intimate relationship between the sinusoid, the Kupffer and the hepatic cells. At this time, the Kupffer cell showed signs of preparing for division; the nucleus with its uneven membrane was filled with dark staining chromatin clumps.

Microscopic sections of the liver from animals sacrificed on day 5, showed both dividing Kupffer and endothelial cells. By late anaphase, the Kupffer cell had lost its cytoplasmic tubules. The cell, now considerably swollen with foamy cytoplasm, had elongated, extended from one wall of the sinusoid to the other (Figure 2). It is interesting that during the mitotic phase, the Kupffer cell never lost complete contact with the wall of the sinusoid.

Although there was considerable swelling of the endothelial cell during its mitotic phase, it too never lost contact with the wall of the sinusoid, nor did it ever attain the size of the Kupffer cell. Notwithstanding these facts, during late anaphase, the cell managed to extend itself across the sinusoid from one wall to the other (Figure 3).

After the reticuloendothelial cell had completed its division, the daughter cells took up new positions, one attached to either side of the wall of the sinusoid (Figure 4). The new cells, both Kupffer and endothelial, repeated this process, accounting for the great increase in reticuloendothelial cells observed in the liver on day 7. On day 9, the process had greatly diminished and no dramatic increase in reticuloendothelial cells per se were seen.

Amid the activity of these cells on days 5, 7 and 9, the newly formed Kupffer and endothelial cells were engaged in a most unique process, revealing their differentiation in the direction characterized as cells belonging to the erythroid series.

Under the conditions of the present study, the increase in reticuloendothelial cells of the liver is entirely a local phenomenon exhibited by existing cells, with no contributions from outside sources[10]. These results lend credence to evidence maintaining that mature macrophages can undergo division[12–16], and demonstrates that the responsiveness of reticuloendothelial cells to intermediate lobe materials is an important bearing on the role of endocrines in the regulation of the reticuloendothelial system[17–21].

Although the reticuloendothelial cells of the liver are unstable, are multipotential and behave according to the nature of the stimulus employed, there is no doubt about their mitotic capabilities.

Zusammenfassung. Gewebe des Hypophysenzwischenlappens und das Kolloid wirken auf Endothelzellen ein. Sie vermögen die retikuloendothelialen Zellen der Leber zur Mitose anzuregen. Diese Zellen scheinen eine wichtige Rolle bei der Übermittlung von endokrinen Stoffen und der Regulation des retikuloendothelialen Systems zu spielen.

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The Relationship Between Cell Division and Cell Specialization in the Mouse Intestinal Epithelium

The steady state concept which characterizes renewing cell populations has been formulated on a statistical basis. Thus, to maintain an equilibrium between cell birth and cell death, one daughter cell of a progenitor (or stem) cell division remains in the proliferative pool, while the other progeny migrates towards the functional compartment and takes on special functions. Therefore, in order to account for this mechanism, several stochastic models depicting the relationship between cell birth and cell specialization have been suggested[1–8]. Until recently, the most widely accepted model has been predicated on an asymmetrical mitosis[1–3,6].

Such a concept, however, does not allow for considerable variation in the life history and function of individual cells within a population. Moreover, recent evidence obtained from a variety of renewing epithelial cell populations, esophagus[5], jejunum[7–9], duodenum[10], has suggested that 3 models may be operating in concert to maintain the steady state, none of which use an asymmetrical division to explain the relationship between division and the subsequent specialization of progeny. Therefore, the present study was undertaken in an attempt to demonstrate the role of individual progenitor cells in the renewal of the duodenal epithelium.

Materials and methods. A total of 46 male Swiss albino mice were utilized. Each animal received a single dorsal s.c. injection of tritium thymidine (hereafter, 3HTdr) labeled at the methyl position, New England Nuclear Corporation, specific activity 6.4 C/m*M*, at a concentration of 0.5 μc/g body weight. The mice were sacrificed by cervical dislocation, 2 per time interval, from $^1/_4$ to 30 h

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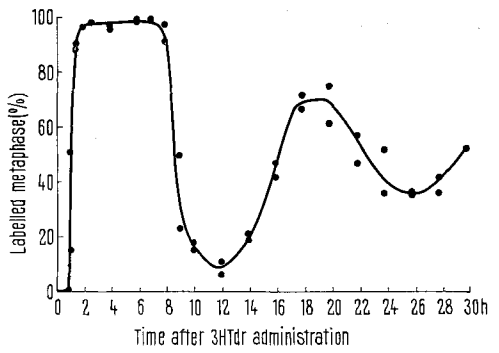
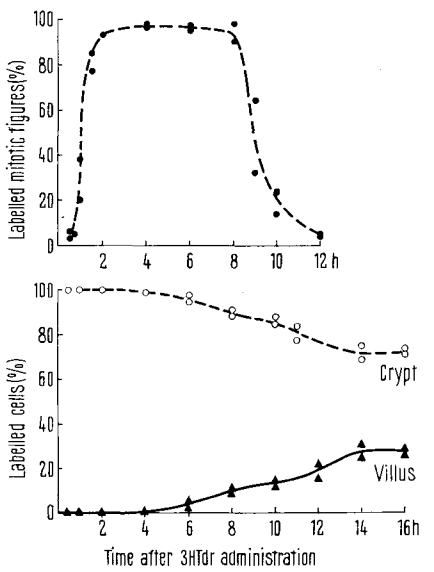


Fig. 1. Curve that demonstrates the appearance and disappearance of labeled metaphase figures at various times after ^{3}HTdr injection. Each symbol represents at least 1 animal and in some cases 2.



Figs. 2 and 3. Curve (upper) that represents the percentage of labelled mitotic figures from $^1/_2$ to 12 h after ^{3}HTdr injection. The lower figure shows the percent of the total labelled cells found at the villus base versus those remaining in the crypt from $^1/_2$ to 16 h after ^{3}HTdr injection. In both figures each symbol represents a single animal and in some cases 2.

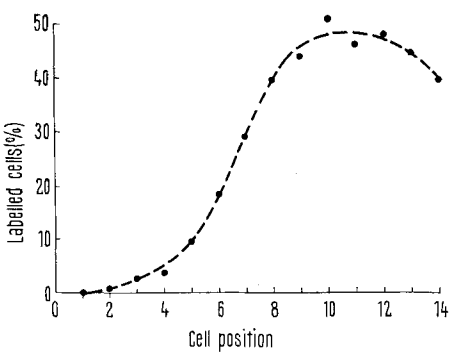


Fig. 4. The percentage of labelled cells at each cell position in the crypt wall beginning with the first cell (1) below the crypto-cillal junction at 30–90 min after ^{3}HTdr administration. Each symbol represents data obtained from 8 animals and a total of 20 crypts per animal.

after 3HTdr administration. Segments of the duodenum, approximately 1 cm long, were taken from an area 0.5 cm below the pylorus. The tissues were fixed in Hollande-Bouin fluid for 3 days, washed in tap water, imbedded in paraffin and sectioned at 5 μ. The sections were coated with NTB2 Nuclear track emulsion and processed for autoradiography as previously described[10].

Autoradiograms were examined to determine: (1) the percentage of labeled mitotic and metaphase figures from $^1/_4$ to 32 h after 3HTdr injection; (2) the position of labeled cells in the crypt wall at 30–90 min after isotope administration; and (3) the rate of migration of labeled daughter cells from their origin in the crypt to their appearance at the villus base from $^1/_2$ to 16 h. The methods for determining these various parameters have been previously reported[10,12]. In the determination of the distribution of labeled cells in the crypt wall, the data on the last 4 cell positions at the base of the crypt were not presented because of high incidence of Paneth cells[12].

Results. The cell cycle and its phases: A curve describing the percent of labeled metaphase figures is presented in Figure 1. Estimates of the mean duration of cell cycle and the S-phase produced values of 13 and 7.5 h, respectively.

Measurement of the average duration of the other phases of the cell cycle were obtained from a labeled mitotic curve prepared from the same animals (Figure 2). The duration of the phases (Table) was estimated from Figure 2 to be G_2 ($^1/_2$ h), D (1 h) and G_1 (4 h).

The distribution of cells in DNA synthesis in the crypt wall: The frequency of labeled cells along the length of the crypt wall below the crypto-villal junction is presented in Figure 4. No labeled cells were found at the crypto-villal junction (cell position 0). At cell position 1 below the junction, only 0.9% of the cells were found in DNA synthesis. The frequency of labeling then rose exponentially, reaching a maximum of 40–52% between cell positions 8 through 14.

Cell migration: The rate of cell migration from the crypt to the villus base is presented in Figure 3. Significant quantities of labeled daughter cells (2–4% of the total labeled population) appeared at the villus base at 6 h after 3HTdr administration. Thereafter, 10–15% were found at 8 h. The maximum number of labeled cells occurred at 14–16 h (about 25%) following thymidine injection. Therefore, approximately 75% of all labelled cells were retained in the crypt for a period up to 16 h after the first labeled cell had divided and 6 h after the last labeled cell underwent division. If the cutoff point for the high probability of being in DNA synthesis is

Average duration of the cell cycle and its phases

Phase	Duration (h)
T	13
G_1	4
S	7.5
G_2	0.5
D	1.0

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established between cell positions 6–7 and $G_2 + M$ takes 1.5 h, then labeled daughter cells migrated from their point of origin to the villus base at a rate of 1.3–1.5 cell positions per h.

Discussion. The distribution of cells in DNA synthesis immediately after 3HTdr injection (Figure 4) suggests that the cryptal population can be subdivided into a region of high proliferation (cell positions 8–14) and a region of cell specialization (cells 1–8). Similar observations have been reported by other investigators[7–9]. However, if attention is focused on the progenitor cells positioned in the deeper regions of the crypt, it appears that an asymmetrical division does not necessarily account for the maintenance of the steady state in the mouse duodenum.

If the rate of cell migration (1.3–1.5 cell positions per h) presented in Figure 3 is compared to the distribution of proliferating cells (Figure 4), it appears that a symmetrical division may be the most common form in the deeper portions of the mouse cryptal epithelium. For example, daughter cells that are produced deep in the crypt (cell positions 10 through 14) can only migrate from 5.2–6.0 cell positions during the G_1 (duration of 4 h) following the division that produced them. Therefore, these progeny arrive in the region (cell positions 5 through 9) conducible to a high probability of proliferation at a time when they are about to enter a new S-phase[7,8,10]. In addition, if the progenitor cells present in the region below cell 14 are considered, e.g., the Paneth zone[12], progeny of these divisions could remain in the crypt for 2 or more cell cycles before they are able to migrate into the regions of cell specialization. Thus, it is concluded that divisions of progenitor cells deep in the crypt will probably produce 2 progenitor cells that will at least enter one more division cycle before they specialize. In order to compensate for this, an equal number of divisions that produce 2 specialized progeny must occur. Inspection of Figures 3 and 4 reveals that such a division could possibly occur beginning with cell positions 9 or 10. Thus, the cutoff point for the decision between 2 types of daughter cell production must lie between cell positions 9 and 10. This is reasoned because the cells most likely to specialize immediately after division and during the short G_1 phase (4 h) are those present in the upper regions (cell positions 1–10). Furthermore, it should be emphasized that a progenitor division could also give rise to 2 progeny, one specialized and the other a progenitor. This phenomenon would depend upon the position of the dividing cell, the rate of migration, the intensity of a possible feedback inhibition, and the final position of the daughter cells before DNA synthesis is either initiated or precluded[7,10].

It has been suggested but not conclusively demonstrated that all cryptal cells are potentially progenitor cells[7,10,11]. Thus, analysis of the changes in the proliferative vs. the maturation zones under a variety of experimental conditions may lead to a greater understanding of those mechanisms that bring about cell specialization[9].

Zusammenfassung. Der Zusammenhang zwischen der Teilung von Ursprungszellen und der Differenzierung ihrer Tochterzellen wurde anhand von Epithelzellen des Duodenums weisser Mäuser untersucht. Um den Zustand des «steady state» zu erhalten, finden die folgenden Arten von Teilung der Ursprungszellen statt: 1) zwei neue Ursprungszellen; 2) zwei differenzierte Tochterzellen; oder 3) eine neue Ursprungszelle und eine differenzierte Tochterzelle.

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Experimental Goiter: Ultrastructure and Autoradiography

Goiters can be induced experimentally by the prolonged feeding of a deficient-iodine diet in many laboratory animals. Previously, ultrastructure and secretory cycle of thyroid cells in control animals have been extensively studied (EKHOLM[1], WISSIG[2], LUPULESCU and PETROVICI[3]), but little is known about the fine structure of goiters (FELDMAN[4]). In particular, few have attempted a correlation between the ultrastructure, radioautography and radiochromatograms in goiter induced by low iodine diet. In spite of the recent interest in other goitrogenic factors, chronic iodine deficiency remains the main cause of goiter.

Biochemical disorders revealed that the triiodothyronine/thyroxine (T3/T4) ratio increases progressively in the follicular cells of the iodine-deficient rat thyroid (STUDER and GREER[5]).

This study deals with the ultrastructural pattern of the iodine-deficient goiters in rats and with the intracellular distribution of radioiodinated proteins.

Materials and methods. For induction of goiter male Wistar rats, weighing 180–200 g, were used. The first group, the controls, received a stock laboratory diet, containing 0.9–1.2 μg I/g food. The second group was fed for 4 months with a modified-Remington low iodine diet, containing 0.03–0.04 μg I/g food.

Radioiodine (^{125}I) was injected i.p. (275 μC) into 5 rats, 2–6 h before sacrificing, for light and electron microscopic autoradiography. The other 15 from each group received i.p. injections of 12 μc ^{131}I for chromatographic analysis of thyroid tissue. For ultrastructural pattern of the

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