Loss from the Small Intestine

BRIAN CREAMER, MD, FRCP, Physician, St Thomas's Hospital, and Senior Lecturer in Medicine, St Thomas's Hospital Medical School, London

In this paper the small intestine is considered as a source of loss, the mirror image of its major function, absorption. It is appropriate to contrast the skin and the gut. The skin lets through little water and electrolyte, although even this may at times hazard the body's economy, and the epidermis divides comparatively slowly with a turnover time of about twenty-eight days. Furthermore, cells are not shed intact but as squames, keratin husks without nuclei and perhaps also without other substances such as iron which are re-circulated before shedding. By contrast, the small intestine of man shows no evidence of conservation but freely sheds cells that are almost intact and allows a fluid flux into the lumen of up to 30 litres a day (Love, 1970).

The terminology of this passage of substances from body to lumen is confused and there are no generally accepted words that cover every facet. Secretion, usually implying an active process, is not wholly appropriate, and excretion implies a loss to the body, which is not always the case. Exsorption, enterosorption and flux have their proponents but apply only to fluid transfer. I shall use the word 'loss' to cover all passage into the lumen and 'net loss' for any resultant body deficit.

Both these terms need qualification; 'loss' is used relatively as most substances are reabsorbed from the lumen, and 'net loss' can only refer to the whole gastro-intestinal tract; but in certain circumstances it can be assumed that the major source of the loss is the small intestine. Cell loss will be termed exfoliation and, by contrast, fluid and molecular loss, exudation.

Cell Exfoliation

The concept of cell turnover in the gut is now a familiar one and the normal patterns and times are well known (Creamer, 1967). Division occurs solely in the crypts where mitoses are abundant and can be counted to arrive at a mitotic index. If the duration of mitosis is known or can be assumed the turnover time can be calculated. Migration of cells from the crypts up the villus is a constant surge with rapid maturation taking place as the cells leave the crypts. By the middle of the villus the enzyme complement appears to be full and the cells are functionally mature. The technique of labelling cells
with tritiated thymidine has been a vivid tool in demonstrating and timing this migration. The turnover time, that is the replacement time for the whole mucosa, is almost constant in small laboratory animals at about two days, but is longer in man, averaging four days, although this is based on very few direct measurements. The probable reason for this difference is mentioned later.

It is the number or volume of cells lost into the gut lumen that is pertinent here. If the gut is washed, cells can be recovered and, using electron microscopy, at least 85 per cent can be shown to be epithelial cells by the demonstration of a brush border (Pink et al., 1970). Croft has developed a technique of measuring the DNA in washings by a colorimetric method; as the DNA content of cells is known, this measurement is a chemical cell count (Croft and Lubran, 1965). Using this technique the cell loss into the human small intestine is 20-50 $\times 10^6$ per minute or 60,000 $\times 10^6$ per day (Croft et al., 1968a).

A different, and highly original, approach to the same problem has been developed by Clarke, who was able to fix cells trapped in the mucus over villi and so count the cells lost from each villus (Clarke, 1971). This is a much more sensitive technique and can show small variations but it can only be applied to the experimental animal. However, the findings of Croft and Clarke are in agreement.

The weight of exfoliated cells is impressive; about 250 g, or half a pound, are lost daily into the human small intestine alone. Clearly, most of the constituents of these cells are reabsorbed. It is instructive to compare this with other parts of the gut and with the skin. The stomach and the skin each lose about $0.5 \times 10^6$ cells/minute and the colon 2 to $5 \times 10^6$ cells/minute. This means that cell exfoliation from the small intestine is over seven times the combined amount from skin, stomach and colon.

The normal mucosa is not only highly dynamic but also highly responsive to many stimuli. It can be shown that cell division declines with even brief fasting and increases with feeding (MacManus and Isselbacher, 1970). In abnormal or diseased states villi alter their shape and become leaf-like, convoluted, or even flattened. It has been shown that shape and cell turnover are intimately linked so that by knowing the shape of a mucosa the turnover can be inferred (Loehry and Creamer, 1969a,b). From animal models it can be shown that the more abnormal the shape the faster the turnover; finger-like villi have a turnover time of four days (the situation in man), leaf-like villi two days (as in the rat), a convoluted mucosa six to twelve hours and a flat mucosa less than six hours (Grace et al., 1970). The increase in turnover time is in part due to the villous cell population being smaller but also reflects a genuine increase in cell production and loss. By direct measurements it can be shown
that cell loss into the lumen is increased in mucosal abnormality both in the rat and man (Loehry et al., 1969; Da Costa et al., 1970; Croft et al., 1969). The normal cell loss can therefore be increased for long periods; the significance of this will be considered later.

**Molecular Exudation**

The concept of a diffusion of molecules from the body through the small intestinal epithelium is at present accepted only in a few isolated examples. At one end of the scale the exudation of a small amount of plasma protein is an established physiological fact. This is demonstrated by a study of iron loss from the mucosa; Crosby and his co-workers have shown that iron is taken up by immature crypt cells and travels up the villus within them (Conrad et al., 1964). If radioactive iron that has been previously protein bound is injected intravenously in the rat it is incorporated in the crypts and can be recovered from the intestinal lumen by perfusion some 36 hours later. At this time the iron can be shown to have entered the lumen in cells. However, perfusions at earlier times show another peak of radioactivity in the lumen at one hour after injection. At this time there is no correlation with DNA in the perfusate and the radioactive material is clearly protein bound iron that has exuded (Loehry et al., 1969).

At the other end of the scale the rapid two-way passage of water and electrolyte across the intestinal mucosa has been extensively studied for decades. Fordtran and his co-workers (1965) have shown that small water-soluble molecules pass freely across but, above a certain size, they claimed that passage did not occur. From this they deduced a theoretical pore size; they envisaged cylindrical pores with a radius of about 8 Å in the jejunum and 3 Å in the ileum. There is, therefore, evidence of macromolecular loss and evidence of small molecular loss but, curiously, hardly any documented findings in the intermediate range.

A variety of substances that had a range of molecular weight from PVP (mean weight 33,000) to urea (60) were examined. By injecting these intravenously into a rabbit, to achieve stepwise increments of plasma concentration and, at the same time, perfusing the whole small intestine, the rate of loss into the lumen can be measured and a plasma clearance calculated (Loehry et al., 1970). The results show that there is a direct relation between molecular weight and plasma clearance, with small molecules having a very rapid clearance (Figs 1 and 2); the plasma clearance of urea is about the same as from one kidney (a fact well known from the early days of treating renal failure). It has subsequently been shown that the same pattern can be demonstrated in man (Loehry and Parrish, 1970). Under natural intact conditions
Fig. 1. The relationship between the logarithm of the molecular weight and the logarithm of the intestinal clearance for a variety of substances in the rabbit. (Courtesy of Gut).

Fig. 2. The relationship between the logarithm of the molecular weight and the logarithm of the intestinal clearance for fractions of PVP in the rabbit. (Courtesy of Gut).
these substances are mostly reabsorbed. For substances with no known absorptive mechanisms, such as PVP, and using a Sephadex column to separate the varying molecular sizes, the permeability of the small intestine from lumen to blood and from blood to lumen is identical. It is therefore inescapable that, in the absence of active transport, the small intestine acts as a semi-permeable membrane showing selectivity only in relation to molecular weight or size, presumably reflecting a distribution of pore size at some anatomical level. We have not yet examined the behaviour of lipid soluble molecules or the weak acids or weak bases selected by pharmacologists for swift absorption. The only exceptions to this exudation are the monosaccharides, glucose and galactose. Even though the blood level is raised to 1,000 mg per cent only very small amounts appear in the intestinal lumen. It is suggestive that a transport mechanism directed in one way repels the outward passage of these monosaccharides.

Theoretically, the barrier to exudation could be at any level between the villous capillary and the brush border. However, intestinal capillaries are known to be fenestrated, and macromolecules such as peroxidase and ferritin are seen to pass freely through (Clementi and Palade, 1969). This leaves the basement membrane (easily penetrated by chylomicrons) and epithelial layer. Epithelial cells are frequently separate in their lower part but are always closely apposed at desmosomes and particularly at the tight junctions. It is thought that these areas are impermeable even to water and electrolyte. The only visible gap is at the extrusion zones on the villous tips; however, they cannot be seen by scanning electron-microscopy. It therefore seems likely that exudation takes place through epithelial cells, and the failure of monosaccharides to exude out would support this. The recently developed concept of IgA passing out into the gut lumen through epithelial cells has opened the possibility of the exudation of macromolecules. The work of Bounous et al., (1966) also suggests that the barrier to exudation is in the surface coat (glycocalyx or fuzzy layer) of the brush border. They were able to show that the small intestine of dogs became abnormally permeable after a period of hypovolaemic shock and this correlated with loss of the PAS positive band in the brush border region. More work is needed before we can be certain of the exact micro-anatomical pathway of exudation and it may be that molecules of differing molecular size take different routes.

**Routes of Loss**

There are, therefore, two routes by which substances can enter the gut lumen from the mucosa; by cell loss (exfoliation) and by direct permeation (exudation). Iron is lost by both routes, although we have not as yet been able
to quantify the amount coming out in each pathway. Vitamin B\textsubscript{12} similarly enters the gut by exudation and exfoliation (Loehry and Creamer, 1969c). Folic acid leaves the body by exudation through the upper small intestine (Creamer and Shiner, 1965) and, as there is folic acid in cells, probably by exfoliation as well.

The weight of cells lost would suggest that protein mostly enters the gut by exfoliation but this is not so. By perfusion techniques protein and cell loss into the small intestine can be directly measured. Using the data for protein and DNA of intestinal epithelial cells prepared in suspensions, the amount of protein loss due to exfoliation can be calculated. Only 12 per cent of intestinal protein comes from cells (Da Costa et al., 1970). Not all the remaining 88 per cent is necessarily plasma protein that is exuded; mucus is a mucoprotein and IgA must make a small contribution. The daily protein loss in man from the small intestine is of the order of 85 g. If the small intestine is damaged, and an altered mucosa can be produced by infestation with \textit{Nippostrongyloides Brasiliensis} in the rat, then both exfoliation and exudation are increased. Interestingly, the ratio of protein lost by these two routes remains constant; it may be that in some circumstances exfoliation and exudation are closely linked.

Fat loss by the small intestinal mucosa has been similarly studied (Cotton, 1970). In contrast to protein, about 80 per cent of the lipid enters the lumen in shed cells. Certainly almost all triglyceride, cholesterol, phosphatidal choline, and phosphatidal ethenolamine leave the mucosa by exfoliation. The only lipids to exude are the fatty acids. In man, the figure for lipid loss into the small intestine can be calculated to be of the order of 10 to 25 g daily in the fasting state and is almost certainly more with normal feeding.

**THE SMALL INTESTINAL LUMEN**

The old concept that the small intestinal lumen is like the outside of the body is quite erroneous. The mucosa contributes a torrent of fluid and half a pound of cells daily to an enteric circulation. To this must be added the pancreatic secretion, rich in protein and electrolyte, gastric secretion, and the biliary flow which includes a vast number of conjugated hormones and vitamins in addition to bile pigments and salts. Almost everything that is present in plasma is present in luminal fluid with the exception of the monosaccharides. Furthermore, there is evidence that the concentration of some of these substances is homeostatically controlled. Nasset (1965) has shown that the ratios of amino acid concentrations are maintained remarkably constant; no matter how bizarre the protein structure ingested the amino acid ratios in the small intestine are unchanged. This is achieved by a swamping of ingested protein with up to seven times the amount of endogenous protein, part of which comes from
the small intestine but most from the pancreas. The luminal fluid is best regarded as a compartment of the extra-cellular fluid. It is reasonable to speculate that there is some biological advantage in this enteric circulation. Absorption may be facilitated by a constant composition; there is evidence of this in amino acid absorption. However, there is another aspect, 'luminal nutrition’. The intestinal epithelial cells are unique in being bathed by two fluids of similar composition, blood and luminal fluid. The concept of luminal nutrition is that some of the epithelial cells’ requirements come from the lumen. There is now good evidence for this concept. Hirschfield and Kern (1969) have shown that under some circumstances amino acids are preferentially taken up and incorporated into protein from the lumen rather than from the blood stream.

**Net Loss**

These movements by exfoliation and exudation present a physiological situation that could be very vulnerable to disease states. If loss is increased or reabsorption diminished or, particularly, if both occur, then net losses can develop. Cholera is a perfect example of a derangement of exudation and reabsorption in the small molecule field, just as the exudative enteropathy of protein represents a similar state at the macromolecular level. There is experimental and clinical evidence that this concept is of considerable importance in small intestinal disease.

When the mucosa is diffusely damaged, both cell loss and exudation increase; a combination of exfoliative and exudative enteropathy. A simple experimental model is the rat infested with *Nippostrongyloides Braziliensis* when the mucosa becomes convoluted and cell turnover is increased, giving a picture somewhat similar to the coeliac syndrome. Perfusion studies reveal a threefold increase in cell loss and in protein loss (Da Costa et al., 1971). Iron loss is increased both by exfoliation and by exudation to about the same degree (Loehry et al., 1969). However, measured in this way, it is not possible to be sure that net loss would occur.

The combination of increased loss into the lumen and decreased reabsorption is found in man in the coeliac syndrome and, probably, in tropical sprue. Cell loss into the jejunum can be measured directly by perfusion of a segment and in the untreated coeliac syndrome has been found to be increased, the highest figure being six times normal (Croft et al., 1968b). The amount of cell loss correlates with the clinical state; those patients who are ill and losing weight have the highest exfoliation rates. With clinical improvement and weight gain the cell loss comes down to normal rates; the data do not permit the conclusion that cell loss contributes to weight loss but it is a possibility.
In a number of instances net loss has been established. Protein-losing exudative enteropathy is now so well documented that little comment is needed. Iron loss has been extensively studied, and here net loss has been conclusively shown; the use of isotopic iron has enabled faecal loss to be measured, while blood can be excluded by chromium labelling. Singh (1970) has demonstrated an excess of body iron in the faeces in the untreated coeliac syndrome, which comes down to normal levels with successful treatment. This fits well with the observation of iron deficiency in spite of normal iron absorption in coeliac patients (Webb et al., 1967). Similar findings have been reported by Sutton et al. (1970) who have also shown iron loss in atrophic gastritis and after partial gastrectomy, thus demonstrating that this concept may have relevance in the pathogenesis of deficiencies from other sites in the gut. It is of considerable interest that iron loss occurs in atrophic gastritis as cell turnover is known to be increased in this condition (Croft et al., 1966).

Under certain circumstances net fat loss can be demonstrated. Faecal fat may exceed intake in coeliac patients on a low fat diet and, even with a free intake, faecal fat can exceed the ingested fat in radiation enteritis (Tankel et al., 1965). In an interesting study on vitamin A, Rowntree (1930) was able to show that coeliac children pass more in the faeces than was present in the diet. As fat enters the lumen almost exclusively by cell exfoliation the increased fat loss in coeliac patients is probably by this route, although in radiation enteritis lymphatic obstruction and rupture may play a part.

Folic acid loss in tropical sprue has been postulated and preliminary supportive evidence produced by Baker (1968). Folic acid absorption tests were frequently normal in his patients, all of whom had folic acid deficiency, and in 7 of 17 cases, excess amounts of labelled folic acid given intravenously were recovered in the stools.

Net loss of calcium in the coeliac syndrome accompanied by osteomalacia has been clearly demonstrated. Melvin et al. (1970) measured calcium absorption and calculated 'total secreted intestinal juice calcium'. Calcium absorption was normal but the endogenous calcium loss was increased with a negative balance. The loss of sodium, potassium, and water is well known and occurs in any state with marked diarrhoea. Cholera represents the extreme example of this loss (Love et al., 1970). Interestingly, isotope studies show that both absorption and exudation are decreased but the balance is disturbed so that net loss results. In the United Kingdom the rare Zollinger–Ellison syndrome with profound watery diarrhoea shows a very similar picture, with marked net loss of water and electrolyte.

Some of these findings might suggest that when the mucosa is damaged the intestinal loss of all molecules is equally increased. However, there is evidence
that there can be selective disturbances. Certainly in cholera net loss appears to be confined to the water and electrolyte range. There is also clear evidence in lymphangiectasis of rupture of a lymphatic with the drainage of chyle into the lumen with predominant protein and fat loss (Mistilis et al., 1965). Between these extremes there may well be a patchy change in permeability. Indeed, Fordtran et al. (1967) have studied permeability and theoretical pore size in the coeliac syndrome. They demonstrated a marked increase in the exudation of water and electrolyte but a diminished passage of urea and larger molecules. They concluded that the abnormality induces an increase in the effective number of small pores but a decrease in the number of larger pores. There are, as yet, too few studies to draw any definite conclusions as to how permeability may be changed in disease.

The technical problems of measuring net loss are much greater than in measuring absorption as the quantity delivered to the lumen remains unknown. It was mainly by using indestructible and non-absorbable substances and markers that the exudative enteropathy of protein was discovered. As with protein most substances entering the lumen are either radically altered by digestion or consumed by the bacterial flora. However, as these problems are overcome, the magnitude of net loss is being appreciated. The frequency of deficiencies in the face of normal absorptive tests has always been clinically anomalous and the recognition of net loss underlines the fact that in most diseases deficiencies are due to a combination of reduced intake, malabsorption and loss.

This article is based on the Watson Smith Lecture delivered at the Royal College of Physicians in February 1971.

References
Baker, S. J. (1968) Vit. and Horm., 26, 537.
Bourns, G., McArdle, A. H., Hodges, D. M., Hampson, R. G. and Gurd, F. N. (1966) Amer. J.
Med., 258, 1969.
Clarke, R. M. (1971) Gut. In press.
Clementi, F. and Palade, G. E. (1969) J. Cell. Biol., 41, 33.
Conrad, M. E., Weintraub, L. R. and Crosby, W. H. (1964) J. Clin. Invest., 43, 963.
Cotton, P. B. (1970) Unpublished observations.
Creamer, B. and Shiner, M. (1965) Lancet, 1, 913.
Creamer, B. (1967) Brit. med. Bull., 23, 226.
Croft, D. N. and Lubran, M. (1965) Biochem. J., 95, 612.
Croft, D. N., Pollack, D. J. and Coghill, N. F. (1966) Gut, 7, 333.
Croft, D. N., Loehry, C. A., Taylor, J. F. N. and Cole, J. (1968a) Lancet, ii, 70.
Croft, D. N., Loehry, C. A. and Creamer, B. (1968b) Lancet, ii, 68.
Da Costa, L., Croft, D. N. and Creamer, B. (1970) Gut, 12, 179.
Fordtran, J. S., Rector, F. C., Ewton, M. F., Soter, N. and Kinney, J. (1965) J. Clin. Invest., 44, 1935.
Fordtran, J. S., Rector, F. C., Locklear, T. W. and Ewton, M. F. (1967) J. Clin. Invest., 46, 287.
Grace, R. H., Loehry, C. A. and Creamer, B. (1970) Unpublished observations.
Hirschfield, J. S. and Kern, F. Jr. (1969) *J. Clin. Invest.*, 48, 1224.
Loehry, C. A. and Creamer, B. (1969a) *Gut*, 10, 6.
Loehry, C. A. and Creamer, B. (1969b) *Gut*, 10, 112.
Loehry, C. A. and Creamer, B. (1969c) *Gut*, 10, 662.
Loehry, C. A., Croft, D. N., Singh, A. K. and Creamer, B. (1969) *Gut*, 10, 6.
Loehry, C. A., Axon, A. T. R., Hilton, P. J., Hider, R. C. and Creamer, B. (1970) *Gut*, 11, 466.
Loehry, C. A. and Parrish, D. (1970) *Communication to Brit. Soc. Gastro-Enterol.*
Love, A. H. G. (1970) *Personal communication.*
Love, A. H. G., Rohde, J. E. and Veall, N. (1970) *Communication to Brit. Soc. Gastro-Enterol.*
MacManus, J. P. A. and Isselbacher, K. J. (1970) *Gastro-enterology*, 59, 214.
Melvin, K. E. W., Hepner, G. W., Bordier, P., Neale, G. and Joplin, G. F. (1970) *Quart. J. Aled.*, 39, 83.
Mistilis, S. P., Skyring, A. P. and Stephen, D. D. (1965) *Lancet*, i, 77.
Nassett, E. S. (1965) *Fed. Proc.*, 24, 953.
Pink, I. J., Croft, D. N. and Creamer, B. (1970) *Gut*, 11, 217.
Rowntree, J. I. (1930) *J. Nutrit.*, 3, 265.
Singh, A. K. (1970) *Brit. J. Haemat.*, 18, 597.
Sutton, D. R., Baird, I. M., Stewart, J. B. and Coghill, N. F. (1970) *Lancet*, ii, 387.
Tankel, H. I., Clark, D. H. and Lee, F. D. (1965) *Gut*, 6, 560.
Webb, M. G. T., Taylor, M. R. H. and Gatenby, P. B. B. (1967) *Brit. med. J.*, 2, 151.

The District Physician

Medicine is in need of reorganisation at all times but never more so than in the closing years of the eighteenth century when Dr John Latham conceived his highly original plan for the ‘Better Regulation of Medical Practitioners, Chemists, Druggists and Vendors of Medicine’. He proposed that England be divided into 16 districts, each with a physician charged with licensing all those concerned with the practice of medicine. In addition, he had to ‘visit and examine all places licensed for the reception of Lunatic or Insane persons’ and to ‘enquire into and examine the state of the Parochial Work-houses, or Poor-houses, and report upon their salubrity and internal economy’. The results of these visitations had to be laid before the Justices in Quarter Sessions or the Judge at the Summer Assize.

Latham considered that his administrative paragon should be over 36 years old and a Fellow of the Royal College of Physicians for more than seven years. His most extraordinary proviso was ‘that no District Physician shall reside within ten miles of any of the Royal Colleges, nor within ten miles of any University of England, Ireland or Scotland, nor hold any Professorship, Lectureship or Office, within or connected with the same’.

The plan was placed before the College in 1804. Latham fell gravely ill at that time and was not able to press his ideas on the College. However, his ideas may well have stirred the College a little because it cautiously declared itself on the side of the reformers.