

This Week's Citation Classic

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Leblond C P & Stevens C E. The constant renewal of the intestinal epithelium in the albino rat. *Anat. Rec.* **100**:357-71, 1948. [Dept. Anatomy, McGill Univ., Montreal, Canada]

At the time when this work was undertaken, it was known that cells arose from mitosis in the epithelial lining of small intestine, but the fate of these cells was obscure. Systematic comparison of the numbers of cells and mitoses led to the conclusion that epithelial cells turned over continually. A cell arising from mitosis in a crypt of the epithelium migrates out of this crypt, ascends the villus and, at the villus tip, drops into the lumen. The duration of the migration has been estimated at less than two days. [The SCI® indicates that this paper has been cited over 320 times since 1961.]

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"The mitotic activity of the intestinal epithelium has often been considered as a regenerative process ensuring the replacement of cells damaged by the powerful enzymes and bacteria present in the gut lumen. Yet abundant mitoses seemed to be present even in the absence of detectable damage. Perhaps, instead of being the static tissue described by classical histologists, the intestinal epithelium might be the site of unsuspected dynamics. At the time when I considered this possibility, a student of British origin, Catherine Stevens, applied for graduate work. I proposed the study of the intestinal epithelium

"Using animals in good health and impeccable methods of fixation, Stevens found mitotic activity in the crypts throughout the length of the small intestine in adult male and female rats, even after penicillin treat-

ment or a five-day fast. Counts revealed that about three percent of the cells were undergoing mitosis at all times of day. Meanwhile, the duration of mitosis was measured by the colchicine method and found to approximate one hour. It was then readily calculated that the mitoses provide enough new cells to replace two-thirds of the population per day.

"The next step was to find what happened to the new cells. In one region of the epithelium—the villus tip—there were signs of death and extrusion of cells. It was, therefore, postulated that the cells arising in the crypts migrated out to become part of the villi and then ascended the villi to drop from the tips into the lumen. The loss should balance cell production to maintain steady state. The whole migration should take less than two days.

"This conclusion appeared surprising to fellow histologists. When Stevens presented these results at a meeting of the American Association of Anatomists, an old histologist from London, Ontario, commented, 'This is too silly for words,' to which she replied, 'It may be silly, but it is true.'

"This work is one of the few which I have published without the support of radioautography. Eventually, however, the rapid migration of epithelial cells from crypt to villus tip was fully confirmed by radioautography, using first ³²P-phosphate, later ¹⁴C-adenine, and especially ³H-thymidine.¹²

"Renewal of the intestinal epithelium was observed in man by Bertalanffy.¹ Recent unpublished calculations indicate that over a quarter of a pound of cells are daily shed into the gut. Recent work in the field has been done by both Cheng and myself.^{4,5}

"Why is there continuous renewal of cells in the gut? With continuous exposure of the cells to enzymes, toxins, and bacteria, ordinary repair mechanisms may not be sufficient for protection, whereas constant supply of new healthy cells provides prompt replacement of weakened areas or gaps and thus anticipates damage."

1. Leblond C P & Messier B. Renewal of chief cells and goblet cells in the small intestine as shown by radioautography after injection of thymidine-³H into mice. *Anat. Rec.* **132**:247-59, 1958.
2. Leblond C P. The time dimension in histology. *Amer J Anat* **116**:1-28, 1965.
3. Bertalanffy F D & Nagy K P. Mitotic rate and renewal rate of the epithelial cells of human duodenum. *Acta Anat* **45**:362-70, 1961.
4. Cheng H & Leblond C P. Origin, differentiation, and renewal of the four main epithelial cell types in the mouse small intestine. *Amer. J Anat* **141**:461-80, 1974.
5. Leblond C P. The life history of cells in renewing systems. *Amer J Anat* In press. February 1981.