of the basic 'sulfonamide' nucleus, the concentration of serotonin has been determined in several intestinal areas following pretreatment with the chemically related drugs, chlorothiazide and tolbutamide.

Male Charles River rats weighing between 280–310 g were randomly divided into 3 groups of 15 animals, housed in colony cages, and fed powdered Purina rat chow with the tryptophan content of 0.22%. Group 1 (control rats) received pure chow. Groups 2 and 3 received 30 mg chlorothiazide (Merck, Sharpe and Dohme) or tolbutamide (Upjohn)/20 g chow. All drugs were continued for 15–25 days and food consumption and weight gain were normal in all groups.

The rats were killed by decapitation between 08.30 and 10.00 on the day of assay, and half inch segments of the upper duodenum, mid-jejunum, terminal ileum and appendix were rapidly removed and prepared as previously described[6]. Serotonin was assayed by the method of BOGDANSKI et al.[7]. Data are presented as mean values ± 1 standard error, and differences between mean values were determined using the *t* test. Results are indicated in the Table.

The serotonin concentration in μg/g mucosa of control and drug treated rats

Tissue	Control	Chlorothiazide	Tolbutamide
Upper duodenum	6.6 ± 0.3	6.2 ± 0.5	6.9 ± 0.3
Mid-jejunum	3.6 ± 0.2	3.6 ± 0.3	3.8 ± 0.2
Terminal ileum	4.2 ± 0.4	4.2 ± 0.2	4.6 ± 0.3
Appendix	14.3 ± 0.09	14.0 ± 0.4	14.7 ± 0.5

Data are expressed as means ± 1 standard error. There are 15 animals/group.

There were no significant differences in the serotonin levels from comparable bowel areas examined between the control group and those rats receiving chlorothiazide or tolbutamide. Thus, it is apparent that the elevated mucosal serotonin levels previously observed in the gastrointestinal tract following sulfamerazine[1] are not related to a non-specific effect of the basic 'sulfonamide' nucleus[8].

Zusammenfassung. Der Serotoningehalt der Schleimhaut im obern Duodenumteil, im mittleren Jejunum, im Ileumendteil und im Appendix von Sprague–Dawley Charles River Rattenmännchen wurde ohne Vorbehandlung und mit Chlorothiazid- und Tolbutamidvorbehandlung spektrophotofluorimetrisch bestimmt. Die Serotoningehalte für die 3 Gruppen vergleichbarer Gewebe waren ähnlich, was zeigt, dass die früher beschriebene Erhöhung des Serotoningehaltes der Schleimhaut nach Sulfamerazinvorbehandlung wahrscheinlich nicht mit einer unspezifischen Wirkung des Sulfonamidteils verbunden ist.

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Comparison of the Cell Cycle and Cell Migration in the Intestinal Epithelium of Suckling and Adult Mice

It has been recently demonstrated that the rate of cell migration is considerably slower in the small intestinal epithelia of suckling rats than in adult animals. This difference was attributed to a slower rate of cellular proliferation and division in the younger rats[1]. However, studies on the age changes in the mean duration of the duodenal cell cycle have shown that the cycle is shortest in suckling mice and gradually lengthens with increasing age[2,3]. Therefore, this investigation was undertaken in an attempt to show that the difference in cell migration is assignable to rapid postnatal growth rather than to great dissimilarities in the cell cycle and proliferative rates.

Methods. Two groups of male Swiss albino mice, aged 10 days (suckling) and 1 year (adult), were utilized. The animals were sacrificed in pairs from $^1/_2$ to 48 h after a single dorsal s.c. injection of tritium thymidine (H^3-T), specific activity 6.4 C/m*M*, methyl labeled, New England Nuclear Corp., at a concentration of $^1/_2$ μc/g body weight. The duodenum was removed, fixed and processed for autoradiography as previously described[4].

The cell cycle for each group was obtained from constructed labeled metaphase curves[2]. The rate of cell migration was determined by measuring the percentage of the villus height (total of 10 villi) that labeled daughter cells had reached at $^1/_2$, 8, 12, 24 and 48 h after H^3-T administration. The average cryptal size (total of 20) and villus height (total of 20) were estimated with a 50-division ocular grid and a B & L stage micrometer. The values were then converted to millimeters (mm). In the analyses of cell migration and sizes, both the crypto-villal junction and extrusion zone were present for villus measurements[5], and measured crypts were longitudinally sectioned[3]. An estimate of cell proliferation was assessed by scoring the number of labeled nuclei/1000 cells in the lamina propria and the cryptal epithelium at $^3/_4$ h after H^3-T injection.

Results. The mean duration of the cell cycle was 12 h in the suckling mice and 14 h in the adult animals. The

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Values for the cell cycle, villus and crypt sizes and the percentage of labeled cells in the mouse duodenal epithelium

Age	Cell cycle (h)	S (h)	G_2 + prophase (h)	Crypt size (mm)	Villus size (mm)	Ratio (villus/crypt)	Lamina propria (%)	Crypt (%)
10 days	12	7.2	0.75–2.0	0.067 ± 0.006	0.41 ± 0.03	6.1	7.7	48.0
1 year	14	7.5	0.75–2.0	0.12 ± 0.01	0.56 ± 0.09	4.7	0.65	34.7

S-phase (about 7.3 h) and G_2+ prophase (0.75–2.0 h) were identical in both groups. The difference in the cell cycle was attributed to dissimilarities in the duration of G_1+ telophase (Table).

The rate of cell migration (Figure) was different in the 2 groups. At $^1/_2$ h labeled cells were found only in the crypts. By 8 h labeled cells were present at the cryptal mouth with only an occasional labeled cell found at the villus base. Labeled cells appeared at the villus base in significant numbers in both groups at 12 h, averaging 2.3 (suckling) and 2.2 (adult) % of the villus height. The migration front advanced to an average distance of 13.8 and 19.7% by 24 h. Greater divergence between the 2 groups occurred at 48 h, i.e. distance of about 36.9 and 52.4% of the villus height, respectively. Extrapolation of the data revealed that labeled cells should reach the extrusion zone at approximately 80 h (adult) and 112 h (suckling) after H^3-T administration.

The average cryptal size was 0.067 mm (suckling) and 0.12 mm (adult). The villus height was 0.41 and 0.56 mm, respectively. The ratio of the villus to the crypt size was almost 30% greater in the young animals (6.1) than in the adult mice (4.7), indicating the larger villus area maintained by a smaller proliferative (crypt) compartment (Table).

The percentage of labeled cells in the lamina propria was 7.5 (suckling) and 0.65 (adult). The cryptal epithelium contained 48.0 and 34.7% labeled cells, respectively (Table).

Discussion. Morphological and enzymatic differences in the intestinal epithelium between suckling and adult animals have been described by several authors[1,2,8–9]. In general, these studies have indicated that enzyme changes occur with differentiation of the intestinal epithelium in relation to diet and morphological specialization[8,9]. However, little evidence exists that correlates changes in cell population kinetics with morphological differentiation.

In the mouse, the crypt of a 10-day-old animal contains approximately 44% fewer cells than adults. The crypt of the suckling mouse increases to adult size by 30 days of age[2,3]. The measurements of the cryptal size (Table) support this conclusion and further suggests that the villus must increase by about 40% in the same period of time. Because of this growth, the shorter cell cycle and the greater number of cells in DNA synthesis would be expected as a direct result of a smaller proliferative compartment in the suckling mice. The larger number of cells in DNA synthesis in the lamina propria of the younger animals also supports this conclusion. Very little growth and renewal would be expected in adult connective tissues.

The slower rate of cell migration in the suckling mice can be explained on the basis of the area that must be maintained by the cryptal population, as well as in villus and cryptal sizes. The ratio of the villus to the cryptal size indicates that the crypt of the suckling mice, although 40% smaller than the adult crypt, must maintain the steady state of the villus epithelium that is 30% greater than the same ratio in the adult animals. Thus, a slower rate of migration is understandable when the difference in size ratios, in addition to the tremendous growth that must take place, are considered.

Finally, it seems appropriate to speculate on the observation that it takes approximately 12 h before labeled cells begin to appear in significant quantities at the villus base in both groups. Similar observations have been made in this laboratory[4] and by CAIRNIE et al.[10,11]. By 12 h after H^3-T injection, initially labeled cells have passed through G_2 and division and have reentered a second cycle[4]. In both groups, therefore, it appears that many of the progenitor cells of the crypt pass through 2 or more cell cycles and others only 1 before migrating out of the crypt. This subject is under investigation at the present time[12].

Zusammenfassung. Die Zellwanderung sowie die Zellvermehrung in den Krypten und auf den Zotten der Dünndarmwandung werden bei säugenden Mäusen mit dem Adulttier verglichen. Die scheinbar herabgesetzte Zellmigration ist auf das bei jungen Mäusen stattfindende Wachstum der Krypten und Zotten zurückzuführen, ist also nicht geringer als bei adulten Tieren.

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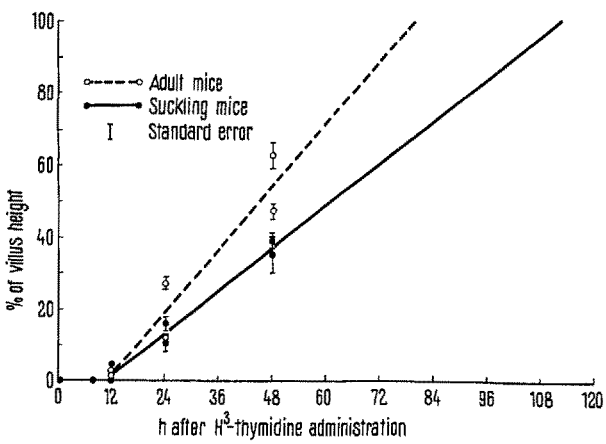

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