REFERENCES

- Barton, A. D. & Young, L. (1943). *J. Amer. chem. Soc.* **65**, 294.
 Berenbom, M. (1947). Thesis, University of Toronto.
 Feigenbaum, J. & Neuberger, C. A. (1941). *J. Amer. chem. Soc.* **63**, 3529.
 Klyne, W. & Marrian, G. F. (1945). *Biochem. J.* **39**, xlv.
 Klyne, W., Schachter, B. & Marrian, G. F. (1948). *Biochem. J.* **43**, 231.
 Laughland, D. H. & Young, L. (1942). *Trans. roy. Soc. Can.* **III**, 36, 166.
 Laughland, D. H. & Young, L. (1944). *J. Amer. chem. Soc.* **66**, 657.
 Lesnik, M. & Nencki, M. (1886). *Ber. dtsh. chem. Ges.* **19**, 1534.
 Mauthner, J. (1881). *Jber. Fortschr. Tierchem.* **11**, 230.
 Paterson, J. Y. F. & Klyne, W. (1948). *Biochem. J.* **43**, 614.
 Young, L., Morrison, A. R. & Billett, F. S. (1950). Unpublished observations.

Chemical and Electrical Energy Relations for the Stomach

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The use of isolated acid-secreting gastric mucosa as experimental material makes it possible to measure concomitantly the rate of respiration (a process which makes energy available), and the rate of acid secretion (a process which requires energy). Moreover, the maximum energy that can be made available from respiration, and the minimum energy required to maintain the secretion, can be calculated. The efficiency of energy conversion can therefore be calculated by comparing the ratio of the rate of acid secretion to the rate of respiration found experimentally with the ratio calculated on the assumption that all the energy from respiration is available to do secretory work. This comparison indicates that the secretory process has a very high efficiency: it approaches 100%.

Similarly, the electrical work done by isolated gastric mucosa can be measured and compared with that available from exergonic processes in the tissue. In addition to this, the passage of an electric current through an acid-secreting gastric mucosa can increase or decrease the rate of acid secretion (Rehm, 1945; Rehm & Hokin, 1948; Crane, Davies & Longmuir, 1948*a, b*), and estimations can be made of the efficiency of these processes.

A part of this work was communicated to the Biochemical Society, on 24 September 1948 (Crane & Davies, 1948*a, b*).

EXPERIMENTAL

Saline media. The salt solutions were those described by Davies & Terner (1949). For manometric experiments the phosphate saline gassed with 100% O₂ was used; for the electrical experiments the bicarbonate saline, gassed with 5% CO₂ + 95% O₂, was used. Both saline solutions contained 0.2% (w/v) glucose.

Preparation of gastric mucosa. Frogs (*Rana temporaria temporaria* L.) were captured locally, housed in an outdoor froggery under natural conditions and provided with an excess of worms and insects for food (Bradford, Crane & Davies, 1950).

The gastric mucosa was washed and isolated immediately after the frog was pithed. For the manometric experiments it was then tied with silk at both ends and weighed (Davies, 1948*a*). For electrical experiments it was opened along the lesser curvature and mounted in a Perspex holder (Crane *et al.* 1948*a*).

Manometric experiments. The Q_{O₂} (μl./mg. dry wt./hr.) of the tied bags of frog gastric mucosa was measured at 25.0° with Warburg manometers in the usual way (Dixon, 1943). Conical cups (20–30 ml. capacity) were used and the CO₂ absorbed by alkali in the centre well. After a 20 min. equilibration period the pressure changes in the manometer were measured for 2–7 hr. Histamine was added from the side arm, when required, to a final concentration of 5 × 10⁻⁵ M, after the basal O₂ uptake had become steady. This was usually 1.5–2.5 hr. after the cups had been put into the bath.

At the end of the incubation the swollen bags of mucosa were removed, and the amounts of HCl produced were determined by weighing and by electrometric titration (Davies, 1948*a*; Davies & Longmuir, 1948).

Electrical experiments. The material, apparatus and methods used for the electrical experiments were similar to those previously described by Crane *et al.* (1948*a, b*). The Perspex holder containing the frog gastric mucosa was mounted between two chambers at 25.0°. The Q_{HCl} (μl./mg. dry wt./hr.) of the mucosa was estimated by measuring the changes in pH of the secretory solution *in situ*, and also by replacing the secretory solution and estimating its acid content either manometrically by the addition of a bicarbonate solution or by electrometric titration.

The potential difference (p.d.) across the mucosa was measured by a battery-operated Marconi pH meter, and potentiometer Type TF 511 C. Saturated calomel electrodes and saturated KCl bridges with internal ground-glass joints, which dipped into the nutrient and secretory solutions, were

used. Current was passed through the mucosa by means of zinc-zinc acetate electrodes separated from the solutions bathing the mucosa by the agar layers previously described (Crane *et al.* 1948a). The resistance was obtained from the slope of the graph p.d. across mucosa against current through it, a correction being applied for the resistance of the solution.

RESULTS

Manometric experiments

Method of comparing the rates of respiration and acid secretion. When the oxygen uptake of a tied bag of gastric mucosa was measured, the amount of hydrochloric acid secreted in response to histamine could not be determined until the bag was opened at

Fig. 1. Variation with time of Q_{O_2} of (a) normal unstimulated frog gastric mucosa, (b) mucosa which secreted acid after the addition of histamine at H, (c) abnormal mucosa with rapidly decreasing rate of respiration. The dotted lines in (b) show how the mean ΔQ_{O_2} (Table 2) was calculated.

the end of the incubation period and the contents removed (Davies & Longmuir, 1948). The average Q_{HCl} after the addition of histamine could then be compared with the average increase in Q_{O_2} during the same period, and their ratio determined. As it was important that the mucosae should not be secreting acid spontaneously before the addition of histamine, these experiments were done in late autumn, winter and early spring, when isolated frog gastric mucosa does not secrete spontaneously (Bradford *et al.* 1950).

Ulcers and perforations occurred regularly in tied bags of frog gastric mucosa which were secreting acid at high rates for 4–6 hr. in the absence of external supplies of carbon dioxide (Davies & Longmuir, 1948). In the present experiments the incubations

were therefore usually continued for only 2–3 hr. after the addition of histamine, and any mucosa which perforated was rejected, since loss of secretion occurred through the hole formed in the bag.

Table 1. Mean rates of acid secretion and respiration of isolated frog gastric mucosa

Mean Q_{HCl} after histamine (μ l./mg. dry wt./hr.)	Mean Q_{O_2} before histamine (μ l./mg. dry wt./hr.)	Mean ΔQ_{O_2} after histamine (μ l./mg. dry wt./hr.)
0.6	-1.4	-0.2
0.9	-1.7	-0.35
1.2	-2.2	-0.15
1.3	-1.5	-0.35
1.4	-0.9	-0.7
1.4	-1.9	-0.2
1.4	-1.8	-0.4
1.5	-1.6	-0.2
1.5	-2.0	-0.6
1.6	-2.0	-0.25
1.7	-2.5	-0.25
1.7	-1.4	-1.15
1.8	-2.5	-0.5
1.9	-2.0	-0.2
1.9	-2.1	-0.3
2.0	-3.0	-0.3
2.0	-2.2	-0.2
2.1	-2.9	-0.2
2.1	-2.6	-0.2
2.2	-2.2	-0.6
2.2	-1.7	-0.5
2.2	-1.9	-0.4
2.3	-2.0	-0.15
2.4	-1.0	-1.0
2.5	-3.2	-0.2
2.5	-1.5	-0.25
2.6	-3.0	-0.4
2.7	-1.9	-0.3
2.8	-2.4	-0.3
3.5	-2.6	-0.55
3.7	-2.6	-0.35
3.8	-2.0	-0.4
4.4	-2.7	-0.35
4.6	-2.1	-0.7

The average Q_{HCl} after the addition of histamine could be determined accurately; the average increase in the value of the Q_{O_2} (mean ΔQ_{O_2}) was subject to greater error, because the value the Q_{O_2} would have attained if the mucosa had not been stimulated was unknown. Fig. 1a shows the variation with time of the rate of respiration of a typical unstimulated mucosa. Fig. 1b is plotted for a mucosa which responded well to histamine. In calculating the mean ΔQ_{O_2} it was assumed that stimulated mucosae would have shown a steady behaviour similar to that of mucosa A if they had not been stimulated. Very occasionally (see Fig. 1c) the respiration rate of a resting mucosa was not maintained, but fell away rapidly. The respiration rate of a small proportion of the stimulated mucosae showed a similar fall; results for these mucosae were rejected.

Rates of respiration and acid secretion. Table 1 gives values of the mean Q_{HCl} after histamine, the mean Q_{O_2} before histamine and the mean ΔQ_{O_2} after histamine, for thirty-four isolated frog gastric mucosae. The ratio mean Q_{HCl} /mean $|Q_{O_2}|$ (the

separate experiments: it was not possible to measure all the variables for the same mucosa. A mean Q_{HCl} of 2.0 was chosen as representative (see Table 1, and also Bradford *et al.* 1950). The Q_{O_2} of -2.1 is an average value for fifty non-secreting isolated frog gastric mucosae (Crane *et al.* 1948*a*); the change of 0.3 in the mean Q_{O_2} during acid secretion is estimated from the results given in Table 1 and results for other mucosae (Davies, 1948*a*). The p.d. of -30 mV. before acid secretion is an average value for ninety-four mucosae and the p.d. decrease of 10 mV. is an average value for a Q_{HCl} of 2 (Crane *et al.* 1948*a*); the values for the resistance are taken from the same source. The latent electric power is the maximum electric power this average mucosa might be expected to produce (i.e. if it were in a circuit with zero external resistance); it is (p.d.)²/resistance, and the values given are for 1 mg. dry wt. (Crane *et al.* 1948*a*; Crane & Davies, 1950).

CALCULATIONS

Energy required for the production of gastric hydrochloric acid

The minimum free energy increase of the reactants (ΔF) which is required for the formation of hydrochloric acid in mammalian gastric mucosa has been calculated by several workers (Hill, 1931; Teorell, 1933; Hanke, 1937; Davenport & Fisher, 1940; Gray, 1943; Rehm, 1945). They all used the formula

$$\Delta F = nRT \log_e a_o/a_{pi},$$

where n is the number of g.mol. of ion secreted, R the gas constant, T the absolute temperature, and a_{pi} and a_o the molar activities of the ions in the plasma and the oxyntic cell secretion respectively. Since the primary gastric acid is approximately isotonic with blood (Babkin, 1950) the concentrations of the ions can be substituted for their activities.

The results do not agree in detail because the workers used different premises. Gray (1943) gives 1532 cal. as the minimum free energy required at 37° to form 1 l. oxyntic cell secretion containing 0.159M-H⁺, 0.007M-K⁺ and 0.166M-Cl⁻. This is 9650 cal./g.mol. hydrochloric acid. For the acid secreted by frog oxyntic cells at 25° a similar calculation gives 8800 cal./g.mol. hydrochloric acid formed at 0.12M concentration. However, the effective minimum free energy required for secretion

Fig. 2. Relation between mean Q_{HCl} and mean ΔQ_{O_2} after histamine for thirty-four isolated frog gastric mucosae. The horizontal and vertical lines represent the estimated errors in the mean ΔQ_{O_2} and Q_{HCl} . The significance of the lines A-C is discussed in the text.

value of $|Q_{O_2}|$ is the positive number with the same numerical value as Q_{O_2}) after histamine had an average value of 0.9 for these mucosae. In Fig. 2 the mean Q_{HCl} after histamine is plotted against the mean ΔQ_{O_2} after histamine for these mucosae; the significance of the three lines through the origin is discussed later.

Electrical experiments

The p.d. across isolated frog gastric mucosa decreases in magnitude when acid secretion commences, either spontaneously or after the addition of histamine (Crane *et al.* 1948*a*). The resistance of the mucosa, which is normally constant for current densities up to at least 0.4 mA./sq.cm. (Crane & Davies, 1950), was found in all of six experiments to increase at the onset of acid secretion (Crane *et al.* 1948*a*). These effects were reversed when acid secretion stopped.

Table 2 gives data for an average isolated frog gastric mucosa at 25.0° (Crane & Davies, 1948*b*). These data were obtained from a large number of

Table 2. *Physical and metabolic data for an average isolated frog gastric mucosa*
(Temp., 25.0°; thickness of mucosa, 0.25 mm.; dry wt. in 1 sq.cm. of holder 9.5 mg.)

Variable	Value before HCl secretion	Value during HCl secretion	Change
Q_{HCl} (μl./mg. dry wt./hr.)	0	2.0	2.0
Q_{O_2} (μl./mg. dry wt./hr.)	-2.1	-2.4	-0.3
Potential difference (mV.)	-30	-20	10
Resistance of mucosa in 1 sq.cm. of holder (Ω-sq.cm.)	210	280	70
Latent electric power, i.e. (p.d.) ² /resistance, for 1 mg. dry wt. (μW./mg. dry wt.)	0.45	0.15	-0.30

of acid may well be higher than the value calculated above on the basis of thermodynamic assumptions (isothermal, reversible reactions in ideal solutions).

It is generally accepted that the primary acid secretion is isotonic with blood collected at a distance from the stomach (Babkin, 1950; see however Linde, Teorell & Öbrink, 1947). This has been taken to imply that no osmotic work is done on the water of the secretion, since its mole fraction remains constant (Gray, 1943; Hollander, 1943). However, acid-secreting gastric mucosa replaces chloride ions from the blood quantitatively by bicarbonate ions (Davenport, 1946; Davies, 1948*a*). Therefore no ions are lost from the blood.

The volume of blood which is used for the production of 1 ml. of gastric juice depends on the rate of secretion; an average value of about 50 ml. can be calculated from the figures of Lim, Ni, Necheles & Chang (1929), Hanke (1937), Mann, Grindlay & Mann (1941) (dogs) and Teorell (1933) (cats). Isolated frog gastric mucosa, at 25° in a Warburg cup with 4.0 ml. nutrient solution, which secretes 0.1 ml. acid (a representative figure) must similarly concentrate the ions in the nutrient solution by 4.0/3.9. However, Ogston (1950) has shown that the osmotic work involved is only about 10 cal./mol. hydrochloric acid for both mammals and amphibia. It is of interest that if all the hydrogen ions come initially from water (discussed by Davies, 1951), about 2.9 ml. water must disappear for each litre of acid gastric juice secreted.

Energy available from metabolism within oxyntic cells, and values of $Q_{\text{HCl}}/|Q_{\text{O}_2}|$

Some thermodynamic relations for metabolic processes obtained by Ogston & Smithies (1948) have been applied to oxyntic cells by Davies & Ogston (1950). The maximum free energy available from the oxidation of glucose by atmospheric oxygen under physiological conditions of temperature, and glucose, oxygen and carbon dioxide concentrations is about 116,000 cal./mol. oxygen. The value 8800 cal./mol. hydrochloric acid, quoted above as the thermodynamic minimum free energy for the formation of frog gastric secretion, gives a maximum value for $Q_{\text{HCl}}/|Q_{\text{O}_2}|$ of about 13; the approximate value of 10,000 cal./mol. used earlier (Crane & Davies, 1948*a*) gives a ratio of 11.6.

The oxidation energy has been considered in two stages: first, the energy of oxidation between atmospheric oxygen and cytochrome *c* (ferri/ferro = 1), 52,000 cal./mol. oxygen, and secondly the rest of the energy, 64,000 cal./mol. oxygen; this division fits in well with the energy requirements of the previously described mechanisms 1 and 2 (Crane & Davies, 1948*a*; Davies & Ogston, 1950).

In mechanism 1 (Robertson & Wilkins, 1948; Conway & Brady, 1948; Crane & Davies, 1948*a*), the hydrogen ions come from the process

this is the overall reaction for glucose oxidation, which gives a $Q_{\text{HCl}}/|Q_{\text{O}_2}|$ ratio of 4. The energy available from oxidations between oxygen and cytochrome *c* is ample to produce the gastric hydrochloric acid. In mechanism 2 (Crane *et al.* 1948*a*; Davies & Ogston, 1950) the energy available from the breakdown of each molecule of creatine phosphate produces two hydrogen ions. Reasons have been presented for believing that this mechanism, using the rest of the oxidation energy, allows values of $Q_{\text{HCl}}/|Q_{\text{O}_2}|$ up to 6.8.

If the increase in metabolism after histamine provides the power used for acid secretion, then the ratio (mean Q_{HCl} for the period of increased respiration after histamine/mean increase in Q_{O_2} for this period) is the same for the whole mucosa as for the secretory units of the oxyntic cells. In Fig. 2 the lines through the origin give the three $Q_{\text{HCl}}/\Delta|Q_{\text{O}_2}|$ ratios just discussed: *A* (13), *B* (6.8), *C* (4). Within experimental errors $Q_{\text{HCl}}/\Delta|Q_{\text{O}_2}|$ could be less than 13 for every mucosa represented in Fig. 2; less than 6.8 for two-thirds of them, and less than 4 for only one-third.

Energy available from electrical processes

The very high efficiencies suggested by the results in Fig. 2, approaching 100% for one-third of the mucosa, make it necessary to consider whether any energy is available for acid secretion from the basal metabolism of the mucosa. The latent electric power of the average mucosa (Table 2) was 0.30 $\mu\text{W.}/\text{mg. dry wt.}$ less during secretion than before, and it seems possible that this power is used for secretory work. Since 1 cal./sec. = 4.2 W., the power required for a Q_{HCl} of 2 in frog gastric mucosa is 0.9 $\mu\text{W.}/\text{mg. dry wt.}$ (using the figure 8800 cal./mol. HCl), so that in this case an appreciable fraction, one-third, of the energy needed for hydrochloric acid secretion would come from basal metabolic energy. It is clear, however, that the whole of the energy needed for high rates of hydrochloric acid secretion could not come from this source: the total latent electric power of a mucosa with a p.d. of even 50 mV. could not support a Q_{HCl} greater than 2.5, and values of 8 or more have been observed.

Using the assumptions on which lines *A* and *B* (Fig. 2) are drawn, the average increase in $|Q_{\text{O}_2}|$ of 0.3 on secretion would provide 1.8 and 0.9 $\mu\text{W.}/\text{mg. dry wt.}$ respectively. If *A* is correct, the increase in Q_{O_2} can provide all the energy needed for hydrochloric acid secretion in the average mucosa if the efficiency of utilization of the energy from increased respiration is 0.9/1.8, or 50%. On the other hand, if

B is correct the efficiency must be 0.9/0.9, or 100 %. But if that part of the metabolic energy represented by the change in the latent electric power is also available for secretion, the efficiency of utilization of the increase in metabolic energy need be only 0.6/1.8, or 33 % for A or 0.6/0.9 or 67 % for B .

DISCUSSION

Rates of respiration and secretion in frog gastric mucosa

In calculating efficiencies, the comparison of the mean Q_{HCl} after histamine stimulation with the increase in the rate of oxygen uptake after stimulation is based on the following four assumptions: (1) the acid collected at the end of the experiments is the whole of the acid secreted; (2) the whole of the increase in respiration of the mucosa following the addition of histamine supplies energy used by the oxyntic cells for the secretion of hydrochloric acid; (3) only aerobic reactions lead to the production of hydrochloric acid; (4) the basal respiration of the whole mucosa is needed to maintain the general integrity of the tissue and does not provide either hydrogen ions or energy for acid secretion.

Assumption (1) is based on the following results. Teorell (1933, 1939, 1947) found that hydrogen ions can diffuse through mammalian gastric mucosa, and Turner (1949) found that back-diffusion of hydrogen ions can also occur in frog and toad gastric mucosa, but that it is negligible unless the pH is less than about 2. In the present series of experiments the pH of the total gastric contents was always above 2 (cf. Davies & Longmuir, 1948) so the loss of hydrogen ions from this cause would be insignificant (cf. Davies & Ogston, 1950).

Evidence in favour of assumption (2) is provided by the fact that the respiratory and secretory activity of only the oxyntic cells respond to histamine; other gastric cells are not affected (Davies, 1948a; Babkin, 1950).

Assumption (3) is probably correct because hydrochloric acid secretion stops when oxygen is removed or its utilization inhibited in both isolated tissue (Ivy, 1943; Davies, 1948a, 1950; Crane, Davies & Longmuir, 1946; Crane *et al.* 1948a) and in the intact stomach (Rehm & Hokin, 1947; Rice & Ross, 1947). In anaerobiosis the p.d. across the mucosa is abolished, and the stomach ferments glucose to lactic acid. It is of interest that oxyntic cells can secrete continuously without fatigue (Hollander, 1943; Babkin, 1950), in contrast to muscle which can do work anaerobically, develop an oxygen debt, and become fatigued.

Assumption (4) presents more difficulties; if it is true, the thermodynamic efficiency of hydrochloric acid production must be remarkably high: it was 50 % or more for about two-thirds of the mucosae

used and 100 % for some, within the experimental error (Fig. 2). Moreover, it would exclude either of the mechanisms 1 and 2 (lines C and B) acting alone, since either would give an efficiency greater than 100 % for many mucosae.

It may be, however, that part of the energy or some of the hydrogen ions from the unstimulated respiration can be utilized for acid secretion. In this case the experimental results do not exclude mechanism 2 (B) or even mechanism 1 (C) alone, since the mean Q_{HCl} of the mucosa for the whole experiment was never greater than the mean Q_{O_2} . This result is expected when phosphate saline gassed with 100 % oxygen is used and carbon dioxide is absorbed by alkali in the centre well of the Warburg cup (Davies & Longmuir, 1948), because there are then no external supplies of carbon dioxide available to the tissue to maintain the acid/base balance within the oxyntic cells. However, during the initial unstimulated respiration there is built up a steady-state concentration of carbon dioxide in the liquid and gas spaces of the manometer. After the onset of secretion some of this carbon dioxide can be used by the mucosa, so a high rate of acid secretion (and of carbon dioxide uptake) can be maintained for a short period, resulting in a Q_{HCl} higher than the stimulated Q_{O_2} (Table 1).

In order to assess the part played in acid secretion by the resting respiration of the whole mucosa, which can be measured, it is necessary to know the fraction of this respiration due to the oxyntic cells. Unfortunately this cannot be determined with techniques at present available. The cells comprise about 10 % or less of the volume of gastric mucosa (Davies & Roughton, 1948), but Engström & Glick (1950) have shown recently that the ratio dry weight/wet weight for dog oxyntic cells is only 0.1, which is half the average for the whole mucosa; their dry weight is therefore only 5 % of that of the whole mucosa. This means that only a small fraction of the resting metabolism of the mucosa occurs in the oxyntic cells. The resting Q_{O_2} of the corpus region of frog gastric mucosa, containing oxyntic cells, which constitute only a small fraction of its dry weight, is however somewhat higher than that of the pyloric antrum (Davies, 1948a), which contains none. Therefore the resting Q_{O_2} of these cells is probably greater than the average Q_{O_2} of the whole mucosa.

Some confirmation of the results in Fig. 2 has been published by Teorell (1949a). He measured the rate of acid secretion of a sheet of isolated frog gastric mucosa stimulated with histamine in a bicarbonate saline gassed with 5 % CO_2 + 95 % O_2 (Teorell & Wersäll, 1945), and then transferred the membrane to a Warburg cup and measured the Q_{O_2} in phosphate saline. This method has the advantage that throughout the experiments carbon dioxide is either available externally, or is continuously reformed from bi-

carbonate (Davies & Longmuir, 1948). Thus no damage occurs, even at high rates of acid secretion. A disadvantage is that the rates of acid secretion and of respiration are measured for consecutive periods, when conditions may not be the same. The Q_{HCl} and Q_{O_2} were measured for four to six mucosae at 15, 20, 25, 28 and 33°. The results showed that ' $Q_{\text{HCl}}/Q_{\text{O}_2}$ ' is of the order of 2.2 (probable variation 1.1–4.4). It is important to realize that the total $|Q_{\text{O}_2}|$ values were used; the comparable average ratio in the present experiments is 0.9. Teorell (1949*a*) did not determine the increase in $|Q_{\text{O}_2}|$ on acid secretion, so his results are not directly comparable with those in Fig. 2. However, they emphasize the remarkably high efficiency of acid-secreting gastric mucosa.

Electrical energies in amphibian and mammalian gastric mucosa

It is shown above that part, but not the whole, of the energy needed for acid secretion in isolated frog gastric mucosa could come from the energy which, in the resting mucosa, is available for doing external electrical work. There is no direct evidence that this is so, but it is consistent with experimental results, and is reasonable on theoretical grounds (Crane *et al.* 1948*a, b*; Davies & Ogston, 1950). The two main experimental results, the decrease in p.d. across the mucosa (and therefore in the electric power available externally) at the onset of acid secretion, and the increase or decrease in the rate of acid secretion by the passage of current through mucosae already secreting acid, according to the direction of the current, were also observed in live dogs (Rehm, 1944, 1945).

Teorell (1949*a*) wrote 'although a covariation between secretion rate and potential could be traced in some single experiments, it was not possible, in our material, to find such a pronounced general relationship between potential and H^+ production, as has recently been argued by Rehm (1944, 1945) and Crane, Davies & Longmuir (1948*a*)'. However, it appears (Teorell, 1949*b*), that in many of his experiments acid secretion was occurring spontaneously before the p.d. changes following the addition of histamine were measured. Both Rehm (1944, 1945, 1950) and the present writers have found that the major change in p.d. takes place at the onset of secretion, and that further increases in the secretory rate normally have smaller effects. This probably accounts for the apparent discrepancy between the results.

Rehm (1944, 1950) and Rehm & Hokin (1947) have pointed out that in dog stomach the rate of acid secretion increases from low to high rates whilst the p.d. across the stomach wall varies by only a few millivolts; the extra electrical energy available is quite insufficient to account for the increased rate of secretion. The increase in the rate of respiration

during acid secretion in mammalian stomach, which would supply energy to maintain all or part of the secretion, has not yet been determined. Further discussion on the electrical energy relations will be postponed until this and other information is available.

Rates of respiration and secretion in mammalian gastric mucosa

It is technically very difficult to measure the oxygen consumption of a mammalian stomach which is actively secreting acid, and rates of secretion measured at the same time as the Q_{O_2} have been much lower than those found in animals not subject to the severe operational trauma needed for such experiments. However, the maximum rates of acid secretion for men and dogs which have been found (Davies, 1948*a, b*) are up to 100 $\mu\text{l./mg. dry wt./hr.}$ for the whole gastric mucosa; the Q_{HCl} of the oxyntic cells must therefore have been at least 2000. This rate of activity is remarkably high compared with metabolic quotients for other mammalian cells (cf. Krebs & Johnson, 1948).

Even on the assumption of 100% efficiency in the secretion of 0.16*M*-hydrochloric acid, the Q_{O_2} of the oxyntic cells must be –170 for ratio *A*, –200 for *B* (mechanism 2) and –500 for *C* (mechanism 1). These figures are about twice those given by Crane & Davies (1948*a*), which were calculated before the results of Engström & Glick (1950) were published (see p. 173). They must be exceeded if the cells are not 100% efficient.

Since $|Q_{\text{O}_2}|$ values for most mammalian tissues are less than 20, maximally secreting oxyntic cells must be amongst the most active mammalian cells. It is, however, unlikely that values of $|Q_{\text{O}_2}|$ as high as 500 occur in any mammalian cells; this supports the view that mechanism 1 above is quantitatively inadequate, and that most of the metabolic energy of oxyntic cells is canalized into making the hydrochloric acid, by mechanisms 1 and 2 acting together as discussed by Davies & Ogston (1950).

Although the oxyntic cells must have such a high rate of respiration, the Q_{O_2} of the gastric mucosa is probably within the range of Q_{O_2} values for other tissues, even when it is secreting acid: the increase in Q_{O_2} of the gastric mucosa due to maximal acid secretion would be only one-twentieth of the values quoted above. It is of interest that most oxyntic cells are separated from each other, with their bases on the outside of the gastric tubules very close to the capillary network. This makes possible the high rates of exchange between these cells and the blood, of oxygen, carbon dioxide, water and substrates, which occur during high rates of acid secretion. A system of highly active cells embedded in a less active structure may also occur in tissues with high average rates of metabolism such as kidney and retina.

SUMMARY

1. Measurements have been made of the mean Q_{O_2} of isolated frog gastric mucosa before histamine stimulation and of the mean Q_{HCl} and Q_{O_2} during the secretory period.

2. Figures are given for the changes on secretion of the p.d., resistance and latent electric power of a representative mucosa, with corresponding Q_{O_2} and Q_{HCl} values.

3. The energy required for the production of

gastric hydrochloric acid is compared with the energy available from metabolism. If the increase in the rate of respiration of the mucosa provides the power for secretion, the efficiency of the secretory process is very high, approaching 100 %. A quantitative discussion is given of the possibility that energy is also available for secretion from the basal metabolic energy, either as a result of the change in latent electric power or otherwise.

4. It is shown that mammalian oxyntic cells are among the most active cells in the body.

REFERENCES

- Babkin, B. P. (1950). *Secretory Mechanism of the Digestive Glands*. New York: Hoeber.
- Bradford, N. M., Crane, E. E. & Davies, R. E. (1950). *Proc. zool. Soc. Lond.* **120**, 471.
- Conway, E. J. & Brady, T. G. (1948). *Nature, Lond.*, **162**, 457.
- Crane, E. E. & Davies, R. E. (1948a). *Biochem. J.* **43**, xliii.
- Crane, E. E. & Davies, R. E. (1948b). *Biochem. J.* **43**, xliii.
- Crane, E. E. & Davies, R. E. (1950). *Trans. Faraday Soc.* **46**, 598.
- Crane, E. E., Davies, R. E. & Longmuir, N. M. (1946). *Biochem. J.* **40**, xxxvi.
- Crane, E. E., Davies, R. E. & Longmuir, N. M. (1948a). *Biochem. J.* **43**, 321.
- Crane, E. E., Davies, R. E. & Longmuir, N. M. (1948b). *Biochem. J.* **43**, 336.
- Davenport, H. W. (1946). *Physiol. Rev.* **26**, 560.
- Davenport, H. W. & Fisher, R. B. (1940). *Amer. J. Physiol.* **131**, 165.
- Davies, R. E. (1948a). *Biochem. J.* **42**, 609.
- Davies, R. E. (1948b). The mechanism of hydrochloric acid production by the stomach. Ph.D. Thesis, University of Sheffield.
- Davies, R. E. (1951). *Biol. Rev.* **26**, 87.
- Davies, R. E. & Longmuir, N. M. (1948). *Biochem. J.* **42**, 621.
- Davies, R. E. & Ogston, A. G. (1950). *Biochem. J.* **46**, 324.
- Davies, R. E. & Roughton, F. J. W. (1948). *Biochem. J.* **42**, 618.
- Davies, R. E. & Turner, C. (1949). *Biochem. J.* **44**, 377.
- Dixon, M. (1943). *Manometric Methods*, 2nd ed. Cambridge University Press.
- Engström, A. & Glick, D. (1950). *Science*, **111**, 379.
- Gray, J. S. (1943). *Gastroenterologia*, **1**, 390.
- Hanke, M. E. (1937). *Science*, **85**, 54.
- Hill, A. V. (1931). *Adventures in Biophysics*. London: Milford.
- Hollander, F. (1943). *Gastroenterology*, **1**, 401.
- Ivy, H. B. (1943). Quoted by Gray (1943).
- Krebs, H. A. & Johnson, W. A. (1948). *Tabul. biol., Berl.*, **19**, 100.
- Lim, R. K. S., Ni, T. G., Necheles, H. & Chang, H. C. (1929). *Chin. J. Physiol.* **3**, 123.
- Linde, S., Teorell, T. & Öbrink, K. J. (1947). *Acta physiol. scand.* **14**, 220.
- Mann, F. D., Grindlay, J. H. & Mann, F. C. (1941). *Amer. J. digest. Dis.* **8**, 451.
- Ogston, A. G. (1950). Private communication.
- Ogston, A. G. & Smithies, O. (1948). *Physiol. Rev.* **28**, 283.
- Rehm, W. S. (1944). *Amer. J. Physiol.* **141**, 537.
- Rehm, W. S. (1945). *Amer. J. Physiol.* **144**, 115.
- Rehm, W. S. (1950). *Gastroenterology*, **14**, 401.
- Rehm, W. S. & Hokin, L. E. (1947). *Amer. J. Physiol.* **149**, 162.
- Rehm, W. S. & Hokin, L. E. (1948). *Amer. J. Physiol.* **154**, 148.
- Rice, H. V. & Ross, R. T. (1947). *Amer. J. Physiol.* **149**, 77.
- Robertson, R. N. & Wilkins, M. J. (1948). *Nature, Lond.*, **161**, 101.
- Teorell, T. (1933). *Skand. Arch. Physiol.* **66**, 225.
- Teorell, T. (1939). *J. gen. Physiol.* **23**, 263.
- Teorell, T. (1947). *Gastroenterology*, **9**, 425.
- Teorell, T. (1949a). *Experientia*, **5**, 409.
- Teorell, T. (1949b). Private communication.
- Teorell, T. & Wersäll, R. (1945). *Acta physiol. scand.* **10**, 243.
- Turner, C. (1949). *Biochem. J.* **45**, 150.