et al. 1967, Schmid *et al.* 1969). In large intestine, however, studies on patients with ulcerative colitis have shown that the potential is often reversed in the diseased areas. This is found when the disease is active and the potential does not always return to normal until some considerable time after an acute attack (Edmonds 1970). In some patients, despite the absence of ulceration, grossly abnormal PD measurements were persistent for months.

Finally, something needs to be said about electric current measurements. The observed potential depends on an electric current provided by the flow of charged particles or ions, and a resistance provided by the permeability barriers of the epithelium. Change of the potential results either from change of current or from change of resistance; measurement of potential alone does not reveal which is responsible. To measure current, techniques developed for studies with other tissues have been applied to intestinal epithelium. In general these are *in vitro* techniques and although measurements can be made in living animals (Edmonds & Marriott 1970) they are not practicable in man.

With an *in vitro* method the electrical resistance of the epithelium can be measured easily if the tissue is mounted as a sheet with both sides bathed by solution in a chamber of the type described by Ussing & Zerahn (1951) which they originally introduced for amphibian skin studies. It is then possible to determine if a change of potential results from altered tissue resistance or whether it reflects a change in ionic transport. In addition to observations on resistance, the current generated by the tissue can be measured and can give information about which ions are chiefly responsible for the potential. When the solutions bathing the epithelium are of identical composition and a current is passed so as to reduce the transepithelial potential to zero, then the value of this so-called short-circuit current must be equal to the sum of all active ionic transport occurring in the epithelium. If at the same time, using radioisotope methods, the actual transport rates of ions are measured, the net ionic movements can be compared with the current. Thus, how much each ion is contributing to the current can be deduced. It is possible, therefore, by using this method to see how changes of potential due to the action of hormones, drugs, substrates, &c., depend on alterations in tissue resistance or depend on changes in the net movement of the various species of ions being actively transported. Clearly such techniques offer considerable assistance in interpreting potential measurements and potential variations under a variety of conditions; unfortunately the practical difficulties have so far confined their use mainly to the *in vitro* situation and so restricted their application.

In summary, therefore, the electrical potential that is measured in the intestine may arise from several sources. The diffusion potentials and osmotically-induced potentials occur in non-living systems, but of particular significance to us are the transfer potentials which are unique to biological systems and associated with active transport. As outlined above, the magnitude of the transfer potentials is dependent on a variety of factors, for example various metabolic and hormonal influences, the part of intestine where measurements are done, and the composition both in regard to electrolytes and nonelectrolytes of the solutions bathing the tissue. If any meaningful interpretation of potential measurements is to be made, these many influences must be defined.

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Intestinal Handling of Urea and Ammonia

The origins of intestinal ammonia are several (Fig 1):

(1) Ingested ammonia. Except when ammonium chloride or ammonium cycle resins are taken by mouth, the amount ingested is likely to be small. Analysis of fæcal dialysate (Metcalfe-Gibson *et al.* 1967) shows no increase in ammonia concentration after ingestion of ammonium salts; the ammonia is probably absorbed high in the small intestine where the pH is favourable to non-ionic diffusion.

(2) Peptic digestion of protein yields some ammonia from glutamine residues (Melville 1935, Webster *et al.* 1958).

(3) Autolysis of bacterial protoplasm in the colon probably provides some ammonia, for the ammonia content of fæces steadily increases after they are shed (Ing & Wrong, unpublished) and the precursor cannot be urea which is not present in normal fæces.

(4) The main source of intestinal ammonia is undoubtedly bacterial hydrolysis of urea. Urea

destruction in normal man is about 45% of the urea pool per day (Walser & Bodenlos 1959), equivalent to 5 g urea or 170 mEq ammonia per day. Although urea hydrolysis occurs in both mouth and stomach, the colon is the major site (Folin & Denis 1912). In uræmia, urea hydrolysis, and hence colonic production of ammonia, is increased in proportion to the blood urea (Scholz 1968, Deane *et al.* 1968, Robson *et al.* 1968, Walser 1970).

The several fates of intestinal ammonia are also shown in Fig 1:

(1) A small amount (average normal 11 mEq/l.) is passed in the fæces (Wrong *et al.* 1965).

(2) Colonic bacteria are probably able to utilize ammonia in the synthesis of their own protoplasm, but the amounts involved are unlikely to be large, as fæcal total nitrogen is normally less than 2 g/day, and the figure is not increased in uræmia (Stanbury & Lumb 1962).

(3) By exclusion, the greater part of the ammonia produced in the intestine must be absorbed. Direct measurement of portal venous ammonia (Folin & Denis 1912, McDermott *et al.* 1954) indicates that this is mainly into the portal vein. Colonic perfusion experiments with buffered solutions of different pH (Castell & Moore 1968) suggest that non-ionic diffusion of ammonia is an important mechanism in such absorption, and further evidence is provided by a highly significant negative correlation between the pH and the ammonia concentration of fæcal dialysate (Wrong 1971). From the work of Jacobs (1927) and Rosenfeld *et al.* (1963), who studied other biological membranes, it appears likely that non-ionic diffusion would be greatly enhanced by the presence of bicarbonate (which is actively secreted by the mucosa of both small and large intestine) and experimental work in the rat confirms that this is so (Swales *et al.* 1970). Bicarbonate not only creates an alkaline medium favourable to non-ionic diffusion, but maintains this alkalinity, in the face of continued generation of hydrogen ion from non-ionic diffusion of ammonia, because carbon dioxide also back-diffuses through the mucosa:

$$NH_4^+ + HCO_3^- \xrightarrow[\uparrow \quad \uparrow]{\text{diffusion}} NH_3 + CO_2 + H_2O$$

Most of the ammonia reaching the liver is recycled into urea in the Krebs-Henseleit cycle, but some is converted into amino acids and hence into tissue protein; the amount of ammonia which follows the latter route appears to be determined mainly by competition between the amino acids arising from dietary protein and the amount of ammonia reaching the liver (Richards *et al.* 1967).

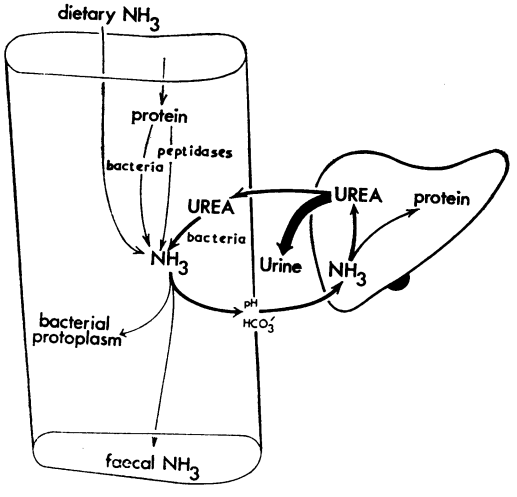

Fig 1 *Enterohepatic circulation of urea and ammonia*

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Use of Closed Jejunal Segments for Studying Intestinal Absorption in Man [*Abridged*]

During the course of a pharmacological study of intestinal absorption, marked species variations came to light (Nissim 1960, 1964, 1965, Hart & Nissim 1963, 1964). It therefore became important to devise a suitable method of studying absorption in man. Intubation techniques in conscious man (Miller & Abbott 1934, Schedl & Clifton 1963, Holdsworth & Dawson 1964) are not accurate enough to detect small changes in absorption and therefore a direct approach to the jejunum was made during operations on the upper abdomen in man.