

**LACTOSE IS DIGESTED BY LACTASE** in the intestine, a single epithelial cell of which is enlarged 37,500 diameters in this scanning electron micrograph made by Jeanne M. Riddle of the Wayne

State University School of Medicine. The cell, on the surface of one of the finger-like villi that stud the lining of the intestine, is in turn covered by innumerable fine processes called microvilli.

# LACTOSE AND LACTASE

Lactose is milk sugar; the enzyme lactase breaks it down. For want of lactase most adults cannot digest milk. In populations that drink milk the adults have more lactase, perhaps through natural selection

by Norman Kretchmer

Milk is the universal food of newborn mammals, but some human infants cannot digest it because they lack sufficient quantities of lactase, the enzyme that breaks down lactose, or milk sugar. Adults of all animal species other than man also lack the enzyme—and so, it is now clear, do most human beings after between two and four years of age. That this general adult deficiency in lactase has come as a surprise to physiologists and nutritionists can perhaps be attributed to a kind of ethnic chauvinism, since the few human populations in which tolerance of lactose has been found to exceed intolerance include most northern European and white American ethnic groups.

Milk is a nearly complete human food, and in powdered form it can be conveniently stored and shipped long distances. Hence it is a popular source of protein and other nutrients in many programs of aid to nutritionally impoverished children, including American blacks. The discovery that many of these children are physiologically intolerant to lactose is therefore a matter of concern and its implications are currently being examined by such agencies as the U.S. Office of Child Development and the Protein Advisory Group of the United Nations System.

Lactose is one of the three major solid components of milk and its only carbohydrate; the other components are fats and proteins. Lactose is a disaccharide composed of the monosaccharides glucose and galactose. It is synthesized only by the cells of the lactating mammary gland, through the reaction of glucose with the compound uridine diphosphate galactose [see *illustrations on next page*]. One of the proteins found in milk, alpha-lactalbumin, is required for the synthesis of lactose. This protein apparently does not actually enter into the

reaction; what it does is “specify” the action of the enzyme galactosyl transferase, modifying the enzyme so that in the presence of alpha-lactalbumin and glucose it catalyzes the synthesis of lactose.

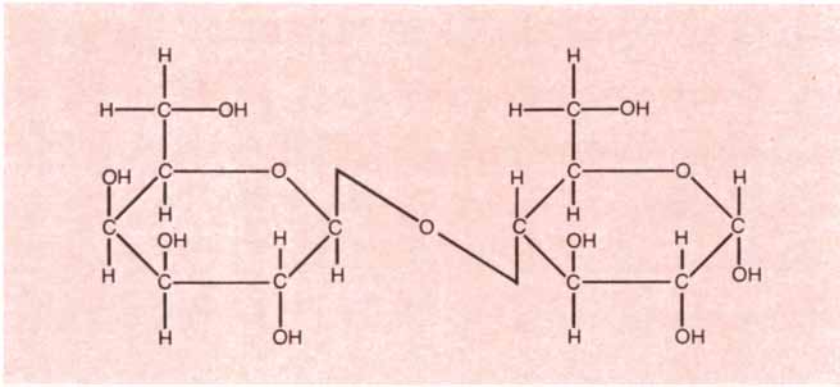
In the nonlactating mammary gland, where alpha-lactalbumin is not present, the enzyme synthesizes instead of lactose a more complicated carbohydrate, N-acetyl lactosamine. Test-tube studies have shown that alpha-lactalbumin is manufactured only in the presence of certain hormones: insulin, cortisone, estrogen and prolactin; its synthesis is inhibited by the hormone progesterone. It is when progesterone levels decrease late in pregnancy that the manufacture of alpha-lactalbumin, and thus of lactose, is initiated [see “Milk,” by Stuart Patton; *SCIENTIFIC AMERICAN*, July, 1969].

The concentration of lactose in milk from different sources varies considerably. Human milk is the sweetest, with 7.5 grams of lactose per 100 milliliters of milk. Cow’s milk has 4.5 grams per 100 milliliters. The only mammals that do not have any lactose—or any other carbohydrate—in their milk are certain of the Pinnipedia: the seals, sea lions and walrus of the Pacific basin. If these animals are given lactose in any form, they become sick. (In 1933 there was a report of a baby walrus that was fed cow’s milk while being shipped from Alaska to California. The animal suffered from severe diarrhea throughout the voyage and was very sick by the time it arrived in San Diego.) Of these pinnipeds the California sea lion has been the most intensively studied. No alpha-lactalbumin is synthesized by its mammary gland. When alpha-lactalbumin from either rat’s milk or cow’s milk is added to a preparation of sea lion mammary gland in a test tube, however,

the glandular tissue does manufacture lactose.

In general, low concentrations of lactose are associated with high concentrations of milk fat (which is particularly useful to marine mammals). The Pacific pinnipeds have more than 35 grams of fat per 100 milliliters of milk, compared with less than four grams in the cow. In the whale and the bear (an ancient ancestor of which may also be an ancestor of the Pacific pinnipeds) the lactose in milk is low and the fat content is high.

Lactase, the enzyme that breaks down lactose ingested in milk or a milk product, is a specific intestinal beta-galactosidase that acts only on lactose, primarily in the jejunum, the second of the small intestine’s three main segments. The functional units of the wall of the small intestine are the villus (composed of metabolically active, differentiated, nondividing cells) and the crypt (a set of dividing cells from which those of the villus are derived). Lactase is not present in the dividing cells. It appears in the differentiated cells, specifically within the brush border of the cells at the surface of the villus [see *illustrations on page 74*]. Lactase splits the disaccharide lactose into its two component monosaccharides, glucose and galactose. Some of the released glucose can be utilized directly by the cells of the villus; the remainder, along with the galactose, enters the bloodstream, and both sugars are metabolized by the liver. Neither Gary Gray of the Stanford University School of Medicine nor other investigators have been able to distinguish any qualitative biochemical or physical difference among the lactases isolated from the intestine of infants, tolerant adults and intolerant adults. The difference appears to be

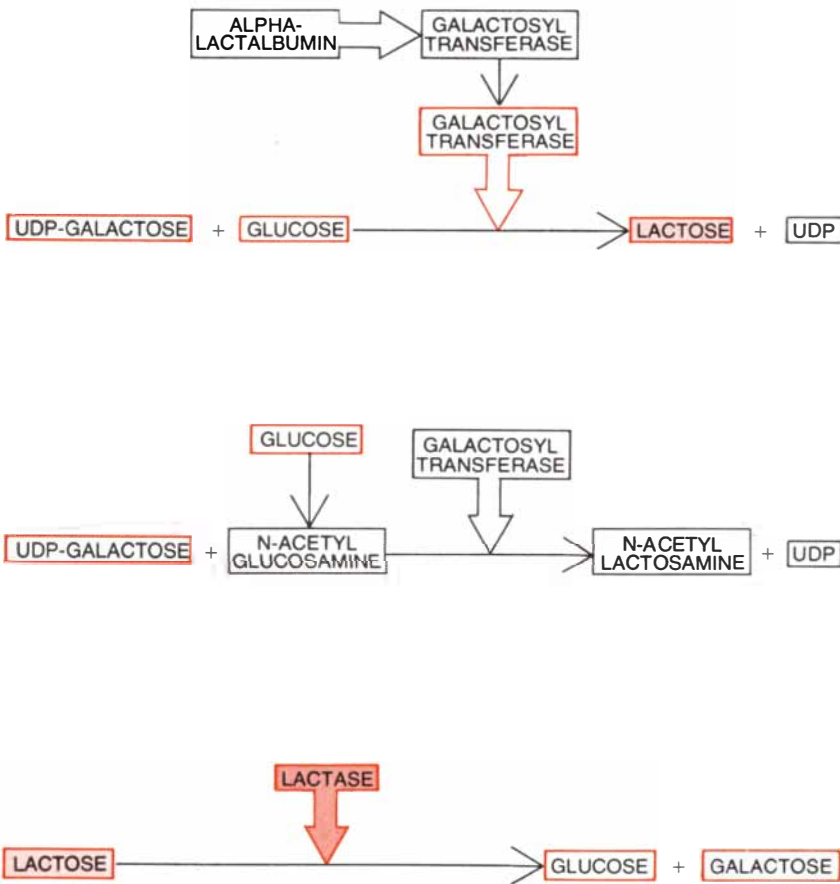


**LACTOSE**, a disaccharide composed of the monosaccharides glucose and galactose, is the carbohydrate of milk, the other major components of which are fats, proteins and water.

merely quantitative; there is simply very little lactase in the intestine of a lactose-intolerant person. In the intestine of Pacific pinnipeds, Philip Sunshine of the Stanford School of Medicine found, there is no lactase at all, even in infancy.

Lactase is not present in the intestine of the embryo or the fetus until the middle of the last stage of gestation. Its

activity attains a maximum immediately after birth. Thereafter it decreases, reaching a low level, for example, immediately after weaning in the rat and after one and a half to three years in most children. The exact mechanism involved in the appearance and disappearance of the lactase is not known, but such a pattern of waxing and waning



**SYNTHESIS OF LACTOSE** in the mammary gland begins late in pregnancy when specific hormones and the protein alpha-lactalbumin are present. The latter modifies the enzyme galactosyl transferase, "specifying" it so that it catalyzes the synthesis of lactose from glucose and galactose (top). In the nonlactating gland the glucose takes part in a different reaction (middle). In intestine lactase breaks down lactose to glucose and galactose (bottom).

activity is common in the course of development; in general terms, one can say that it results from differential action of the gene or genes concerned.

Soon after the turn of the century the distinguished American pediatrician Abraham Jacobi pointed out that diarrhea in babies could be associated with the ingestion of carbohydrates. In 1921 another pediatrician, John Howland, said that "there is with many patients an abnormal response on the part of the intestinal tract to carbohydrates, which expresses itself in the form of diarrhea and excessive fermentation." He suggested as the cause a deficiency in the hydrolysis, or enzymatic breakdown, of lactose.

The physiology is now well established. If the amount of lactose presented to the intestinal cells exceeds the hydrolytic capacity of the available lactase (whether because the lactase level is low or because an unusually large amount of lactose is ingested), a portion of the lactose remains undigested. Some of it passes into the blood and is eventually excreted in the urine. The remainder moves on into the large intestine, where two processes ensue. One is physical: the lactose molecules increase the particle content of the intestinal fluid compared with the fluid in cells outside the intestine and therefore by osmotic action draw water out of the tissues into the intestine. The other is biochemical: the glucose is fermented by the bacteria in the colon. Organic acids and carbon dioxide are generated and the symptoms can be those of any fermentative diarrhea, including a bloated feeling, flatulence, belching, cramps and a watery, explosive diarrhea.

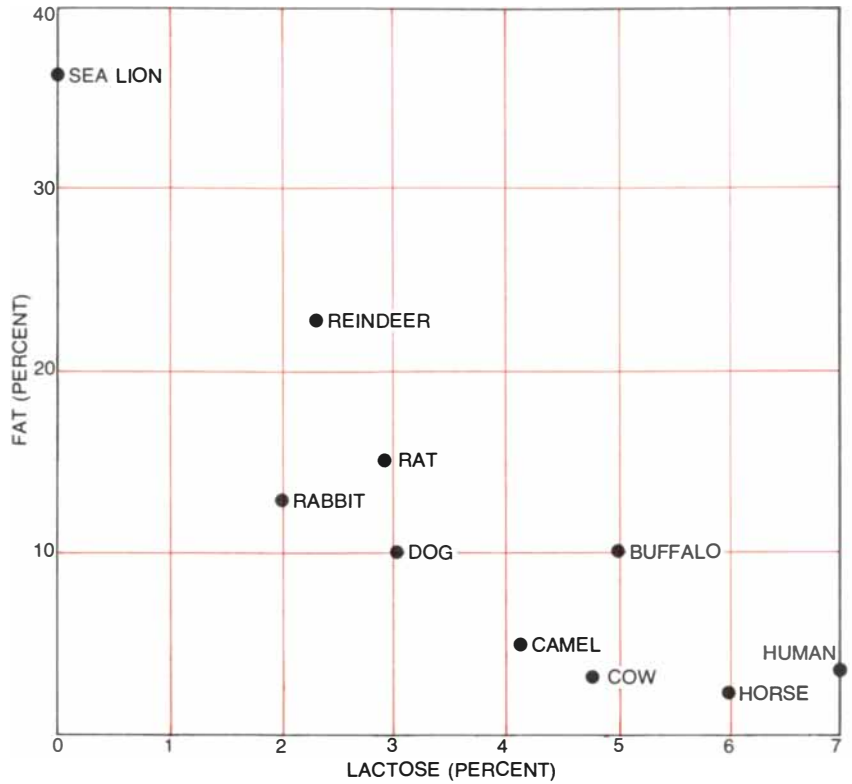
At the end of the 1950's Paolo Durand of the University of Genoa and Aaron Holzel and his colleagues at the University of Manchester reported detailed studies of infants who were unable to digest lactose and who reacted to milk sugar with severe diarrhea, malnutrition and even death. This work stimulated a revival of interest in lactose and lactase, and there followed a period of active investigation of lactose intolerance. Many cases were reported, including some in which lactase inactivity could be demonstrated in tissue taken from the patient's intestine by biopsy. It became clear that intolerance in infants could be a congenital condition (as in Holzel's two patients, who were siblings) or, more frequently, could be secondary to various diseases and other stresses: cystic fibrosis, celiac disease, malnutrition, the ingestion of certain drugs, surgery and even non-

specific diarrhea. During this period of investigation, it should be noted, intolerance to lactose was generally assumed to be the unusual condition and the condition worthy of study.

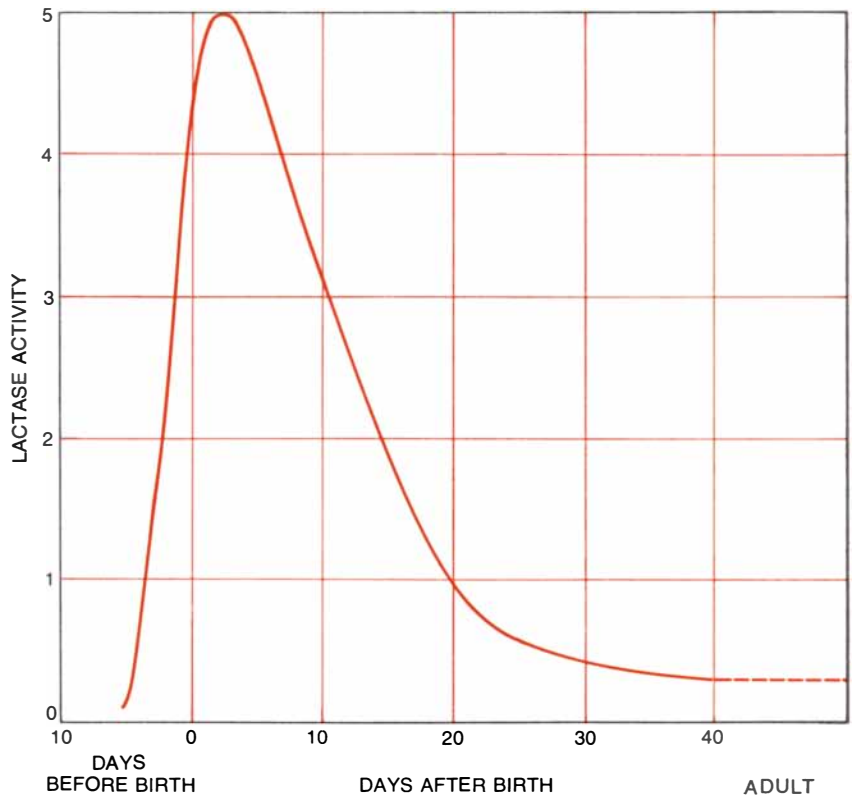
In 1965 Pedro Cuatrecasas and his colleagues and Theodore M. Bayless and Norton S. Rosensweig, all of whom were then at the Johns Hopkins School of Medicine, administered lactose to American blacks and whites, none of whom had had gastrointestinal complaints, and reported some startling findings. Whereas only from 6 to 15 percent of the whites showed clinical symptoms of intolerance, about 70 percent of the blacks were intolerant. This immediately suggested that many human adults might be unable to digest lactose and, more specifically, that there might be significant differences among ethnic groups. The possibility was soon confirmed: G. C. Cook and S. Kajubi of Makerere University College examined two different tribes in Uganda. They found that only 20 percent of the adults of the cattle-herding Tussi tribe were intolerant to lactose but that 80 percent of the non-pastoral Ganda were intolerant. Soon one paper after another reported a general intolerance to lactose among many ethnic groups, including Japanese, other Orientals, Jews in Israel, Eskimos and South American Indians.

In these studies various measures of intolerance were applied. One was the appearance of clinical symptoms—flatulence and diarrhea—after the ingestion of a dose of lactose, which was generally standardized at two grams of lactose per kilogram (2.2 pounds) of body weight, up to a maximum of either 50 or 100 grams. Another measure was a finding of low lactase activity (less than two units per gram of wet weight of tissue) determined through an intestinal biopsy after ingestion of the same dose of lactose. A third was an elevation of blood glucose of less than 20 milligrams per 100 milliliters of blood after ingestion of the lactose. Since clinical symptoms are variable and the biopsy method is inconvenient for the subject being tested, the blood glucose method is preferable. It is a direct measure of lactose breakdown, and false-negative results are rare if the glucose is measured 15 minutes after lactose is administered.

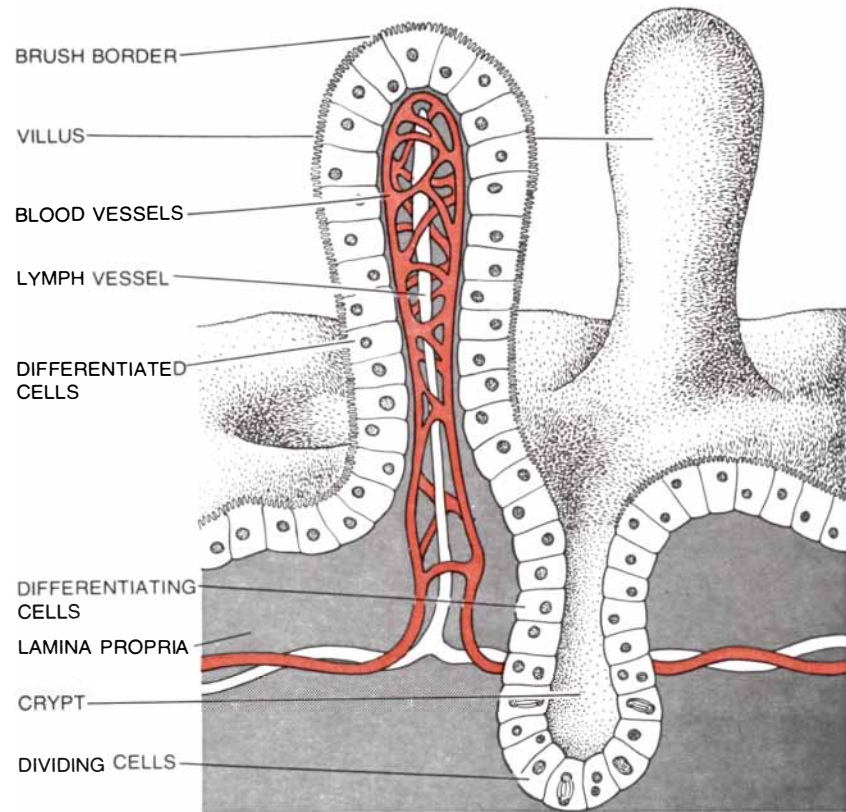
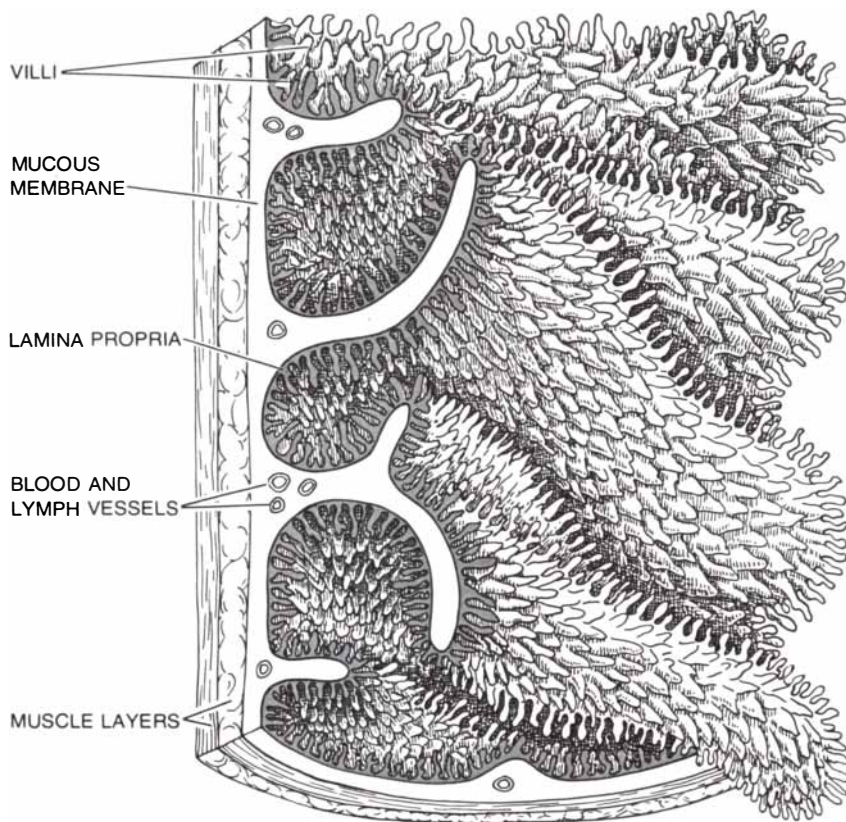
By 1970 enough data had been accumulated to indicate that many more groups all over the world are intolerant to lactose than are tolerant. As a matter of fact, real adult tolerance to lactose has so far been observed only in northern Europeans, approximately 90 percent of whom tolerate lactose, and in the



CONCENTRATION OF LACTOSE varies with the source of the milk. In general the less lactose, the more fat, which can also be utilized by the newborn animal as an energy source.



LACTASE is present in mammals other than man, and in most humans, in the fetus before birth and in infancy. The general shape of the curve of enzyme activity, shown here for the rat, is about the same in all species. Enzyme activity, given here in relative units, is determined by measuring glucose release from intestinal tissue in the presence of lactose.



**WALL OF SMALL INTESTINE**, seen in longitudinal section (*top*), has outer muscle layers, a submucosa layer and an inner mucous membrane. The mucous membrane (*bottom*) has a connective-tissue layer (lamina propria), which contains blood and lymph capillaries, and an inner surface of epithelial cells. The cells multiply and differentiate in the crypts and migrate to the villi. At what stage the lactase is manufactured is not known; it is found primarily in the microvilli, which constitute the brush border of the differentiated cells.

members of two nomadic pastoral tribes in Africa, of whom about 80 percent are tolerant. Although many other generally tolerant groups will be found, they will always belong to a minority of the human species. In this situation it is clearly more interesting and potentially more fruitful to focus the investigation on tolerant people in an effort to explain adult tolerance, a characteristic in which man differs from all other mammals.

There are two kinds of explanation of adult tolerance to lactose. The first, and perhaps the most immediately apparent, originates with the fact that most people who tolerate lactose have a history of drinking milk. Maybe the mere presence of milk in the diet suffices to stimulate lactase activity in the individual, perhaps by "turning on" genes that encode the synthesis of the enzyme. Individual enzymatic adaptation to an environmental stimulus is well known, but it is not transferable genetically. The other explanation of tolerance is based on the concept of evolution through natural selection. If in particular populations it became biologically advantageous to be able to digest milk, then the survival of individuals with a genetic mutation that led to higher intestinal lactase activity in adulthood would have been favored. An individual who derived his ability to digest lactose from this classical form of Darwinian adaptation would be expected to be able to transfer the trait genetically.

These two points of view have become the subject of considerable controversy. I suspect that each of the explanations is valid for some of the adult tolerance being observed, and I should like to examine both of them.

The possibility of individual adaptation to lactose has been considered since the beginning of the century, usually through attempts to relate lactase activity to the concentration of milk in the diet of animals. Almost without exception the studies showed that although there was a slight increase in lactase activity when a constant diet of milk or milk products was consumed, there was no significant change in the characteristic curve reflecting the developmental rise and fall of enzymatic activity. Recently there have been reports pointing toward adaptation, however. Some studies, with human subjects as well as rats, indicated that continued intensive feeding of milk or lactose not only made it possible for the individual to tolerate the sugar but also resulted in a measurable increase in lactase activity. The discrepancy among the findings could be partly

attributable to improvement in methods for assaying the enzyme activity.

On balance it would appear that individual adaptation may be able to explain at least some cases of adult tolerance. I shall cite two recent studies. John Godell, working in Lagos, selected six Nigerian medical students who were absolutely intolerant to lactose and who showed no physiological evidence of lactose hydrolysis. He fed them increasing amounts of the sugar for six months. Godell found that although the students did develop tolerance for the lactose, there was nevertheless no evidence of an increase of glucose in the blood—and thus of enzymatic adaptation—following test doses of the sugar. The conjecture is that the diet brought about a change in the bacterial flora in the intestine, and that the ingested lactose was being metabolized by the new bacteria.

In our laboratory at the Stanford School of Medicine Emanuel Leibel and Sunshine found that in rats given lactose the usual pattern of a developmental decrease in lactase activity is maintained but the activity level is somewhat higher at the end of the experiment. The rise in activity does not appear to be the result of an actual increase in lactase synthesis, however. We treated the rats with actinomycin, which prevents the synthesis of new protein from newly activated genes. The actinomycin had no effect on the slight increase in lactase activity, indicating that the mechanism leading to the increase was not gene activation. It appears, rather, that the presence of additional amounts of the enzyme's substrate, lactose, somehow "protects" the lactase from degradation. Such a process has been noted in many other enzyme-substrate systems. The additional lactase activity that results from this protection is sufficient to improve the rat's tolerance of lactose, but that additional activity is dependent on the continued presence of the lactose.

Testing the second hypothesis—that adult lactose tolerance is primarily the result of a long-term process of genetic selection—is more complicated. It involves data and reasoning from such disparate areas as history, anthropology, nutrition, genetics and sociology as well as biochemistry.

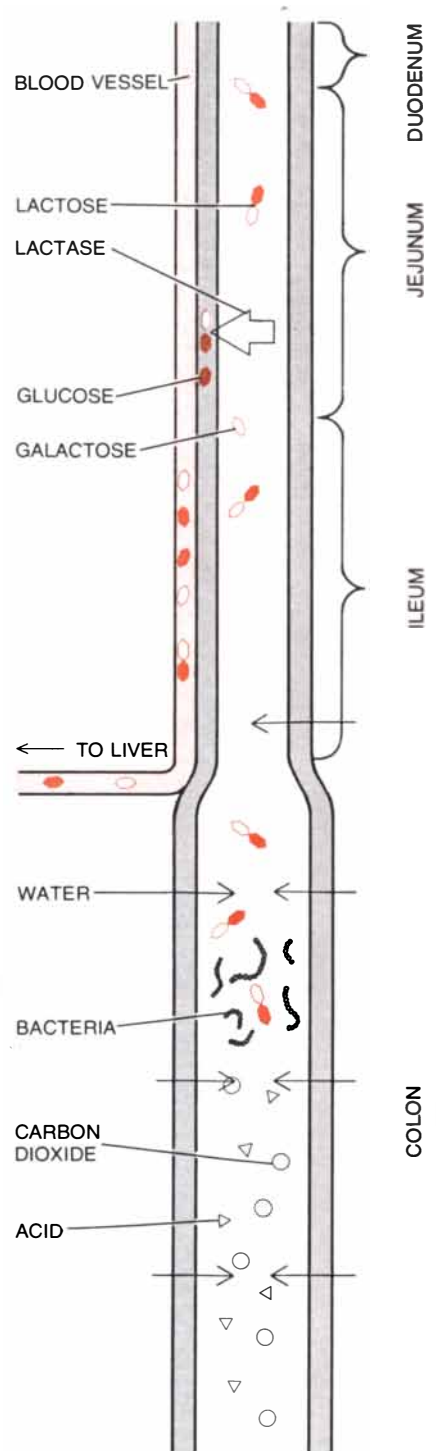
As I have noted, the work of Cuatrecasas, of Bayless and Rosensweig and of Cook and Kajubi in the mid-1960's pointed to the likelihood of significant differences in adult lactose tolerance among ethnic groups. It also suggested that one ought to study in particular black Americans and their ancestral pop-

ulations in Africa. The west coast of Africa was the primary source of slaves for the New World. With the objective of studying lactose tolerance in Nigeria, we developed a joint project with a group from the University of Lagos Teaching Hospital headed by Olikoye Ransome-Kuti.

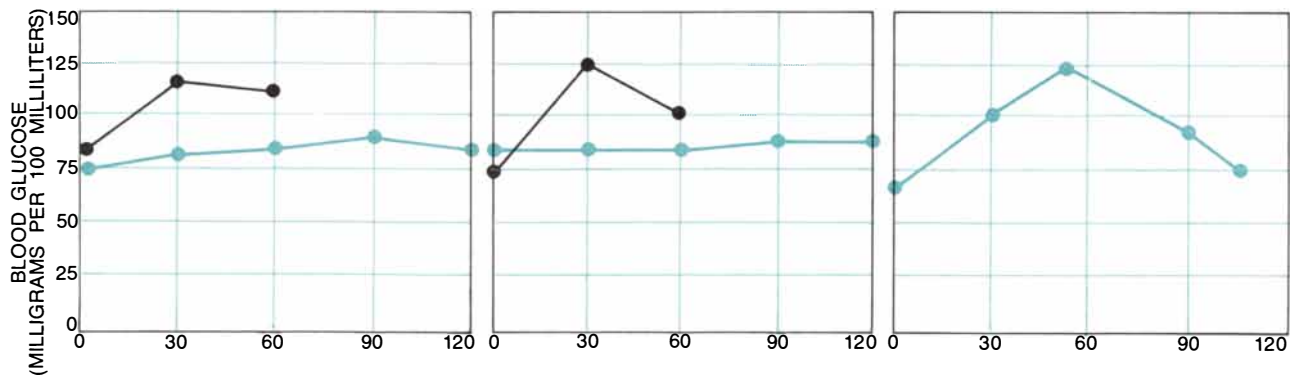
The four largest ethnic groups in Nigeria are the Yoruba in western Nigeria, the Ibo in the east and the Fulani and Hausa in the north. These groups have different origins and primary occupations. The Yoruba and the Ibo differ somewhat anthropometrically, but both are Negro ethnic groups that probably came originally from the Congo Basin; they were hunters and gatherers who became farmers. They eventually settled south of the Niger and Benue rivers in an area infested with the tsetse fly, so that they never acquired cattle (or any other beast of burden). Hence it was not until recent times that milk appeared in their diet beyond the age of weaning. After the colonization of their part of Nigeria by the British late in the 19th century, a number of Yoruba and Ibo, motivated by their intense desire for education, migrated to England and northern Europe; they acquired Western dietary habits and in some cases Western spouses, and many eventually returned to Nigeria.

The Fulani are Hamites who have been pastoral people for thousands of years, originally perhaps in western Asia and more recently in northwestern Africa. Wherever they went, they took their cattle with them, and many of the Fulani are still nomads who herd their cattle from one grazing ground to another. About 300 years ago the Fulani appeared in what is now Nigeria and waged war on the Hausa. (The Fulani also tried to invade Yorubaland but were defeated by the tsetse fly.) After the invasion of the Hausa region some of the Fulani moved into villages and towns.

As a result of intermarriage between the Fulani and the Hausa there appeared a new group known as the town-Fulani or the Hausa-Fulani, whose members no longer raise cattle and whose ingestion of lactose is quite different from that of the pastoral Fulani. The pastoral Fulani do their milking in the early morning and drink some fresh milk. The milk reaches the market in the villages and towns only in a fermented form, however, as a kind of yogurt called *nono*. As the *nono* stands in the morning sun it becomes a completely fermented, watery preparation, which is then thickened with millet or some other cereal. The final product is almost completely



**DIGESTION OF LACTOSE** is accomplished primarily in the jejunum, where lactase splits it into glucose and galactose. Some glucose is utilized locally; the rest enters the bloodstream with the galactose and both are utilized in the liver. In the absence of enough lactase some undigested lactose enters the bloodstream; most goes on into the ileum and the colon, where it draws water from the tissues into the intestine by osmotic action. The undigested lactose is also fermented by bacteria in the colon, giving rise to various acids and carbon dioxide gas.



LACTOSE INTOLERANCE is determined by measuring blood glucose after ingestion of lactose. The absence of a significant rise in blood glucose after lactose ingestion (*color*) as contrasted with a rise in blood glucose after ingestion of sucrose, another sugar

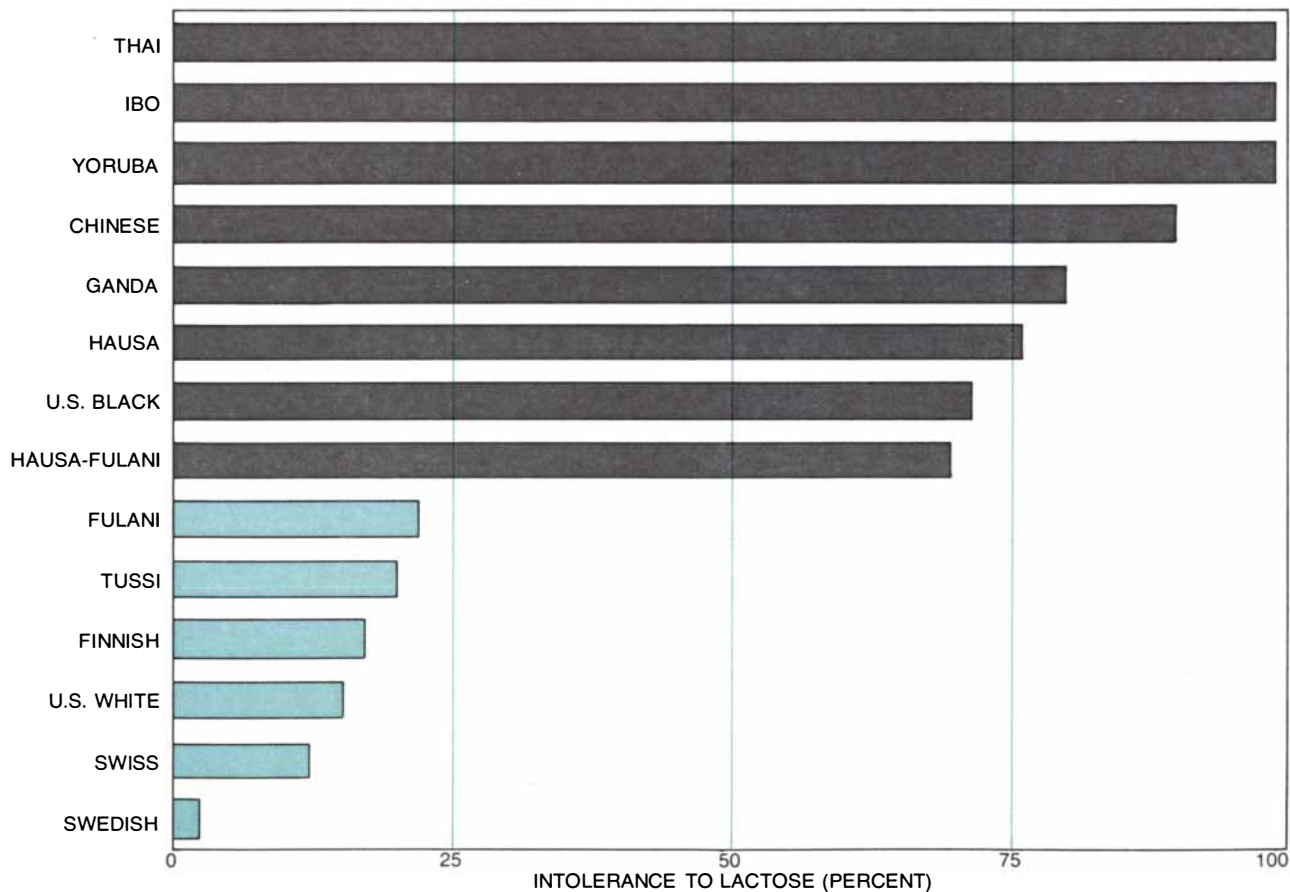
(*black*), indicates that a Yoruba male (*left*) and an American Jewish male (*middle*) are lactose-intolerant. On the other hand, the definite rise in blood glucose after ingestion of lactose in a Fulani male (*right*) shows that the Fulani is tolerant to lactose.

free of lactose and can be ingested without trouble even by a person who cannot digest lactose.

We tested members of each of these Nigerian populations. Of all the Yorubas above the age of four who were tested, we found only one person in whom the blood glucose rose to more

than 20 milligrams per 100 milliliters following administration of the test dose of lactose. She was a nurse who had spent six years in the United Kingdom and had grown accustomed to a British diet that included milk. At first, she said, the milk disagreed with her, but later she could tolerate it with no adverse side effects. None of the Ibos who

were studied showed an elevation of glucose in blood greater than 20 milligrams per 100 milliliters. (The major problem in all these studies is determining ethnic purity. All the Yorubas and Ibos who participated in this portion of the study indicated that there had been no intermarriages in their families.) Most of the Hausa and Hausa-Fulani



INTOLERANCE VARIES WIDELY among populations. The bars are based on tests conducted by a number of investigators by different methods; they may not be strictly comparable or accurate-

ly reflect the situation in entire populations. Among the groups studied to date lactose intolerance is prevalent except among northern Europeans (and their descendants) and herders in Africa.

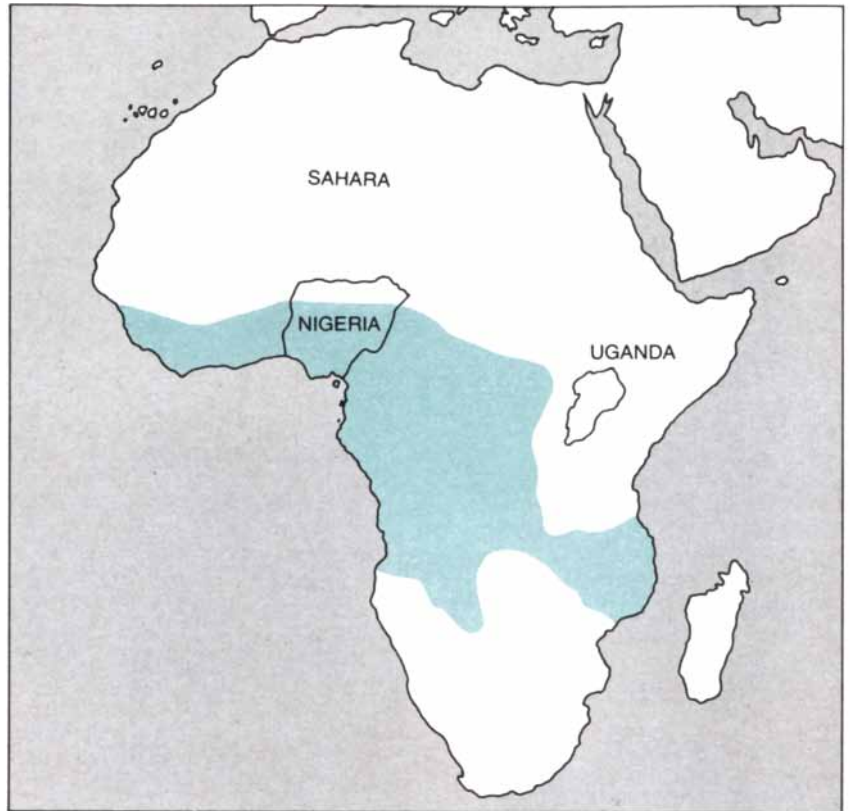
(70 to 80 percent) were intolerant to lactose. In contrast most of the nomadic Fulani (78 percent) were tolerant to it. In their ability to hydrolyze lactose they resembled the pastoral Tussi of Uganda and northern Europeans more than they resembled their nearest neighbors.

Once the distribution of lactose intolerance and tolerance was determined in the major Nigerian populations, we went on to study the genetics of the situation by determining the results of mixed marriages. One of the common marriages in western Nigeria is between a Yoruba male and a British or other northern European female; the reverse situation is less common. Our tests showed that when a tolerant northern European marries a lactose-intolerant Yoruba, the offspring are most likely to be lactose-tolerant. If a tolerant child resulting from such a marriage marries a pure Yoruba, then the children are also predominantly tolerant. There is no sex linkage of the genes involved: in the few cases in which a Yoruba female had married a northern European male, the children were predominantly tolerant.

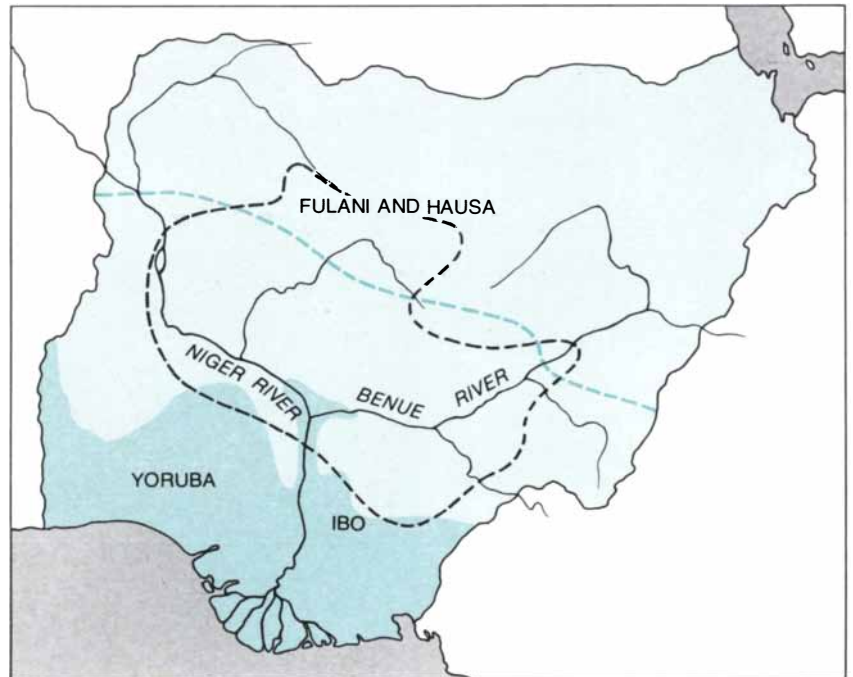
On the basis of these findings one can say that lactose tolerance is transmitted genetically and is dominant, that is, genes for tolerance from one of the parents are sufficient to make the child tolerant. On the other hand, the children of two pure Yorubas are always intolerant to lactose, as are the children of a lactose-intolerant European female and a Yoruba male. In other words, intolerance is also transmitted genetically and is probably a recessive trait, that is, both parents must be lactose-intolerant to produce an intolerant child. When the town-dwelling royal line of the Fulani was investigated, its members were all found to be unable to digest lactose—except for the children of one wife, a pastoral Fulani, who were tolerant.

Among the children of Yoruba-European marriages the genetic cross occurred one generation ago or at the most two generations. Among the Hausa-Fulani it may have been as much as 15 generations ago. This should explain the general intolerance of the Hausa-Fulani. Presumably the initial offspring of the lactose-tolerant Fulani and the lactose-intolerant Hausa were predominantly tolerant. As the generations passed, however, intolerance again became more prevalent. The genes for lactase can therefore be considered incompletely dominant.

The blacks brought to America were primarily Yoruba or Ibo or similar West African peoples who were originally



**GEOGRAPHICAL EXTENT** of dairying coincides roughly with areas of general lactose tolerance. According to Frederick J. Simoons of the University of California at Davis, there is a broad belt (color) across Africa in which dairying is not traditional. Migrations affect the tolerance pattern, however. For example, the Ganda, a lactose-intolerant group living in Uganda, came to that milk-drinking region from the nonmilking central Congo.



**LARGEST ETHNIC GROUPS** in Nigeria are the Ibo in the east, the Yoruba in the west and the Hausa and Fulani in the north. Map shows regions of mangrove swamp or forest (dark color) and grassland or desert (light color). Southern livestock limit (broken colored line) is set by climate, vegetation and tsetse fly infestation (broken black line).



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intolerant to lactose. American blacks have been in this country for between 10 and 15 generations, in the course of which a certain complement of white northern European genes has entered the black population. Presumably as a result lactose intolerance among American blacks has been reduced to approximately 70 percent. One can speculate that if this gene flow eventually stopped, lactose intolerance would approach 100 percent among American blacks.

What events in human cultural history might have influenced the development of tolerance to lactose in the adults of some groups? Frederick J. Simoons of the University of California at Davis has proposed a hypothesis based on the development of dairying. It would appear that the milking of cattle, sheep, goats or reindeer did not begin until about 10,000 years ago, some 100 million years after the origin of mammals and therefore long after the mammalian developmental pattern of lactase activity had been well established. Man presumably shared that pattern, and so adults were intolerant to lactose. When some small groups of humans began to milk animals, a selective advantage was conferred on individuals who, because of a chance mutation, had high enough lactase activity to digest lactose. A person who could not digest lactose might have difficulty in a society that ingested nonfermented milk or milk products, but the lactose-tolerant individual was more adaptable: he

could survive perfectly well in either a milk-drinking or a non-milk-drinking society.

The genetic mutation resulting in the capability to digest lactose probably occurred at least 10,000 years ago. People with the mutation for adult lactase activity could be members of a dairying culture, utilize their own product for food (as the Fulani do today) and then sell it in the form of a yogurt (as the Fulani do) or cheese to the general, lactose-intolerant population. These statements are presumptions, not facts, but they are based soundly on the idea that tolerance to lactose is a mutation that endowed the individual with a nutritional genetic advantage and on the basic assumption, which is supported by fact, that lactose intolerance is the normal genetic state of adult man and that lactose tolerance is in a sense abnormal.

What are the implications of all of this for nutrition policy? It should be pointed out that many people who are intolerant to lactose are nevertheless able to drink some milk or eat some milk products; the relation of clinical symptoms to lactose ingestion is quantitative. For most people, even after the age of four, drinking moderate amounts of milk has no adverse effects and is actually nutritionally beneficial. It may well be, however, that programs of indiscriminate, large-scale distribution of milk powder to intolerant populations should be modified, or that current moves toward supplying lactose-free milk powder should be encouraged.

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FULANI WOMAN offers *nono*, a yogurt-like milk drink, for sale in the marketplace of a town in northern Nigeria. The pastoral Fulani drink fresh milk. The partially fermented *nono*, with reduced lactose content, is tolerated by villagers who could not digest milk.