Reprinted from NUTRITION REVIEWS
Vol. 17, No. 3, March, 1959
Printed in U.S.A.

ADAPTATION TO LACTOSE

Lactose is the only carbohydrate found in substantial amount in milk. It alone accounts for approximately half the total solids in this, the first food of all mammals. The ability of young animals to digest this sugar, therefore, is an absolute necessity for survival.

It has been known for many years that the digestion of lactose starts with hydrolysis of the disaccharide to its component monosaccharides glucose and galactose, which are then absorbed and utilized. This hydrolysis is catalyzed by lactase, an enzyme present in the small-intestinal mucosa.

Lactase, since it cleaves the β-galactosidic linkage in lactose, is a β-galactosidase. However, not all β-galactosidases attack lactose. There is present in most animal tissues, including liver, kidney and spleen, and also the intestinal mucosa, a β-galactosidase which does not break down lactose at an appreciable rate (N. S. C. Heilskov, *Studies on Animal Lactase*, Munksgaard, Denmark, 1956). This could explain why, although β-galactosidase activity has been found outside the digestive tract, lactose injected into the bloodstream is not metabolized, but is excreted unchanged. The natural substrates of this more generally distributed β-galactosidase are unknown. For those studying lactose metabolism, this enzyme assumes an added importance in that attempts to use chromogenic substrates (e.g., orthonitrophenyl β-D-galactoside) as substrates for lactose must account for non-lactase-β-galactosidase activity.

In the last decade of the nineteenth and first decade of the twentieth century, a number of physiologists in this country and abroad were interested in the digestion of lactose. Their studies suggested that the major location of lactose digestion was in the small intestine and that the intestines of young mammals were more active in hydrolyzing lactose than those of older ones. E. Fischer and W. Niebel (*Sitzber. Akad. Wiss. Berlin, p. 73 (1896)*) suggested that the feeding of young animals on lactose (milk) might be responsible for their higher "lactose ferment" activity. That is, that lactase production by the intestine is an adaptation to lactose.

A controversy soon arose between those who believed in the adaptation theory and those who felt that there was no experimental evidence to support the hypothesis. At one time Pavlov, himself, suggested that pancreatic enzymes were produced in response to the type of food ingested (B. P. Babkin, *Secretory Mechanism of the Digestive Glands*, Hoeber, New York, 2nd ed. 1950). There were claims and counterclaims made, supported by various experimental data, but without the concept of pH, and adequate awareness of the dangers of bacterial contamination, it was not possible to achieve clearcut answers.

R. H. A. Plimmer (*J. Physiol.* **35,** *20 (1907)*) in a review of previous work on the subject, and based on much work of his own, using better assay conditions, concluded that lactose adaptation in the pancreas does not occur. He went on to look for evidence of lactose adaptation in the intestine of rat, guinea pig, rabbit, pig and chicken. He found none, and concluded that neither the pancreas nor the intestine can be made to adapt to lactose. Recent work substantiates Plimmer's observation that the feeding of lactose to weaning animals does not keep the lactase activity at the high level present in the very young (N. S. C. Heilskov, *Acta physiol. Scandinav.* **24,** *84 (1951)*; J. E. Fischer, *Am. J. Physiol.* **188,** *49 (1957)*).

In order to gain perspective on the problems of adaptation, let us, at this point, digress for a moment from studies in higher animals and consider briefly what is known

about the adaptation of bacterial populations. Much work has been done on the means by which a bacterial population succeeds in growing under particular conditions, such as ion concentration, pH, aeration, sources of carbon, and nitrogen.

For example, *Escherichia coli* can use lactose as its only source of carbon and energy, if allowed to "adapt." Basically, two types of adaptation are possible: either there are cells in the population which, as is, are capable of growing on the lactose, and these cells are selected for, and grow up rapidly, or the presence of lactose evokes the production of an enzyme (or enzymes) which then enables any cell so affected to grow on the lactose. In the former case, while the total enzyme activity of the population will go up, the amount of enzyme in a given cell will be the same as the amount of enzyme in the cell originally selected for, whereas in the latter case the enzyme content per cell will increase. This situation, where a compound evokes enzyme production, is referred to as induced enzyme synthesis.

Many investigators (J. Lederberg, *J. Bacteriol.* **60,** *381 (1950)*; J. Monod and M. Cohn, *Advances in Enzymol.* **13,** *67 (1952)*; M. Cohn, *Bacteriol. Rev.* **21,** *140 1957*)) have studied in great detail the induced synthesis of *E. coli* β-galactosidase (lactase). They have shown that the enzyme can hydrolyze a variety of alkyl and aryl β-galactosides, and that most of these compounds can serve, not only as a source of sugar, but as inducers for β-galactosidase. Further, Monod has shown that exposure of the cells not only to hydrolyzable galactosides, but to non-hydrolyzed thiogalactosides, can, *under the proper conditions*, result in the synthesis by the cells, of β-galactosidase. It is the necessary conditions which are of interest here, since certain of them may give clues to understanding adaptation in animals.

Using thiogalactosides, it is possible to get induction of galactosidase while the cells are contentedly growing on another sugar. Thus induction of galactosidase in strains which will not grow on lactose can be studied, and from the results much can be learned of the mechanism and requirements of induction. There are two types of such strains: in one there is an hereditary defect which renders the cell incapable of producing galactosidase, and in the other, an hereditary defect which keeps the cell from producing an enzyme-like system which is responsible for facilitating the entrance of galactosides into the cell. If inducer concentrations high enough to overcome the natural permeability barrier of the cell are used with the latter strain, induction occurs (L. A. Herzenberg, *Biochim. Biophys. Acta* **31,** 525 (1959)). However, with this impermeable (cryptic) strain, lactose itself, regardless of concentration, will not induce galactosidase, an observation as yet to be satisfactorily explained.

Thus, genetic makeup is a key factor in allowing induction. Bacteria must be genetically competent of responding to inducer. Permeability of the cell to inducer is important, as well as the choice of inducer. Age and state of nutrition of the cell too, among other factors, influence the cell's inducibility.

Bearing in mind the necessary conditions for adaptation in bacterial populations, let us re-examine Plimmer's conclusion that "neither the pancreas nor the intestines of animals can be made to adapt themselves to any particular diet" (R. H. A. Plimmer, *J. Physiol.* **35,** *20 (1907) p. 30*).

Several questions are immediately suggested: 1) Is lactose an inducer of lactase in animals, or is there perhaps another inducer (a β-galactoside, a hormone?) for lactase in animals? 2) Are cells of the intestinal mucosa of weanlings and adults "genetically" competent to respond to lactose (or any other inducer) and produce lactase, or has the process of differentiation and development resulted in the loss of a characteristic perhaps originally present in animal cells? 3) Since dietary lactose never reaches the bloodstream in a significant amount in adult animals, is it possible that it never reaches a site where it can act effectively as an inducer? Even if this site were in the intestinal mucosa, it is possible to imagine that the

lactose is broken down before it either can penetrate the intestinal mucosa sufficiently to induce or build up a sufficient concentration in the cell to bring about induction.

The questions raised suggest that it might be better to look for induction in very young animals, where the intestine might contain cells which have not yet lost the ability to adapt, and where the intestinal wall has not yet thickened and is still somewhat permeable to most substances.

The pattern of appearance and increase of lactase in fetal and newborn animals could be interpreted as an enzyme induction phenomenon. Recent work (N. S. C. Heilskov, *Studies on Animal Lactase*, Munksgaard, Denmark (1956)) has shown that intestinal lactase increases during the latter part of gestation and reaches a maximum specific activity a short time after birth. It is possible that fetal and infant intestinal mucosa cells, still genetically competent to produce lactase, are induced to form lactase by exposure to some substance present late in fetal life and early in lactation. This "substance" could be lactose, liberated into the mother's bloodstream and entering the fetus via the placenta, and later possibly entering the infant's bloodstream due to a more permeable intestinal wall. It might also be a hormone such as prolactin, whose presence coincides with the period of increased synthesis of the enzyme. Whatever the details, there is a definite possibility that lactase can be induced in mammals.

Adaptation by animals to lactose, however, is not limited to induction of lactase. Rats fed a diet rich in lactose develop diarrhea, but after continued administration of the sugar, the animals adapt to the unnatural diet conditions and the diarrhea subsides (L. K. Riggs and A. Beaty, *J. Dairy Sci.* **30,** *939 (1947)*).

Fischer and her collaborators have shown that the weight of intestinal mucosa of lactose-adapted rats has increased about 50 per cent, giving the adapted individuals larger amounts of lactase without increasing the amount of lactase per intestinal mucosa cell (J. E. Fischer, *Am. J. Physiol.* **188,** *49 (1957)*). In addition, these animals develop a larger cecum (J. V. Lawrence, J. E. Fischer, T. S. Sutton and H. H. Weiser, *Ohio J. of Sci.* **56,** *87 (1956)*). It was also shown that lactose disappeared from the intestine about 50 per cent faster in adapted animals (J. E. Fischer and T. S. Sutton, *J. Dairy Sci.* **36,** *7 (1953)*), and presumably was hydrolyzed and utilized by the animals. There have been other studies, not as fully analyzed as Fischer's case where, after an initial diarrhea, various animals have been shown to adapt to the lactose diet (H. S. Mitchell and W. M. Dodge, Jr., *J. Nutrition* **9,** *37 (1935)*; E. O. Whittier, C. A. Cary and N. R. Ellis, *Ibid.* p. 521).

The animal, then, has two mechanisms for dealing with lactose. The infant, who depends on lactose for nourishment, is provided with a mechanism which, even before birth, has begun to raise the lactase level in the cells of the intestinal mucosa. This level, generally highest soon after birth, falls slowly (probably due to a decreasing rate of synthesis of lactase) until it reaches a basal level after weaning. From this time on, the basal level prevails, and in order to handle large amounts of lactose, the animal is forced to resort to a second mechanism, that of increasing the mass of the intestinal mucosa in order to have sufficient lactase to deal with the increased dietary burden.

An understanding of what triggers lactase synthesis towards the end of fetal life and the factors which maintain a constant lactase level in the adult intestinal mucosa even though the animal may need more lactase, would be of theoretical significance and would certainly rapidly find practical applications.

* LEONARD A. HERZENBERG *and* LEONORE A. HERZENBERG

* *Laboratory of Cell Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland*