us to be able to test our model against this data: 1) the CO_2 pressure in the lumen, which has a significant effect on the blood pH, and, more important perhaps; 2) we need to know the relationship between luminal pCO_2, blood pCO_2 and intramural pCO_2. Either we need to invent a mucus-surface epithelial CO_2 submodel as part of our model in the same way as the oxyntic cell is modelled here, with appropriate independent diffusion parameters, or (more simply) the blood pH could have been measured as well. This model can, therefore, be viewed as a guide to experimental data needed to test its underlying assumptions. As an example of a prediction that could be made, we present the following "experiment," similar to that performed by Kivilaakso et al. (1978): infuse a solution of either NaCl at pH 7 or 120 mM HCl at a constant rate into a stomach. In addition, either perfuse the stomach with air to lower the CO_2 or perfuse it with CO_2 at atmospheric pressure. Finally, perform this experiment either in the presence or absence of histamine stimulation of secretion. Then any of the concentrations in the blood or lumen may be predicted. Table 6 shows some output simulating these cases. Note that whether HCl or NaCl was infused made no difference to the venous blood pH and pCO_2.

CONCLUSION

We have formulated a new quasidynamic model of normal physiological gastric acid secretion. Its evolutionary fore-

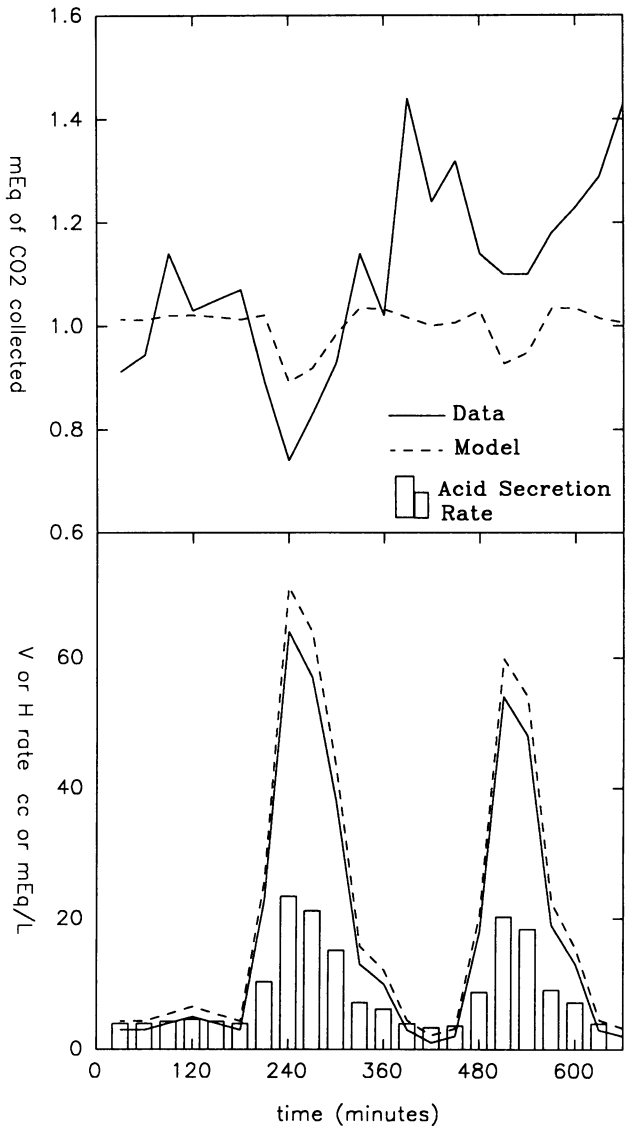

FIGURE 5 Dog no. 1, weight 22 kg, Q_b = 125 ml/min.

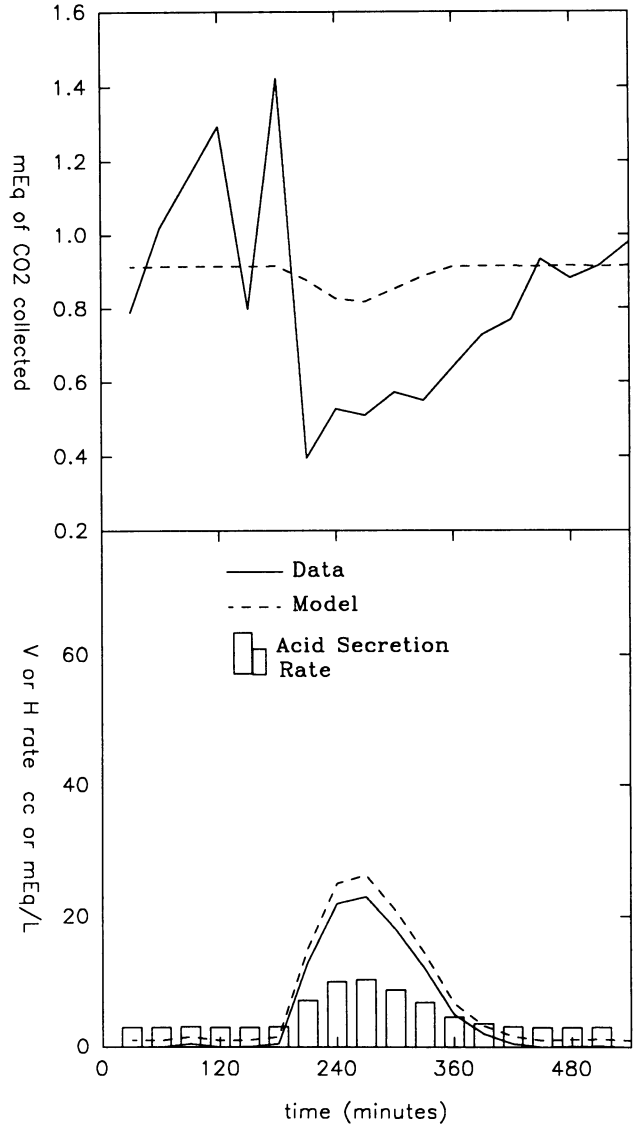

FIGURE 6 Dog no. 2, weight 15 kg, Q_b = 55 ml/min.

bearers include classic macroscopic theories of secretion such as the two-component Pavlov-Hollander, Teorell, Hirschowitz, and Rosemann models as well as cell/molecular mechanism models by Davenport, Sachs, and many others. This model can be solved in closed form in the low stomach pH range in the steady-state. Using this model we attempt to bring together experimental data on lumen ion concentrations and pCO_2 with pH and pCO_2 changes observed in the gastric microcirculation. In addition, the mechanism at the heart of our model, the surface epithelial cell alkaline secretion driven by the oxyntic cell acid secretion, helps to illuminate the stomach's ability to survive any level of its own acid secretion. By contrast, the duodenum bicarbonate secretion has neither the rich (and automatically increasing when necessary) supply of blood born bicarbonate nor the concentration dependent transport mechanism which automatically adjusts the level of bicarbonate delivered.

This work could now proceed in many future directions. More detailed cell models, possibly including transient effects, could be included. The carbonic anhydrase reaction, treated here as a simple equilibrium, could be dealt with more rigorously, including some experimental knowledge about the location of the enzyme in the mucosa. Saturating effects could be included in the Cl^-/HCO_s^- exchanger. With these additions it might be possible to test the effect of inhibitors of the various transporters and enzymes in the system. Other changes along these lines might include modelling the flow of blood and change in the thickness of the mucus layer as a result of prostaglandins, ethanol, or NSAIDs. Combined with a surface epithelial model, such work could lead to a better understanding of ulcer formation in pathophysiological states. It would be a challenge to formulate a realistic model without undue complexity which would relax the open circuit condition, allowing net electrical current to pass from cell to cell within the upstream and downstream region or between the two; certainly it would be interesting to test this condition by measuring the flow of electrical current in the

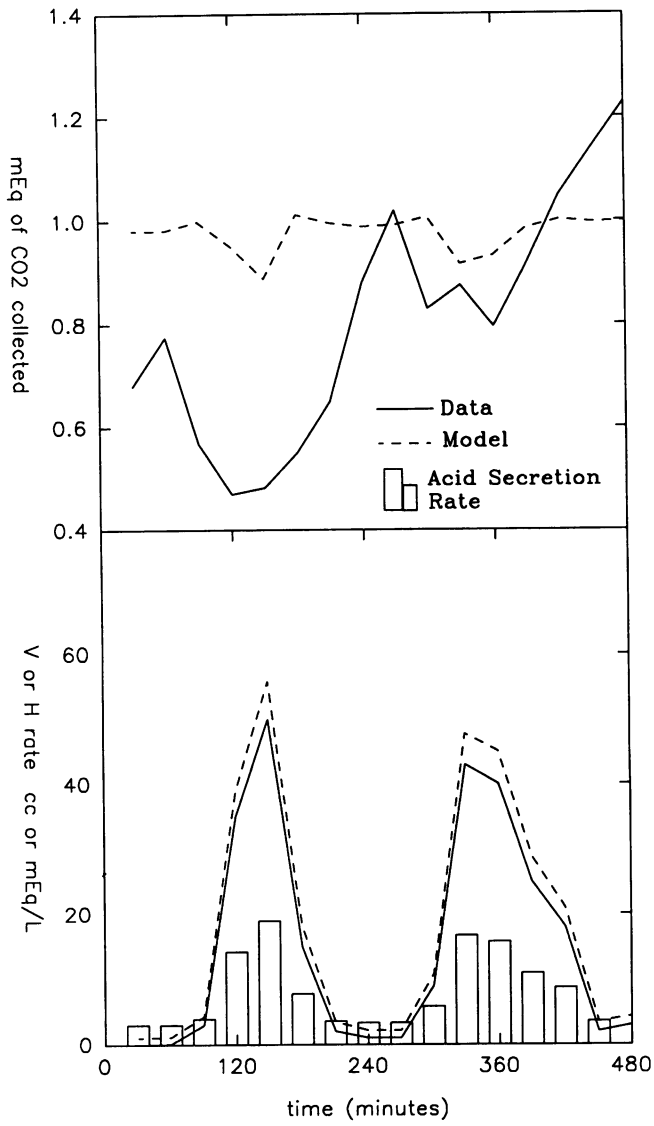

FIGURE 7 Dog no. 3, weight 18 kg, Q_b = 105 ml/min.

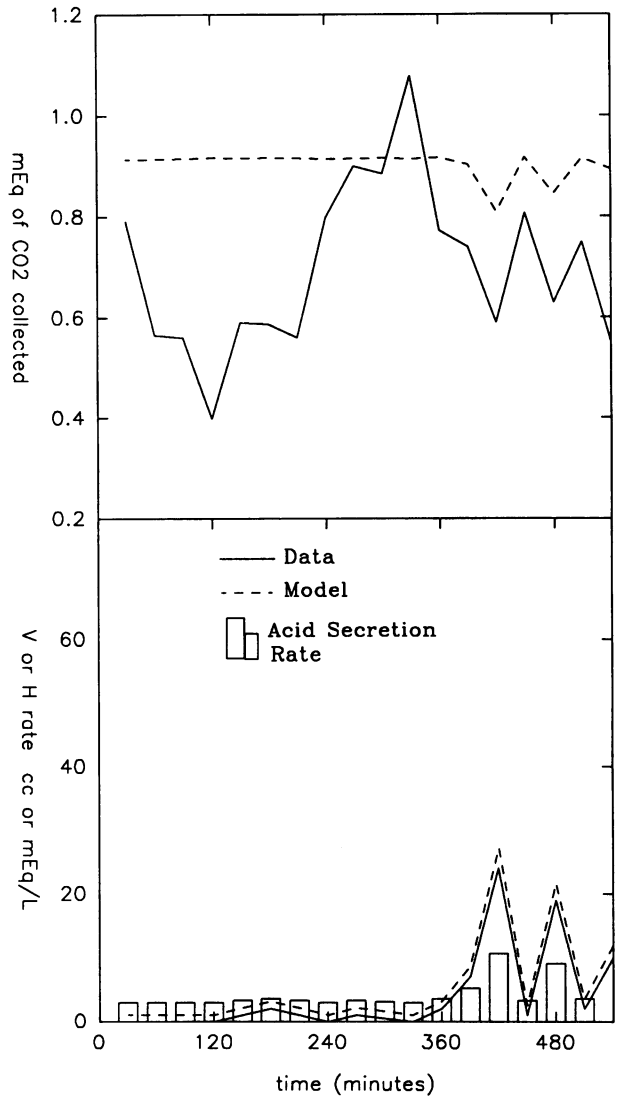

FIGURE 8 Dog no. 4, weight 14 kg, Q_b = 55 ml/min.

gastron. Finally, there are many experiments already performed which have not been compared with the current model's predictions yet. Discrepancies, such as the K^+ uptake, can provide insight into both model improvement and new experiments.

In partial fulfillment of the requirements for the Doctor of Philosophy, The City University of New York (A. M. de Beus, 1992).

APPENDIX A: EFFECTIVE TRANSPORTER ACROSS THE SEC

Consider a linear (nonsaturating) transporter of the form:

$$J_0 \equiv q_a[B_b C_L(y) - B_L(y)C_b]|_{(y=0)} \tag{A1}$$

where y is the distance from the epithelial apical membrane into the mucus layer so that $B_L(y)$ and $C_L(y)$ correspond to the luminal concentrations at some $y = L_y$. One-dimensional steady-state chloride diffusion in the mucus is governed by the following differential equation (D.E.) and Boundary condition (B.C.):

$$\text{D.E.: } D_c \frac{\partial^2 C_L}{\partial y^2} = 0$$
$$\text{B.C.: } D_c \frac{\partial C_L}{\partial y}|_{(y=0)} = J_0 \tag{A2}$$

where D_C is the diffusion constant of chloride in mucus. In accordance with Engel et al.'s (1984) analysis, and imposing electroneutrality on motion in the mucus, we can solve Eq. A2 as follows.

$$C_L(y) = \frac{J_0}{D_c} y + C_L(y=0) \qquad B_L = B_L(y=0) - \frac{J_0}{D_c} y \tag{A3}$$

By substitution, it is now possible to determine the difference between Eqs. A1 and 18 in the model, which uses C_L,B_L at (effectively) $y = 0$ rather than at $y = L_y$:

$$J_0 \equiv q_a[B_b C_L(y) - B_L(y)C_b]|_{(y=0)} = \left.\frac{q_a[B_b C_L(y) - B_L(y)C_b]}{\left[1 + \dfrac{q_a L_y (C_b + B_b)}{D_c}\right]}\right|_{(y=L_y)} \tag{A4}$$

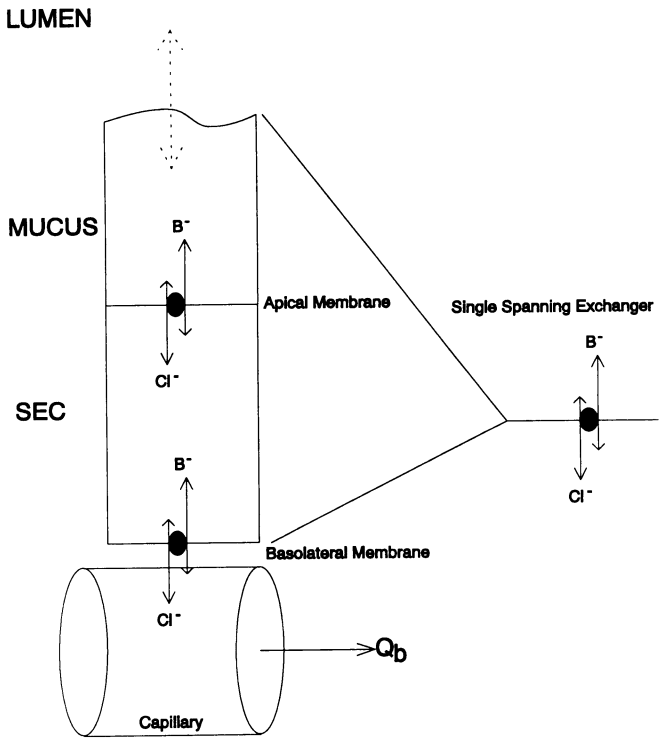

FIGURE 9 Surface epithelial cell (SEC) and mucus reduction to single spanning exchanger.

Of course since $B_b + C_b = B_0 + C_0$, a constant, it is obvious that one-dimensional diffusion in a mucus layer combined with a transporter of the form (Eq. A1) may be represented by a transporter of the same form spanning the mucus layer, as in Eq. 18, with the parameter q_a simply being redefined according to Eq. A4. A second basolateral exchanger (with constant q_b) could be put in series with Eq. A4 to correct for the difference between B_b,C_b and B_i,C_i (inside the SEC) since the B_b,C_b terms in Eqs. A1–A4 should represent cellular values for exchange across the apical membrane while Eq. 18 uses capillary values. In the steady-state, material conservation would imply

$$q_b[B_bC_i - B_iC_b] = \left.\frac{q_a[B_iC_L(y) - B_L(y)C_i]}{\left[1 + \dfrac{q_aL_y(C_b + B_b)}{D_c}\right]}\right|_{(y=L_y)} \quad \text{(A5)}$$

If $B_i + C_i$ is a constant in the SEC to preserve electroneutrality in the absence of other significant ion movement (this is a very simple SEC model with only apical and basolateral Cl^-/B^- exchangers) then Eq. A5 and $B_i + C_i$ = constant may be solved simulataneously for C_i/C_b and B_i/B_b both equal to a constant. Substitution into Eq. A5 would then result in the same form as equation (Eq. 18) spanning the whole epithelial layer as in Fig. 9, with the following form:

$$\frac{q_aq_b(C_i + B_i)(B_bC_L(y) - B_L(y)C_b)|_{(y=L_y)}}{q_b\left[1 + \dfrac{q_aL_y(C_b + B_b)}{D_C}\right](C_b + B_b) + q_a(C_L + B_L)|_{y=L_y}}$$

$$\equiv q_{eff}(B_bC_L(y) - B_L(y)C_b)|_{y=L_y} \quad \text{(A6)}$$

Note that in the main body of the text $C_L = C_L(y)$ evaluated at $y = L_y$.

APPENDIX B: ANALYTIC SOLUTIONS

Finding an analytic (closed form) solution of equations (Eqs. 1–26) is not straightforward: the major difficulty is that the carbonic anhydrase reaction term $Q[H,B,N]$ in each chamber and the epithelial exchange function $\tilde{a}(x)$ are nonlinear. First, assume that the carbonic anhydrase reaction is swift enough to be approximately at equilibrium so that the Henderson-Hasselbach equation applies everywhere. Using the usual pre-equilibrium assumptions standard for catalysis the representation of the reaction follows.

$$Q[H, B, N] = \frac{k_1[\kappa N - HB]}{f[H, B, N]}; \qquad f[H, B, N] > 0 \quad \text{(B1)}$$

In saying that the reaction is very fast we mean that $k_1 \to \infty$. In order for the reaction rate Q to remain bounded $N \to HB/\kappa$. We will therefore *algebraically* eliminate each Q from Eqs. 1–25 (*nota bene*: but do not remove it from the system of equations) and establish $\kappa N = HB$ (the Henderson-Hasselbach equation) at every point. Second, if we are only interested in physiologic solutions to our model at first, we will assume pH ranges in the gastric pit and blood compatible with the secreting or nonsecreting (as opposed to baseline secreting) state a priori. In the secreting stomach we will assume that the pH in the gastric pit/lumen is 1–2 implying $B \ll N$ and $B \ll H$, whereas in the nonsecreting gastric pit/lumen and in the blood, the pH will be at least 6 implying $H \ll N$ and $H \ll B$.

In the capillary, for $0 < x < L_e$, the pH is assumed to be high enough so that $H_b \ll B_b$, pH>5 being easily sufficient. In the upstream region, $x<L_p$, subtracting Eq. 9 from 10 and assuming $B_b - H_b \approx B_b$ yields, upon integration,

$$B_b(x) = B_0 + \frac{p_1}{Q_b}x. \quad \text{(B2)}$$

Equations 12–13 are simply integrated to yield the following.

$$C_b(x) = C_0 - \frac{p_1 + 3p_2}{Q_b}x \quad \text{(B3)}$$

$$K_b(x) = K_0 - \frac{3p_2}{Q_b}x \quad \text{(B4)}$$

Equation 11 and its counterparts for CO_2 are far more difficult to solve since the CO_2 transport between chambers are all mutually interdependent as well as dependent on T. Adding Eqs. 9 to 11 and assuming $H_b + N_b \approx N_b$ yields, in the upstream region:

$$-Q_b\frac{dN_b}{dx} + 3p_2 + D_s[N_p - N_b] = 0 \quad \text{(B5)}$$

whereas adding Eqs. 14 and 16 in the downstream region it yields the following.

$$-Q_b\frac{dN_b}{dx} + D_e[N_L - N_b] = 0 \quad \text{(B6)}$$

Equation 4 is linear in $N_b(x)$ (upstream), N_p, and N_L since $Q[H_p,B_p,N_p] = p_1 + 3p_2$ as noted earlier, and adding Eqs. 20 and 21 and assuming low pH in the secreting stomach so that $B_L + N_L \approx N_L$ yields the following.

$$Q_d(N_d + B_d) - Q_vN_L + T + \int_0^{L_p} D_m[N_p - N_L]\,dx + \int_{L_p}^{L_e} D_e[N_b - N_L]\,dx = 0 \quad \text{(B7)}$$

We have explored various simplifications in the CO_2 equations to render them amenable to solution in terms of Q_v and T, which will be determined below. 1) The assumption that CO_2 diffusion across cell membranes is very fast compared to other forms of transport (D_m and $D_s \to \infty$), such as convection, is common in models of gas exchange in the lung. It can be shown that this assumption cannot satisfy $N_b(L_e) < N_0$, the unusual arterial-venous drop in pCO_2 seen in the stomach as well as the high luminal pCO_2 also observed $N_L > N_0$ (Miyagi et al., 1966; Rune and Henriksen, 1969; Flemström, 1987). 2) However, neither the parietal cells nor the gastric epithelial

cells are thin gas-exchanging barriers; in fact, the first are large cells buried in the gastric pit and the others have a significant mucus layer coating them. Another limiting case lets CO_2 diffusion across the lumen wall be very slow (D_m and $D_e \to 0$). An argument in favor of this approximation is that if diffusion out of the stomach and into the blood were rapid then the high pCO_2 gradients observed between lumen and blood would dissipate in the steady-state. 3) But gas exchange between the parietal cell and the blood should be as rapid as possible to satisfy the high metabolic needs of the ATPase H^+/K^+ pump, and while CO_2 diffusion is undoubtedly low across the mucus lining, ($D_s \to \infty$ and $D_e \to 0$) it would be advantageous for the parietal cell (via D_m) to utilize CO_2 in the lumen to make H^+ and HCO_3^-, since the CO_2 supply available due to metabolism and arterial supply might be inadequate (Miyagi et al., 1966; Eichenholz et al., 1967). 4) But since D_m includes the distance into the pit and the relatively small surface area of the pit, it is better to assume that $D_m \to 0$ rather than $D_e \to 0$ because of the large area represented by surface epithelial cells. In summary, we derive the following equations using $D_s \to \infty$ and $D_m \to 0$:

$$\forall(x \le L_p)\colon N_b(x) = N_p(x) = \left[\frac{M_p - p_l}{Q_b}\right]x + N_0$$

$$\forall(x > L_p)\colon N_b(x) = N_L\left[1 - \exp\left(\frac{D_e(L_p - x)}{Q_b}\right)\right] + N_b(L_p)\exp\left(\frac{D_e(L_p - x)}{Q_b}\right) \quad \text{(B8)}$$

$$N_L = \frac{Q_d(N_d + B_d) + T + [Q_bN_0 + (M_p + p_l)L_p]\left[1 - \exp\left(\frac{D_e(L_p - L_e)}{Q_b}\right)\right]}{Q_v + Q_b\left[1 - \exp\left(\frac{D_e(L_p - L_e)}{Q_b}\right)\right]} \quad \text{(B9)}$$

T remains to be determined. In the blood downstream, for $L_p < x < L_e$, only the chloride and bicarbonate concentrations remain to be determined. The potassium is constant and the proton concentration is found using $H_bB_b = \kappa N_b$ and one of the above simplifications for N_b. Subtracting Eq. 14 from 15 and assuming $B_b - H_b \approx B_b$ as usual at pH>5 yields, upon integration:

$$B_b(x) = B_b(L_p) - \frac{1}{Q_b}\int_{L_p}^{x} \tilde{a}(u)\,du \quad \text{(B10)}$$

whereas integrating Eq. 17 directly yields the following.

$$C_b(x) = C_b(L_p) + \frac{1}{Q_b}\int_{L_p}^{x} \tilde{a}(u)\,du \quad \text{(B11)}$$

Note that the complete integral at $x = L_e$ in Eqs. B10 and B11 is T (see Eq. 19). Addition of Eqs. B10 and B11 shows that the sum $C_b(x) + B_b(x)$ is constant in the downstream region. Substitution of $B_b(x) = B_0 + C_0 - 3p_2L_p/Q_b - C_b(x)$ from Eqs. B2–B3 into Eq. 17 using Eq. 18 yields, upon integration:

$$x - L_p = \frac{Q_b}{q_a}\int_{C_b(L_p)}^{C_b(x)}\left[\frac{du}{C_L\left(B_0 + C_0 - \frac{3p_2L_p}{Q_b}\right) - u(B_L + C_L)}\right] \quad \text{(B12)}$$

which is readily integrated and inverted (for finite Q_b) to yield the following.

$$C_b(x) = \left(C_0 + B_0 - \frac{3p_2L_p}{Q_b}\right)\frac{C_L}{C_L + B_L} - \frac{\left(B_0 + \frac{p_lL_p}{Q_b}\right)C_L - \left(C_0 - \frac{(p_l + 3p_2)L_p}{Q_b}\right)B_L}{C_L + B_L} \times \exp\left[-\frac{C_L + B_L}{Q_b}q_a(x - L_p)\right] \quad \text{(B13)}$$

In addition, we require that $C_LB_b > C_bB_L$ for invertibility. Evaluate T by substitution as follows.

$$T = Q_b\frac{\left(B_0 + \frac{p_lL_p}{Q_b}\right)C_L - \left(C_0 - \frac{(p_l + 3p_2)L_p}{Q_b}\right)B_L}{C_L + B_L} \times \left\{1 - \exp\left[-\frac{C_L + B_L}{Q_b}q_a(L_e - L_p)\right]\right\} \quad \text{(B14)}$$

Gastric outflow; no pyloric obstruction ($Q_v \neq 0$)

In the stomach lumen, for all $Q_v > 0$, in Eq. 20 assume a low pH < 2 to get $H_L - B_L \approx H_L$, substitute $H_L = \kappa N_L/B_L$ to yield:

$$B_L = \frac{\kappa Q_v N_L}{p_lL_p - T + Q_d(H_d - B_d)} \quad \text{(B15)}$$

Integration of Eq. 23 over $[0,L_p]$ yields the following.

$$C_L = \frac{Q_dC_d - T + (p_l + 3p_2)L_p}{Q_v} \quad \text{(B16)}$$

Equations B9 and B14–B16 are simultaneous equations in C_L, B_L, and N_L. They are, furthermore, transcendentally simultaneous by virtue of Eq. B14, and hence analytically unsolvable. Let us take the limit when $C_bB_L/C_LB_b \ll 1$. Physiologically, this limit simply asserts that the exchange of chloride and bicarbonate across the epithelial cell layer is dominated by the blood bicarbonate and the lumen chloride with very little reverse reaction. The solution for H_L becomes, upon substitution of $B_L = \kappa N_L/H_L$ into Eq. B15 as follows.

$$H_L = \frac{p_lL_p - T + Q_d(H_d - B_d)}{Q_v} \quad \text{(B17)}$$

The equation for T then becomes

$$T = (Q_bB_0 + p_lL_p)\left\{1 - \exp\left[-\frac{C_L}{Q_b}q_a(L_e - L_p)\right]\right\} \quad \text{(B18)}$$

which depends only upon C_L, uncoupling the equations for H_L,N_L. Substitution yields

$$C_L + \frac{1}{Q_v}(Q_bB_0 + p_lL_p)\left\{1 - \exp\left[-\frac{C_L}{Q_b}q_a(L_e - L_p)\right]\right\} = \frac{Q_dC_d + (p_l + 3p_2)L_p}{Q_v} \quad \text{(B19)}$$

a single transcendental in C_L. If $C_Lq_a(L_e - L_p)/Q_b$ is sufficiently small the exponential may be approximated by its linear expansion, giving:

$$C_L = \frac{Q_b[Q_dC_d + (p_l + 3p_2)L_p]}{Q_vQ_b + (Q_bB_0 + p_lL_p)(L_e - L_p)q_a}. \quad \text{(B20)}$$

Back substitution of C_L into Eq. B18 yields T for solution of N_L and H_L. Note that the size of $C_Lq_a(L_e - L_p)/Q_b$ is a measure of the rate of epithelial cell ion transport versus convection in the blood. At low pH $T \ll p_lL_p$, implying low transport rates of epithelial cells compared to those of oxyntic cells. K_L and S_L are found by simple integration of Eq. 24 and rearrangement of Eq. 25 as follows.

$$K_L = \frac{Q_dK_d + 3p_2L_p}{Q_v}; \qquad S_L = \frac{Q_dS_d}{Q_v} \quad \text{(B21)}$$

Gastric pouch ($Q_d = 0$ and $Q_v = 0$):

If the outlet to Q_v is blocked, as in a gastric pouch, the preceding analysis fails. First, conditions must be put on the potassium and sodium fluxes to ensure the existence of a solution; no outflow implies no inflow, therefore: 1) K_d and S_d must be zero. 2) The excess potassium secretion provided by p_2 must be zero. This second condition can be met either by setting the pump rate p_2 equal to zero or by replacing the Na^+/H^+ antiport with a Na^+ channel in the parietal cell model. This second option would also affect the other ionic flows, resulting in $g_k^{(2)} = -2p_2$ and $s + g_c^{(1)} = s + g_k^{(1)} = p_1$, making the obvious (and straightforward) changes in the resulting solutions for capillary and lumen concentrations. The solution for C_L would then require that $p_1L_p = T$. Note that in general only N_L and C_L are determined under these conditions; the pH, K_L, and S_L depend on the initial conditions. If we start out with pure HCl in the lumen, we use the low pH approximation provided by Eq. B18 to solve for C_L:

$$C_L = \frac{Q_b}{q_a(L_e - L_p)} \ln\left[1 + \frac{p_1 L_p}{Q_b B_0}\right] \qquad \text{(B22)}$$

N_L is obtained by substitution of p_1L_p for T, while the solution for H_L is identical to that for C_L, reflecting the overall electroneutral transport in and out of the lumen in this model. B_L is determined using the equilibrium equation, while K_L and S_L are zero. Note that Eq. B22 implies that there must be a maximum p_1L_p at which $C_L = ão_L/2$ when $Q_v = 0$.

REFERENCES

Alberts, B., D. Bray, J. Lewis, M. Raff, K. Roberts, and J. Watson. 1989. Molecular Biology of the Cell. 2nd edition. Garland Publishing, Inc., New York. 1218 pp.

Apell, H. 1989. Electrogenic properties of the Na, K pump. *J. Membr. Biol.* 110:103–114.

Ashley, S. W., D. I. Soybel, and L. Y. Cheung. 1986. Measurements of intracellular pH in Necturus antral mucosa by microelectrode technique. *Am. J. Physiol.* 250:G625-G632.

Ashley, S. W., D. I. Soybel, C. D. Moore, and L. Y. Cheung. 1987. Intracellular pH (pH_i) in gastric surface epithelium is more susceptible to serosal than mucosal acidification. *Surgery.* 102(2):371–379.

Atkins, P. W. 1986. Physical Chemistry. 3rd edition. W. H. Freeman & Co., New York. 857 pp.

Berglindh, T. 1984. The mammalian gastric parietal cell in vitro. *Am. Rev. Physiol.* 46:377–392.

Behn, U. 1897. Ueber wechselseitige diffusion von elektrolyten in verdünnten wässerigen lösungen, insbesondere über diffusion gegen das concentrationsgefälle. *Ann. Phys., Lpz., N. F.* 62:54–67.

Browne, J. S. L., and A. M. Vineberg. 1932. The interdependence of gastric secretion and the CO_2 Content of the Blood. *J. Physiol. (Lond.).* 75: 345–363.

Cantor, C., and P. Schimmel. 1980. Biophysical Chemistry. W. H. Freeman & Co., New York. 1371 pp.

Cheung, L. Y. 1978. Enhancement of gastric mucosal tolerance to hydrogen ions (H^+) by intraarterial infusion of sodium bicarbonate. *Surg. Forum.* 29:408–409.

Cheung, L. Y., and S. W. Ashley. 1987. Gastric blood flow and mucosal defense mechanisms. *Clin. Invest. Med.* 10(3):201–208.

Cheung, L. Y., and L. A. Sonnenschein. 1984. Measurement of regional gastric mucosal blood flow by hydrogen gas clearance. *Am. J. Surg.* 147: 32–36.

Cuppoletti, J., and G. Sachs. 1984. Regulation of gastric acid secretion via modulation of a chloride conductance. *J. Biol. Chem.* 259(23):14952–14959.

Darnell, J., H. Lodish, and D. Baltimore. 1986. Molecular Cell Biology. Scientific American Press. New York. 617–750.

Davenport, H. 1966. Physiology of the Digestive Tract. 3rd edition. Year Book Medical Publishers, Chicago. 93–116.

Davenport, H. W. 1967. Chapter 43 - Physiological structure of the gastric mucosa. *In* Handbook of Physiology, Section 6 - Alimentary Canal Vol. II, Secretion. C. F. Code, and W. Heidel et al., editors. American Physiological Society, Wash. DC. 151 pp. 761, 772.

de Beus, A. M. 1992. Ph. D. thesis. City University of New York, New York.

Demarest, J., D. Loo, and G. Sachs. 1989. Activation of apical chloride channels in the gastric oxyntic cell. *Science (Wash. DC).* 245:402–404.

Demarest, J. R., and T. E. Machen. 1989. Chapter 10—Electrophysiology of gastric ion transport. *In* Handbook of Physiology, Section 6—The Gastrointestinal System Vol. III, "Salivary, Gastric, Pancreatic, and Hepatobiliary Secretion." S. G. Schultz, J. G. Forte, and B. B. Rauner, editors. American Physiological Society, Bethesda, MD. 189–201.

Eichenholz, A., D. McQuarrie, A. S. Blumentals, and A. Vennes. 1967. Unique acid-base parameters of gastric venous blood during secretory activity. *J. Appl. Physiol.* 22:580–583.

Elliot, A., L. Risholm, and K. J. Öbrinck. 1942. The exchange diffusion of hydrochloric acid through the gastric mucosa in man. *Acta Med. Scand.* CX, fasc. IV-V:267–281.

Emås, S., K. G. Swan, and E. D. Jacobson. 1967. Chapter 42—Methods of Studying gastric secretion. *In* Handbook of Physiology, Section 6—Alimentary Canal Vol. II, Secretion. C. F. Code, and W. Heidel et al., editors. American Physiological Society, Wash. DC. 745.

Engel, E., A. Peskoff, G. Kauffman, and M. Grossman. 1984. Analysis of hydrogen ion concentration in the gastric gel mucus layer. *Am. J. Physiol.* 247(*Gastro-intest. Liver Physiol. 10*):G321-G338.

Fendler, K., H. van der Hijden, G. Nagel, J. de Pont, and E. Bamberg. 1988. Pump Currents generated by renal Na^+K^+ ATPase and gastric H^+K^+-ATPase on black lipid membranes. *In* Progress in Clinical and Biological Research, 268B. J. Skou, J. Nørby, A. Maunsbach, and M. Esmann, editors. Alan R. Liss, Inc., New York. 501–510.

Flemström, G. 1987. Gastric, and Duodenal Mucosal Bicarbonate Secretion. *In* Physiology of the Gastrointestinal Tract. 2nd edition. L. Johnson, and J. Christensen, editors. Raven Press, New York. 1011–1029.

Flemström, G., and A. Garner. 1989. Chapter 16 - Secretion of bicarbonate by gastric and duodenal mucosa. *In* Handbook of Physiology, Section 6 The Gastrointestinal System Vol. III, "Salivary, Gastric, Pancreatic, and Hepatobiliary Secretion." S. G. Schultz, J. G. Forte, and B. B. Rauner, editors. American Physiological Society, Bethesda, MD. 309–314.

Flemström, G., and L. Turnberg. 1984. Gastroduodenal defense mechanisms. *Clin. Gastroenterol.* 13:327–354.

Forte, J. 1970. Hydrochloric acid secretion by gastric mucosa. *In* Membranes and Ion Transport 3. E. Bittar, editor. Wiley-Interscience, New York. 111–165.

Forte, J., T. Machen, and K. Öbrink. 1980. Mechanisms of gastric H^+, and Cl^- transport. *Annu. Rev. Physiol.* 42:111–126.

Forte, T., T. Machen, and J. Forte. 1977. Ultrastructural change in oxyntic cell associated with secretory function: a membrane-recycling hypothesis. *Gastroenterology.* 73:941–955.

Frölich, O., and R. Gunn. 1986. Erythrocyte anion transport: the kinetics of a single-site obligatory exchange system. *Biochim. Biophys. Acta.* 864: 169–194.

Goldman, D. 1943. Potential impedence and rectification in membranes. *J. Gen. Physiol.* 27:37–60.

Grossman, M. I. 1967. Chapter 47 - Neural and hormonal stimulation of gastric acid secretion. *In* Handbook of Physiology, Section 6 - Alimentary Canal Vol. II, Secretion. C. F. Code, and W. Heidel et al., editors. American Physiological Society, Wash. DC. 849.

Gunn, R., and O. Frölich. 1979. Asymmetry in the mechanism for anion exchange in human red blood cell membranes. Evidence for reciprocating sites that react with one transported anion at a time. *J. Gen. Physiol.* 74:351–374.

Guth, P. H., H. Baumann, M. I. Grossman, D. Aures, and J. Elashoff. 1977. Measurement of gastric mucosal blood flow in man. *Gastroenterology.* 72: 1066, 1977.

Guth, P. H., F. W. Leung, and G. L. Kauffman. 1989. Physiology of Gastric Circulation. *In* Handbook of Physiology, Section 6 - The Gastrointestinal System Vol. I, "Motility, and Circulation," Part 2. S. G. Schultz, J. D. Wood, and B. B. Rauner, editors. American Physiological Society, Bethesda, MD. 1375–1377.

Guyton, A. 1986. Textbook of Medical Physiology. 7th ed. W. B. Saunders Co., Philadelphia. 1057 pp.

Harris, J., and I. Edelman. 1964. Chemical concentration gradients and electrical properties of gastric mucosa. *Am. J. Physiol.* 206(4):769–782.

Hersey, S., G. Sachs, and K. Kasbekar. 1985. Acid Secretion by frog gastric mucosa is electroneutral. *Am. J. Physiol.* 248(*Gastrointest. Liver Physiol.* 11):G246-G250.

Hirschowitz, B. I. 1989. Chapter 8 - Neural and hormonal control of gastric secretion. *In* Handbook of Physiology, Section 6 - The Gastrointestinal System Vol. III, "Salivary, Gastric, Pancreatic, and Hepatobiliary Secretion." S. G. Schultz, J. G. Forte, and B. B. Rauner, editors. American Physiological Society, Wash. DC. 127–157.

Hirst, B. H. 1989. Chapter 15 - Gastric mucosal barrier. *In* Handbook of Physiology, Section 6 - The Gastrointestinal System Vol. III, "Salivary, Gastric, Pancreatic, and Hepatobiliary Secretion." S. G. Schultz, J.G. Forte, and B. B. Rauner, editors. American Physiological Society, Wash. DC. 280–298.

Hollander, D. and A. S. Tarnawski, editors. 1989. Gastric Cytoprotection - A Clinician's Guide. Plenum Medical Book Co., New York.

Hodgkin, A., and A. Huxley. 1952. Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *J. Physiol.* 116:449–472.

Hunt, J., and B. Wan. 1967. Chapter 44 - Electrolytes of mammalian gastric juice. *In* Handbook of Physiology, Section 6 - Alimentary Canal Vol. II, Secretion. C. F. Code, and W. Heidel et al.,editors. Am. Phys. Soc. 781–804.

Hviid-Larsen, E., and B. Rasmussen. 1982. Chloride channels in toad skin. *Proc. R. Soc. Lond. B. Biol. Sci.* 299:413–434.

Ito, S., and G. Schofield. 1974. Studies on the depletion and accumulation of microvilli and changes in the tubulovesicular compartment of mouse parietal cells in relation to gastric acid secretion. *J. Cell Biol.* 63:364–382.

Kivilaakso, E., and G. Flemström. 1984. HCO_3^- secretion and surface pH gradient in rat duodenum exposed to luminal acid. *Scand. J. Gastroenterology.* 19(Suppl. 92):51–54.

Kivilaakso, E., D. Fromm, and W. Silen. 1978. Effect of the acid secretory state on intramural pH of rabbit gastric mucosa. *Gastroenterology.* 75: 641–648.

Kivilaakso, E., D. Fromm, and W. Silen. 1981. Chapter 22 - Pathogenic and protective mechanisms in experimental gastric mucosal injury. *In* Basic Mechanisms of Gastrointestinal Mucosal Cell Injury. J. W. Harmon, editor. Williams & Wilkins, Baltimore. 415 pp.

Knauf, P., L. Spinelli, N. Mann, B. Diefenbach, D. Kozody, and D. Restepo. 1989. Tests of the ping-pong model for anion transport in red blood cells and HL60 promyelocytic leukemic cells. *In* Anion Transport Protein of the Red Cell Membrane. N. Hamasaki, and M. Jennings, editors. Elsevier Science Publishing Co., New York. 15–25.

Konturek, S. J. 1989. Chapter 9—Inhibition of gastric acid secretion. *In* Handbook of Physiology, Section 6—The Gastrointestinal System Vol. III, "Salivary, Gastric, Pancreatic, and Hepatobiliary Secretion." S. G. Schultz, J. G. Forte, and B. B. Rauner, editors. American Physiological Society, Wash. DC. 163–165.

Kurtz, L. D., and B. B. Clark. 1947. The inverse relationship of the secretion of hydrochloric acid to the tension of carbon dioxide in the stomach. *Gastroenterology.* 9:594–602.

Läuger, P. 1980. Kinetic properties of ion carriers and channels. *J. Membr. Biol.* 57:163–178.

Läuger, P., W. Stephan, and E. Frehland. 1980. Fluctuations of barrier structure in ionic channels. *Biochim. Biophys. Acta.* 602:167–180.

Lechene, C. 1988. Physiological role of the Na-K pump. *In* Progress in Clinical and Biological Research. 268A. J. Skou, J. Nørby, A. Maunsbach, and M. Esmann, editors. Alan R. Liss, Inc., New York. 171–194.

Lew, V., and R. Bookchin. 1986. Volume, pH, and ion-content regulation in human red cells: analysis of transient behaviour with an integrated model. *J. Membr. Biol.* 92:57–74.

Lew, V., H. Ferreira, and T. Moura. 1979. The behaviour of transporting epithelial cells. I. Computer analysis of a basic model. *Proc. R. Soc. Lond. B. Biol. Sci.* 206:53–83.

Lee, P., C. Code, and J. Scholer. 1955. The influence of varying concentrations of sodium chloride on the rate of absorption of water from the stomach and small bowel of human beings. *Gastroenterology.* 29:1008–1015.

Lorentzon, P., G. Sachs, and B. Wallmark. 1988. Inhibitory effects of cations on the gastric H^+,K^+-ATPase. *J. Biol. Chem.* 263:10705–10710.

Machen, T. E., and J. G. Forte. 1979. Gastric Secretion. *In* Membrane Transport in Biology. Vol. IV Transport Organs. G. Giebisch, D. C. Tosteson, and H. H. Ussing, editors. Springer-Verlag, New York. 693–747.

Makhlouf, G. M., J. P. A. McManus, and W. I. Card. 1966. A quantitative statement of the two-component hypothesis of gastric secretion. *Gastroenterology.* 51:149–171.

Malagelada, J. 1977. Quantification of gastric solid-liquid discrimination during digestion of ordinary meals. *Gastroenterology.* 72:1264–1267.

Malagelada, J. R., and F. Azpiroz. 1989. Chapter 23—Determinants of gastric emptying and transit in the small intestine. *In* Handbook of Physiology, Section 6—The Gastrointestinal System Vol. I, "Motility, and Circulation," Part 2. S. G. Schultz, J. D. Wood, and B. B. Rauner, editors. American Physiological Society, Wash. DC. 917–922.

Malinowska, D., and G. Sachs. 1984. Cellular mechanisms of acid secretion. *Clin. Gastroenterol.* 13:309–326.

Meeroff, J. 1984. Ulcer disease of the upper gastrointestinal tract. *Hosp. Pract.* October:77–99.

McIver, M. A., A. C. Redfield, and E. B. Benedict. 1926. Gaseous exchange between the blood and the lumen of the stomach and intestines. *Am. J. Physiol.* 76:92–111.

Milhorn, H. T., and P. E. Pulley. 1968. A theoretical study of pulmonary capillary gas exchange and venous admixture. *Biophys. J.* 8:335–357.

Miyagi, S., C. P. Shoemaker, and S. R. Powers. 1966. Carbon dioxide metabolism in the intact mammalian stomach. *Surgery.* 59:1083–1091.

Muallem, S., D. Blissard, E. Cragoe, Jr., and G. Sachs. 1988. Activation of the Na^+/H^+ and Cl^-/HCO_3^- exchange by stimulation of acid secretion in the parietal cell. *J. Biol. Chem.* 263:14703–14711.

Muallem, S., C. Burnham, D. Blissard, T. Berglindh, and G. Sachs. 1985. Electrolyte transport across the basolateral membrane of the parietal cells. *J. Biol. Chem.* 260:6641–6653.

Negulescu, P., A. Harootunian, R. Tsien, and T. Machen. 1990. Fluorescence measurements of cytosolic free Na concentration, influx, and efflux in gastric cells. *Cell Regul.* 1:259–268.

Nordgren, B. 1963. The rate of secretion and electrolyte content of normal gastric juice. *Acta Physiol. Scand.* 58(suppl.):202.

Öbrinck, K. J. 1948. Studies on the kinetics of the parietal secretion of the stomach. *Acta Physiol. Scand.* 15(suppl.):51.

Paradiso, A., R. Tsien, J. Demarest, and T. Machen. 1987. Na-H and Cl-HCO_3 exchange in rabbit oxyntic cells using fluorescence microscopy. *Am. J. Physiol. (Cell Physiol. 22)*:C30-C36.

Perez, A., D. Blissard G. Sachs, and S. Hersey. 1989. Evidence for a chloride conductance in secretory membrane of parietal cells. *Am. J. Physiol.* 256 (*Gastrointest. Liver Physiol. 19*):G299-G305.

Peskin, C. 1982. Mathematics in Medical Physiology: An Introductory Course. Courant Institute of Mathematical Sciences.

Press, W., B. Flannery, S. Teukolsky, and W. Vetterling. 1988. Numerical Recipes in C, The Art of Scientific Computing. Cambridge University Press, New York.

Rehm, W. 1972. Some aspects of the problem of gastric hydrochloric acid secretion. *Arch. Intern. Med.* 129:270–278.

Rehm, W. 1953. Electrical resistance of resting and secreting stomach. *Am. J. Physiol.* 172:689–699.

Rehm, W. 1956. Effect of electric current on gastric hydrogen ion and chloride ion. *Am. J. Physiol.* 185:325–331.

Rehm, W. S., C. F. Butler, S. G. Spangler, and S. S. Sanders. 1970. A model to explain uphill water transport in the mammalian stomach. *J. Theor. Biol.* 27:433–453.

Rehm, W., and M. LeFevre. 1965. Effect of dinitrophenol on potential, resistance, and H^+ rate of frog stomach. *Am. J. Physiol.* 208:922–930.

Rehm, W., and S. Sanders. 1975. Implications of the neutral carrier Cl^--HCO_3^- exchange mechanism in gastric mucosa. *Ann. NY Acad. Sci.* 264: 442–455.

Rossi, R., and P. Garrahan. 1988. A Comparison between the empirical behaviour of the Na, K ATPase and the predictions of the Albers-Post model. *In* Progress in Clinical and Biological Research. 268A. J. Skou, J. Nørby, A. Maunsbach, and M. Esmann, editors. Alan R. Liss, Inc., New York. 349–354.

Rune, S. J. 1966. Comparison of the rates of gastric acid secretion in man after ingestion of food and after maximal stimulation with histamine. *Gut.* 7:344–350.

Rune, S. J., and F. W. Henriksen. 1969. Carbon dioxide tensions in the proximal part of the canine gastrointestinal tract. *Gastroenterology.* 56: 758–762.

Rutten, M. J., R. Delcore, D. I. Soybel, C. D. Moore, and L. Y. Cheung. 1989.

Effects of cations and pH on apical membrane potential of in vitro Necturus antrum. *Am. J. Physiol.* 256:G798–807.

Sachs, G., L. Faller, L., and E. Rabon. 1982. Proton/hydroxyl transport in gastric and intestinal epithelia. *J. Membr. Biol.* 64:123–135.

Sachs, G., S. Muallem, S., and S. Hersey. 1988. Passive and active transport in the parietal cell. *Comp. Biochem. Physiol.* 90A:727–31.

Silen W., Schiessel, R., and A. Merhav. 1980. Mechanism of protection of amphibian gastric mucosa by nutrient HCO_s^-. *In* Hydrogen Ion Transport in Epithelia. I. Schultz et al., editors. Elsevier/North-Holland Biomedical Press, New York. 373–378.

Solomon, A., B. Chasan, J. Dix, M. Lukacovic, M. Toon, and A. Verkman. 1983. The aqueous pore in the red cell membrane: band 3 as a channel for anions, cations, nonelectrolytes, and water. *Ann. NY Acad. Sci.* 414: 97–124.

Soybel, D. I., S. W. Ashley, Z. Y. Yan, R. A. Swarm, and L. Y. Cheung. 1986. Regional gastric mucosal blood flow after parietal cell vagotomy in dogs. *Surgery.* 100:167–174.

Starlinger, M., R. Jakesz, R., J. B. Matthews, Ch. Yoon, and R. Schiessel. 1981. The relative importance of HCO^{-3} and blood flow in the protection of rat gastric mucosa during shock. *Gastroenterology.* 81:732–735.

Stein, W. 1986. Transport and Diffusion across Cell Membranes. Academic Press, Inc., San Diego. 685 pp.

Stevens, M. H., R. C. Thirlby, and M. Feldman. 1987. Mechanism for high PCO_2 in gastric juice: roles of bicarbonate secretion and CO_2 diffusion. *Am. J. Physiol.* 253(*Gastrointest. Liver Physiol.* 16):G527-G530.

Stewart, B., B. Wallmark, and G. Sachs. 1981. The interaction of H^+, and K^+ with the partial reactions of gastric ($H^+ + K^+$)-ATPase. *J. Biol. Chem.* 256:2682–2690.

Takeuchi, K., D. Magee, J. Critchlow, J. Matthews, and W. Silen. 1983. Studies of the pH gradient and thickness of frog gastric mucus gel. *Gastroenterology.* 84:331–340.

Teorell, T. 1949. Membrane electrophoresis in relation to bio-electrical polarization effects. *Arch. Sci. Physiol.* 3:205–218.

Thull, N., and W. Rehm. 1956. Composition and osmolarity of gastric juice as a function of plasma osmolarity. *Am. J. Physiol.* 185:316–324.

Tosteson, D. C., and J. F. Hoffman. 1960. Regulation of cell volume by active cation transport in high and low potassium sheep red cells. *J. Gen. Physiol.* 44:169–194.

Ueda, S., D. Loo, D., and G. Sachs. 1987. Regulation of K^+ channels in the basolateral membrane of Necturus oxyntic cells. *J. Membr. Biol.* 97:31–41.

Ussing, H. 1949. The distinction by means of tracers between active transport and diffusion. *Acta Physiol. Scand.* 19:43–56.

Villegas, L. 1962. Cellular location of the electrical potential difference in frog gastric mucosa. *Biochim. Biophys. Acta.* 64:359.

Villegas, L. 1963. Action of histamine on the permeability of the frog gastric mucosa to potassium and water. *Biochim. Biophy. Acta.* 75:377–386.

Weiss, L. 1977. Histology: Cell and Tissue Biology. 5th ed. Elsevier North-Holland Biomedical Press, New York. 1219 pp.

Wenzl, E., and T. Machen. 1989. Intracellular pH dependence of buffer capacity and anion exchange in the parietal cell. *Am. J. Physiol.* 257 (*Gastrointest. Liver Physiol. 20*):G741-G747.

Wieth, J., O. Andersen, J. Brahm, P. Bjerrum, and C. Borders. 1982. Chloride-bicarbonate exchange in red blood cells: physiology of transport and chemical modification of binding sites. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 299:383–399.

Wolosin, J. 1985. Ion transport studies with H^+-K^+-ATPase-rich vesicles: implications for HCl secretion and parietal cell physiology. *Am. J. Physiol.* 248 (*Gastrointest. Liver Physiol.* 11):G595-G607.

Wolosin, J., and J. Forte. 1983. Kinetic properties of the KCl transport at the secreting apical membrane of the oxyntic cell. *J. Membr. Biol.* 71: 195–207.

Wood, J. G., G. M. Wicina, and L. Y. Cheung. 1990. Effect of histamine and 1,4-methylhistamine on gastric vascular resistance in dogs. *Am. J. Physiol.* 258:G440–446.