Changes in the villous pattern of the human jejunum associated with heavy radiation damage

GEORGE WIERNIK¹

From the Department of Radiotherapy, St. Thomas' Hospital, London

EDITORIAL SYNOPSIS These studies support the theory that changes in the mucosal pattern of the small intestine can be transitory and can alter rapidly.

The architecture of the small intestinal mucosa appears to be closely linked to the epithelial cell system which forms the lining of the crypt and the covering of the villus. It has been shown that the structure of the normal villus becomes unrecognizable when the epithelial cells covering it are lost (Wiernik, Shorter, and Creamer, 1962). The variations in small intestinal villous shape have been related to the dynamics of the epithelial cells of the mucosa (Creamer, 1962; 1964a) as well as to other factors, such as changes in the luminal environment (Creamer, 1964b; Johnstone and Adams, 1964) and possibly the presence of malignant disease (Creamer, 1964c).

The different patterns of villous shape found in the small intestine were classified by Holmes, Hourihane, and Booth (1961a and b) and the classification has been elaborated by Salem, Truelove, and Richards (1964), who also showed a definite correlation between the clinical state of the patient and the villous pattern seen in a small intestinal biopsy. Salem *et al.* (1964) postulated that small intestinal abnormalities might be transitory and stated that, in order to settle this point decisively, it would be necessary to obtain serial biopsies. Such a study has now been conducted in six patients.

METHODS

The patients from whom the serial biopsies were obtained received post-operative irradiation for carcinoma of the stomach. They had had either a partial or a total gastrectomy so that peroral biopsy was made very much easier as the pylorus and duodenum did not have to be negotiated. The details of the method have been reported elsewhere (Wiernik, 1966a).

¹Present address: Department of Radiotherapy, Churchill Hospital, Oxford.

The jejunal biopsy specimen was examined under the dissecting microscope, then blocked in wax and sections cut. The block was molten again and the mucosal pattern along the cut surface was compared with the histological appearances.

Irradiation was given by a cobalt teletherapy unit.

RESULTS

The results reported here refer only to changes in the mucosal pattern and are part of a larger study based on 71 biopsies obtained from the six patients. Details of the x-ray doses employed, of epithelial cell counts, and of the histological appearances are published elsewhere (Wiernik, 1966, a, b, and c).

Complete biopsy series are not available in each case, but where comparable specimens were obtained these agreed so closely that a fairly complete pattern has been established. The pre-irradiation biopsies showed a normal mucosal pattern (Fig. 1) which was similar to that seen in operative specimens obtained from patients not suffering from carcinoma whose jejunal mucosa was considered to be normal. The majority of villi are finger-like but some leaf-shaped villi are also present. The histological section (Fig. 2) shows long villi with normal crypts.

Following irradiation mitotic activity in the crypts diminishes and the number of epithelial cells lining both the crypt and covering the villus decreases (Wiernik, 1966a) until the villi become unrecognizable by day 11 so that the mucosa looks flat (Fig. 3). The histological appearances show that not only is the villous structure lost but the crypts also are so severely damaged that no normal structure can be recognized in them (Fig. 4).

When the mucosa recovers from the radiation damage the villous pattern that has formed by day 53

FIG. 1.

FIG. 3.

FIG. 2.

FIG. 4.

FIG. 1. *Dissecting microscope appearances of pre-irradiation normal jejunal mucosa.*

FIG. 2. *Histological section taken from cut surface shown in Fig. 1 revealing normal villi and crypts.*

FIG. 3. *Dissecting microscope appearances following heavy radiation damage showing a flat mucosa.*

FIG. 4. *Histological section taken from cut surface shown in Fig. 3 revealing gross radiation damage to crypts and complete loss of villous structure.*

FIG. 5.

FIG. 5. *Dissecting microscope appearances following recovery from heavy irradiation damage showing convoluted and folded villous ridges.*

FIG. 6.

FIG. 6. *Histological section taken from cut surface shown in Fig. 5 revealing crypt structures of normal appearance with low, broad villous structures spanning several crypts.*

is one of convoluted and folded villous ridges (Fig. 5) and the histological sections show that these broad villous structures span several crypts of normal appearance (Fig. 6).

DISCUSSION

A single large dose of irradiation damages the crypt epithelial cells so that their number decreases, prob-

ably through the elimination of lethally damaged cells and mitotic inhibition (Wiernik, 1966a). When further sufficiently large doses of irradiation are given without an intervening period for recovery no new cells are produced in the crypt to replenish the loss of epithelial cells from the extrusion zone at the tip of the villus, and so the villus becomes progressively shorter (Wiernik, 1966b) and finally the villous structure becomes unrecognizable (Fig. 3). The dis-

secting microscope appearances at this stage are thus similar to those seen in severe forms of idiopathic steatorrhoea (Creamer, 1962) and ulcerative colitis (Salem *et al.*, 1964) when the mucosa is described as flat. This transition from a normal mucosa to a flat mucosa appears to have a different mechanism in rodents (Wiernik *et al.*, 1962) where the whole villous epithelial covering is shed and the villous structure becomes unrecognizable in 72 hours; in the human mucosa the villus becomes progressively shorter and a flat mucosa is only seen after 11 days. This difference does not appear to be solely dependent on epithelial cell turnover time though this is probably twice as long in the human subject as in rodents (Lipkin, Sherlock, and Bell, 1963; MacDonald, Trier, and Everett, 1964).

The appearances of a flat mucosa under the dissecting microscope are similar both in idiopathic steatorrhoea and following heavy radiation damage but the histological sections show a marked difference. When the flat mucosa is caused by radiation damage the underlying crypt structures have become virtually unrecognizable (Fig. 4), whereas in idiopathic steatorrhoea a large number of branched glands are commonly seen and in ulcerative colitis long hyperplastic crypts have been reported.

Biopsies have been obtained up to six months after the irradiation treatment which caused the intestinal mucosa to become flat. The mucosa appears to reach equilibrium about one month after the completion of treatment; no material changes in the mucosa have been noted between one and six months (Wiernik, 1966b). The change in mucosal pattern from finger-like villi to villous ridges is associated with a villous epithelial cell row count which does not rise above two-thirds the pre-treatment value, despite the fact that the crypt epithelial cell population returns to virtually its normal size (Wiernik, 1966b). A certain degree of caution has to be exercised, however, in interpreting epithelial cell row counts, as these only represent data based on a two-dimensional estimation and results based on three-dimensional data have shown previously unrecognized changes (Wimber and Lamerton, 1963).

Details of the intervening histological changes which follow radiation damage and during the process of repair are reported elsewhere (Wiernik, 1966c).

These observations support the theory put forward that changes in the mucosal pattern of the small intestine are transitory and can alter rapidly. In previously reported studies the patients with a flat mucosa have been severely ill, which was not the case when the flat mucosa was induced by irradiation, as under these circumstances only a strictly localized portion of the intestine was affected.

The alterations in mucosal pattern appear to be directly associated with the changes in the epithelial cell system that forms the surface of the villus and lines the crypt. When the number of epithelial cells produced in the crypt is diminished, the villus becomes shorter and conversely when, after only minor radiation damage, repopulation in the crypt is followed by the overshoot phenomenon (Wiernik, 1966a), then the villus too becomes longer than normal though the shape is not altered in this case. Following heavy radiation damage, on the other hand, when the mucosa becomes flat and the crypt structures become grossly disorganized, recovery is associated with a changed villous pattern which remains materially unaltered for up to six months, but it is not known whether after a further period the pattern returns to normal.

SUMMARY

The normal finger-like villi of the human jejunal mucosa have been observed to become progressively shorter following irradiation until their structure is unrecognizable and the mucosal surface appears flat. When recovery takes place the mucosa forms convoluted and folded villous ridges instead of finger-like villi, this being associated with apparent changes in the proportion of epithelial cells on the villus and in the crypt. These findings show that the mucosa is capable of changing rapidly from one type of pattern to another and it is suggested that these changes are directly linked with alterations in the epithelial cell system that forms the lining of the villus and the crypt.

I wish to thank Dr. J. A. C. Fleming, Physician-in-Charge, Department of Radiotherapy, and Dr. B. Creamer for their help and encouragement; Mrs. Dorothy Barton for technical assistance; the Medical Research Council for a personal grant and the salary of a technician.

This work forms part of an M.D. thesis submitted to the University of London.

REFERENCES

- Creamer, B. (1962). Dynamics of the mucosa of the small intestine in idiopathic steatorrhoea. *Gut*, 3, 295-300.
- (1964a). Variations in small-intestinal villous shape and mucosal dynamics. *Brit. med. J.*, 2, 1371-1373.
- (1964b). Small-intestinal mucosal dynamics and the environment. *Ibid.*, 2, 1373-1375.
- (1964c). Malignancy and the small-intestinal mucosa. *Ibid.*, 2, 1435-1436.
- Holmes, R., Hourihane, D. O'B., and Booth, C. C. (1961a). Dissecting-microscope appearances of jejunal biopsy specimens from patients with 'idiopathic steatorrhoea'. *Lancet*, 1, 81-83.
- , — (1961b). The mucosa of the small intestine. *Postgrad. med. J.*, 37, 717-724.
- Johnstone, J. M., and Adams, J. F. (1964). Jejunal mucosal appearances after total gastrectomy. *Gut*, 5, 60-63.

- Lipkin, M., Sherlock, P., and Bell, B. (1963). Cell proliferation kinetics in the gastrointestinal tract of man. II. Cell renewal in stomach, ileum, colon, and rectum. *Gastroenterology*, **45**, 721-729.
- MacDonald, W. C., Trier, J. S., and Everett, N. B. (1964). Cell proliferation and migration in the stomach, duodenum, and rectum of man: radioautographic studies. *Ibid.*, **46**, 405-417.
- Salem, S. N., Truelove, S. C., and Richards, W. C. D. (1964). Small-intestinal and gastric changes in ulcerative colitis: a biopsy study. *Brit. med. J.*, **1**, 394-398.
- Wiernik, G. (1966a). The *in-vivo* cell kinetics of a normal human tissue. In course of publication.
- (1966b). Investigation of the effect of fractionated regimes of irradiation in normal tissues. *Brit. J. Radiol.*, In the press.
- (1966c). A histological study of radiation damage and repair in the human jejunal mucosa. *J. Path. Bact.*, In the press.
- , Shorter, R. G., and Creamer, B. (1962). The arrest of intestinal epithelial 'turnover' by the use of x-irradiation. *Gut*, **3**, 26-31.
- Wimber, D. R., and Lamerton, L. F. (1963). Cell population studies on the intestine of continuously irradiated rats. *Radiat. Res.*, **18**, 137-146.