Increased Turnover of Intestinal Mucosal Cells of Germfree Mice Induced by Cholic Acid[1] (35876)

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The physiological investigation of vertebrate bile acids over the last half century has produced extensive information about utilization, turnover rates, pool types, enterohepatic circulation, bacterial decomposition, liver reconjugation, and metabolic pathways. However, knowledge of the specific functions of bile acids with respect to intestinal physiology has been slow in developing.

In studies of bile acid metabolism in germfree rats it has been observed that practically the only bile acid formed, utilized, and excreted is taurocholic acid (1). By contrast, in conventional rats, the taurocholic acid is hydrolyzed by bacteria in the intestine to taurine and cholic acid. The conventional mouse has essentially the same bile acid metabolism as the rat (2). Since the intestinal tracts of conventional and germfree mice manifest many differences structurally and functionally (3), it is appropriate to question to what degree these differences result from the difference in the form of bile acids and salts present. One such difference observed by several investigators (4–7) is that in the germfree mouse the migration of mucosal cells from the crypts to the tips of the villi (*i.e.*, the life-span of the cells) takes twice as long in the germfree mouse as in the conventional mouse—4 vs 2 days. It has also been noted that germfree mice survive irradiation in the gut death range (3000 R) for a period twice as long as conventional mice (7 vs 3.5 days). This increased survival time of germfree mice has been attributed to the longer life of its mucosal cells (7), which possibly is the result of the presence of taurocholic acid or the absence of cholic acid.

The purpose of the present research was to investigate the role of bile acids in regulating the turnover of intestinal mucosal cells. We were specifically interested in seeing if the turnover rate of these cells in the germfree mouse could be accelerated to that of the conventional mice by altering the composition of the bile acids present in the small intestine.

Materials and Methods. Three groups of CFW germfree mice, 21 days old, consisting of 10 males and 10 females each, were placed on a steam-sterilized starch–casein diet (8). For one group this diet was supplemented with 0.15% cholic acid (General Biochemicals, Chagrin Falls, Ohio); for a second group, with 0.15% taurocholic acid (Mann Research Laboratory, Westbury, New York). The third group was given only the basic diet, and thus served as the control group. The mice were maintained germfree in Trexler flexible plastic isolators (9) by procedures standardized at the Lobund Germfree Life Laboratory. At 7 months of age, each animal received 15 μCi of tritiated thymidine ip. Daily thereafter one male and one female from each group were sacrificed and histological sections of the ileum were prepared. The sections were developed for radioautography according to the method of Messier and Leblond (10). Two parameters were measured daily in determining the rate of turnover of the epithelial cells: (i) the percentage of mucosal cells on the villi labeled by the tritiated thymidine; and (ii) the percentage of the height of the villi traversed by the uppermost or leading labeled cell since the time of the administration of

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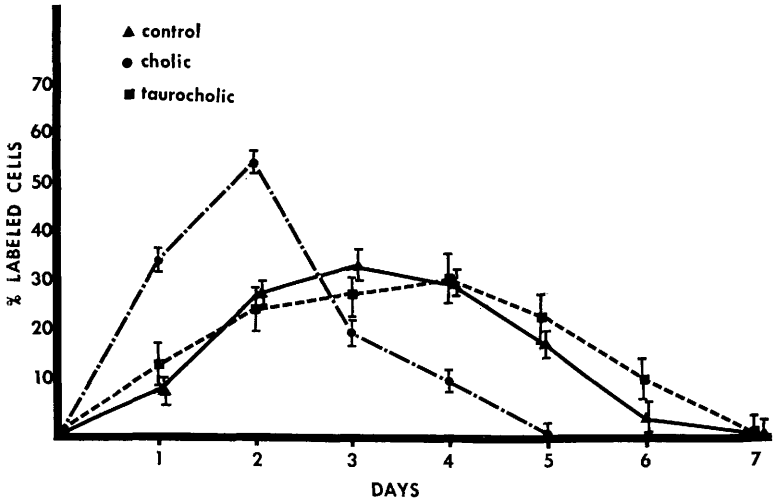

FIG. 1. The percentage of mucosal cells on the villi carrying the radioactive label vs time.

the tritiated thymidine. These percentages were calculated from cell counts and measurements of 50 intact villi of specimens from each time interval and were plotted with their standard errors.

Results. In Figure 1, the percentages of mucosal cells on the villi carrying the radioactive label are plotted for the three groups. In the group receiving taurocholic acid and in the control group, the greatest number of labeled cells appeared on the villi 3 or 4 days after the mice received tritiated thymidine. All labeled cells had disappeared from the villi in these two groups at 7 days. There is no significant difference between the curves for the two groups. However, in the group given cholic acid the labeled cells reached their greatest number on the villi on the second day and were all gone by the fifth day.

In Figure 2, there is no significant difference between the lines representing the migration of labeled cells along the villi of mice given taurocholic acid and control mice receiving no supplement. At 4 days following the dose of tritiated thymidine the label has progressed over 96% of the length of the villi. Extrapolation of this line to intersect the 100% line gives a transit time from the crypt to the extrusion from the tip of the villus of 4.44 days. For those mice on the diet supplemented with cholic acid, the label at the end of the second day is already close to the tip of the villus, having migrated over 94% of the villus length. Extrapolation of this line gives a total transit time of 2.12 days.

Discussion. In this experiment, the addition of cholic acid to the diet of germfree mice shortened the life-span of the mucosal cells from 4.44 days to 2.12 days. These values are in close agreement with a previous study of the life-span of mucosal cells of germfree mice in which it was determined that the transit time in germfree mice was 4.3 days vs 2.1 days in conventional mice (7). The presence of cholic acid in the intestinal tract accelerates the turnover of the cells on the villi. This is reflected also by the shortened time in which the greatest number of labeled cells appear on the villi in cholic acid fed mice and by the faster disappearance of the labeled cells from the villi. The peak is reached 2 days after giving tritiated thymidine. Thereafter, the percentage of labeled cells decreases because they are being extruded from the tips of the villi. This process is delayed by 2 days in both the controls and those receiving the taurocholic acid supplement. How cholic acid stimulates cell turnover is not known.

A number of enteric organisms have the capacity of hydrolyzing taurocholic acid to cholic acid in conventional animals (11). These organisms apparently effect physiologi-

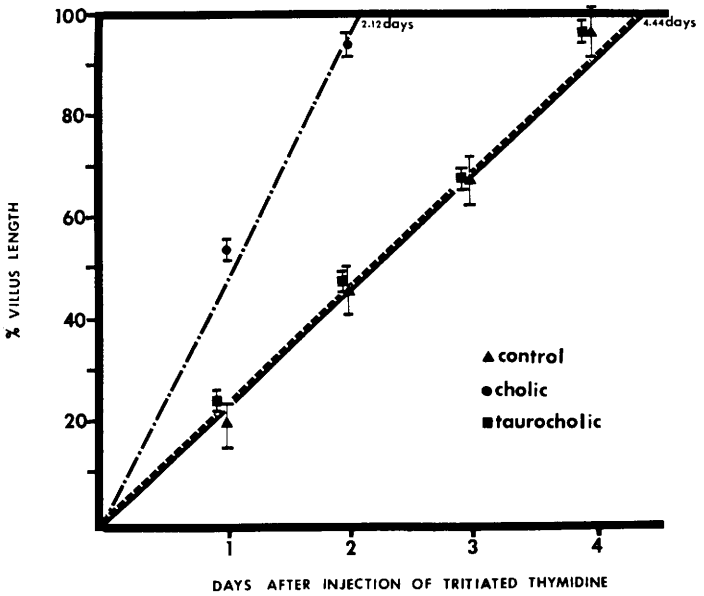

FIG. 2. The migration of the labeled mucosal cells along the length of the villus.

cal changes in the host by metabolizing substances of host origin in the gastrointestinal tract. The extent and significance of these alterations remain to be evaluated.

Summary. When germfree mice are fed a diet supplemented with cholic acid, the turnover of intestinal mucosal cells is reduced from 4.44 to 2.12 days, which is the turnover time in conventional mice. It is concluded that cholic acid, which is produced in conventional mice by hydrolyzing enzymes of bacterial origin, has a regulatory effect on intestinal mucosal cell turnover.

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