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## DNA Loss, Cell Loss and Epithelial Turnover in the Intact Human Colon

The life span of the epithelial cell of the human colon is 4–8 days (Lipkin 1965), which is rather longer than that of human stomach or small intestine (Creamer 1967). By contrast, epithelial cells of human skin last 26–28 days (Rothberg *et al.* 1961). These estimates have been made by mitosis counts, tritium-labelled thymidine and $^{14}$C-labelled glycine techniques, but these methods do not give information on total cellular turnover of individual epithelial organs. By estimating the rate of deoxyribonucleic acid (DNA) loss we have calculated total cell loss and turnover in human stomach (Croft *et al.* 1966), skin (Croft, Lim & Taylor 1968) and small intestine (Croft, Loehry, Taylor & Cole 1968). In this paper we describe the application of the method to the study of turnover and loss of cells from the entire human colon.

Ten healthy volunteers swallowed a tube which passed through the entire small intestine to the cæcum (Levitan *et al.* 1962). After a preliminary washout, fluids of various compositions and containing the unabsorbable marker polyethylene glycol (PEG) were introduced into the cæcum at a constant rate of 15 ml/min. The fluid traversed the whole colon and was then collected from the rectum. DNA and PEG were measured in the specimens. From the rate of infusion of PEG and the concentration of PEG and DNA in the specimen, the rate of loss of DNA into the lumen was calculated and expressed in ng atoms DNA-P per min. In the specimens $1\times10^6$ to $1\times10^7$ bacteria were present (Gorbach *et al.* 1967) but they did not account for a significant amount of the DNA.

In 6 subjects eleven hourly perfusions were performed using isosmolar saline. The mean rate of DNA loss was 91·7 (S.D. 47·5) ng atoms DNA-P per min. Isosmolar mannitol was perfused on five occasions in 2 subjects and the mean value of 45·9 ng atoms DNA-P per min was not significantly different. Two subjects were perfused with both hyperosmolar (650 mOsm) urea and with hyperosmolar (650 mOsm) mannitol. Five hourly perfusions were performed with each solution. Rates of DNA loss with hyperosmolar urea were normal but with hyperosmolar mannitol they were significantly higher in both subjects (Fig 1).

We believe that the mean rate of DNA loss for the subjects perfused with isosmolar saline reflects physiological DNA and cell loss from the entire intact human colon. From the known DNA content of human cells (Davidson *et al.* 1951) it can be calculated that this rate of DNA loss represents a loss of 2–5 million cells per minute. This is five to ten times the value for human stomach, but only one-tenth of the value for the whole human small intestine. Our large bowel value is of the same order as DNA and cell loss from the whole skin in patients with generalized exfoliative psoriasis (Croft, Lim & Taylor 1968), who lose about 20 g of dry skin scales per twenty-four hours.

The increased loss of DNA that occurred with the hyperosmolar mannitol implied that the large bowel mucosa reacted to this substance as though

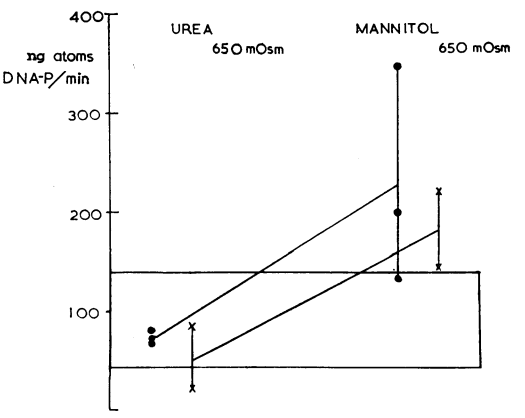


Fig 1 *Large bowel DNA loss from intact human colon. The rectangular area represents two standard deviations around the mean loss for normal colon, perfused with isosmolar saline. This rate of DNA loss represents the loss of 2–5 million cells per min. Two subjects (● and ×) were perfused with hyperosmolar (650 mOsm) urea and with hyperosmolar (650 mOsm) mannitol. DNA loss was normal using urea (on left of figure), but significantly increased with mannitol (on right of figure)*

it were an irritant (Croft 1963). Mannitol in high concentration damages intestinal mucosa (Kameda *et al.* 1968) and our data suggest that it does so by removing cells. This finding is relevant to measurement of fluid shifts and pore size in studies using hyperosmolar mannitol (Hindle & Code 1962, Fordtran *et al.* 1965).

There are three common epithelial diseases in which we have found DNA (or cell) loss to be high; the high cell loss is due to a high turnover of epithelial cells in these conditions. They are: psoriasis in which epithelial cell turnover and loss is some eight times normal (Croft, Lim & Taylor 1968), atrophic gastritis in which it is some three times normal (Croft *et al.* 1966) and active cœliac syndrome in which it is some four times normal (Croft, Loehry & Creamer 1968). It is of interest that the rate of DNA loss from a 30 cm rectal stump of a patient with ulcerative colitis suggested that cell loss was at least three times normal. This is a preliminary observation and it is yet to be established what proportion of the DNA arose from epithelial cells. Perhaps exfoliative disease is a risk in any epithelial organ and ulcerative colitis is an example in the large bowel.

In conclusion, DNA loss has been used to measure cell loss from the entire human large bowel. In the steady state DNA loss from normal mucosa was 91·7 (S.D. 47·5) ng atoms DNA-P per min, which indicated a normal turnover of 2–5 million cells per minute. Perfusion of large bowel mucosa with mannitol caused increased DNA loss due to an irritative (cell-removing) effect on the mucosa. Diseases with high loss and turnover of epithelial cells include psoriasis, atrophic gastritis, active cœliac syndrome and possibly ulcerative colitis.

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## Pharmacologically Active Peptides and their Effects upon the Human Colon *in vitro*

There are many active polypeptides which are either stored or formed in the tissues. They are of a relatively simple structure and often have potent stimulatory effects upon smooth muscle. Some of these substances have been synthesized and are now freely available. This paper will describe the effects of vasopressin, angiotensin and bradykinin upon the human ileum and colon.

The method of investigation has been described in detail previously (Fishlock & Parks 1966). Strips of muscle were taken from macroscopically healthy ileum and colon and then set up in an isolated organ bath containing a modified Krebs' solution and gassed with 95% $O_2$ and 5% $CO_2$ at 37°C. The responses of the muscle were recorded by means of an isotonic lever writing on a kymograph drum.

*Vasopressin* (L-8 vasopressin, Sandoz Ltd): Neither the longitudinal nor circular muscle of the terminal part of the human ileum responds to vasopressin (concentrations up to 0·1 unit/ml have been tested). Similarly, neither muscle layer of the sigmoid colon contracts in the presence of this substance. But vasopressin does cause a prolonged contraction of the circular muscle of both the transverse colon and the upper part of the descending colon (Fig 1). The longitudinal muscle of both these regions is insensitive (Moriya & Fishlock 1968, unpublished observations).

*Angiotensin:* Both muscle layers of the human sigmoid colon contract with low concentrations of angiotensin (i.e. from 10 ng/ml upwards). Pharmacological analysis has shown that its effect on the sigmoid colon is brought about by directly stimulating the smooth muscle cells of the preparation (Fishlock & Gunn 1969). This is somewhat different from its effects upon the human ileum. Both muscle layers contract but a large part of the response is mediated through the nervous component of the intestinal wall. This part of the investigation has demonstrated that the cholinergic intramural nerves of the ileum are sensitive to angiotensin but those of the colon are not.

*Bradykinin:* This polypeptide contracts most smooth muscle preparations and is released during the inflammatory response at least at some sites.

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