DISCUSSION

These experiments demonstrate an increased turnover state in the small intestinal mucosa of the lactating rat. The exact stimulus to this remains obscure, but as the hypertrophy is related to increased food consumption (Campbell and Fell, 1964) it is possible that it may represent a reaction of the mucosa to produce an increased surface area in response to an increase in work load, similar to that seen after intestinal resection (Loran and Althausen, 1966). It could be suggested that the crypts are stimulated in some way to step up the rate of cell production, and this, without a comparative increase in cell loss, would produce a hypertrophied mucosa. Whatever the mechanisms, however, the results are to produce an increased output of cells from the crypts and this is probably responsible for the enlarged villi and the increased prominence of the inter villous ridges.

SUMMARY

An increased rate of epithelial cell production was demonstrated in lactating rats. This caused hyperplasia of the villi and at the same time increased prominence of the inter villous ridges.

REFERENCES


Part III Mucosal structure and dynamics in the rat infested with the nematode Nippostrongylus brasiliensis

The histological changes in the upper small intestinal mucosa of rats infested with Nippostrongylus brasiliensis are now well established (Symons and Fairbairn, 1962; 1963). The histological appearances in severely infested animals are similar in many respects to those seen in coeliac disease, with reduced or absent villous projections, lengthened crypts, and an increase in mitotic figures. Symons (1965) has studied cell kinetics in infested animals by the use of tritiated thymidine, and has demonstrated an increased cell production in the crypts, and an increase in cell migration on the villi. Although there were changes in the progenitor cycle of cells before gross changes were apparent in crypt and villous morphology, Symons could not be sure whether the increased turnover state was due to a direct effect of the parasite or secondary to an increased loss of cells from trauma at the tips of villi. In another communication (Loehry, Croft, Singh, and Creamer, 1968) we have studied cell loss in infected animals by means of deoxyribonucleic acid loss and excretion of $^{59}$Fe. These experiments showed a considerable increase of cell loss on the ninth day of infection. It thus seems established that by this time the effect of the parasite is to produce a 'flattened' mucosa with increased cell loss possibly stimulating increased production. The aim of this study was to relate this dynamic state to the three-dimensional mucosal structure.

METHODS

Male albino rats were infected by subcutaneous injection of 5,000 to 10,000 larvae of Nippostrongylus brasiliensis from a culture obtained by incubating faeces of an infected rat with active charcoal at 2°C. Animals were killed on the ninth day of infection and the small intestinal mucosa was examined by an autolysed technique and photographed under the dissecting microscope.

RESULTS

Figures 1, 2, and 3 are photographs of the autolysed upper jejunal mucosa taken respectively from a normal control rat, from one with a moderate infection (5,000) larvae, and from one with a severe infection (10,000 larvae). In the normal mucosa (Fig. 1) the triangular-shaped villi are apparent, many lying on their sides, and many crypts. In the mucosa from the moderately infected rat (Fig. 2) most of the villi are longer and shorter and many of the intervillous ridges have now hypertrophied. In the mucosa from the severely infected animal (Fig. 3) the mucosa is quite flat. Villous projections are practically absent, and the whole structure of the...
Three-dimensional structure of the small intestinal mucosa related to mucosal dynamics

**FIG. 1.** Autolysed jejunal mucosa from a normal rat. Many of the triangular-shaped villi are lying on their sides. Note how crypts outnumber villi. ×70.

**FIG. 2.** Autolysed jejunal mucosa from a moderately infested rat (5,000 larvae). Villi are shortened and intervillous ridges are enlarged. Many of the crypts are also dilated. ×70.

**FIG. 3.** Autolysed jejunal mucosa from a severely infested rat (10,000 larvae). The mucosa is flat, and closely resembles the autolysed flat mucosa in coeliac disease. ×70.
mucosa is made up from hypertrophied inter villous ridges. This picture is very similar to the appearances of the autolysed flat human mucosa in cases of coeliac disease (Loehry and Creamer, 1968).

DISCUSSION

In the rat infested with the nematode *Nippostrongylus brasiliensis*, there is a considerable increase of cell loss with increased cell production. This situation may be closely analogous to that in human coeliac disease. By perfusing a segment of duodenum in patients with a normal and a flat mucosa, Croft, Loehry, Taylor, and Cole (1968) have been able to estimate cell loss in a known segment, and have suggested an increased rate of cell loss per unit surface area in the patients with a flat mucosa. The mitotic activity in the flat mucosa also is high (Shiner and Doniach, 1960; Padykula, Strauss, Ladman, and Gardner, 1961; Yardley, Bayless, Norton, and Hendrix, 1962) suggesting increased cell output.

It is the response of the mucosal architecture to this situation that produces the characteristic morphological features seen in coeliac disease: the primary increase in cell loss causes the villi to shorten while the possible compensatory increase in cell production causes hypertrophy of the inter villous ridges and the formation of convolutions and a flat mucosa.

The experiments with methotrexate, lactating rats, and *Strongyloides*-infected rats have demonstrated how the changes in mucosal structure are related to alterations in mucosal dynamics, and how the final structure will depend at any one time on the relationship between cell production and cell loss. The mucosa moulds and remoulds with amazing rapidity when the dynamic state is altered, but the final structure can always be understood in reference to the normal migration lines of the epithelial cells.

SUMMARY

The dynamic state of the small intestinal mucosa in rats infested with *Nippostrongylus brasiliensis* is that of considerably increased epithelial cell loss with an increase in cell production in the crypts. The three-dimensional structure of the mucosa was studied in infected animals after autolysis. The increased cell loss produced shortening of the villi, and the increased cell output hypertrophy of inter villous ridges so that convoluted and flat mucosa were seen. The similarity between this model and coeliac disease was shown.

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REFERENCES


