Since the 1940s, numerous cases of non-insulin-dependent diabetes mellitus (NIDDM) have been observed in certain American Indian populations. Extremely high prevalence rates of NIDDM occur most strikingly in several tribes of Paleo-Indians, whose ancestors migrated to North America >11,000 yr ago. Archaeological evidence from that period indicates that certain groups of Paleo-Indians maintained an arcticlike hunter-gatherer life-style in an area in temperate North America ranging from Wyoming to Arizona. This life-style featured a reliance on unpredictable big game species as a major food source. However, at this time, big game species were becoming extinct. It is hypothesized that those Paleo-Indians who relied on big game as a food source developed a “thrifty” genotype that allowed a selective advantage during the periods of fasting that occurred between big game kills. It also is hypothesized that this thrifty genotype in these Indians may contribute to NIDDM when a sedentary life-style is adopted and food sources are constant. Because insulin resistance in muscle is a major feature of NIDDM, it is possible that insulin resistance per se is the phenotypic expression of the thrifty genotype. Diabetes 40:161-65, 1991

In the last century, non-insulin-dependent diabetes mellitus (NIDDM) was uncommon among all American Indian tribes. Since the 1940s, some but not all tribes have developed very high prevalence rates of NIDDM (1). NIDDM is very common among the Pimas of Arizona, who have the highest reported NIDDM prevalence in the world (~50% of adults >35 yr old; 2) and have been the subject of several epidemiological studies (3-10). NIDDM is also prevalent among many other Indian tribes, e.g., the Papagos, Yumas, and Comanches (11,12). However, Alaskan and Canadian Athapaskans, Aleuts, Eskimos, Navajo, and some Apache tribes have lower NIDDM rates than the Pimas (11,13,14).

The recent appearance of NIDDM among many American Indian tribes may be due to the interaction of a susceptible genotype and life-style changes. In this perspective, we use the archaeological record of early American Indians to provide clues as to how a susceptible genotype might have been selected in American Indians and why it might be more common among some tribes than others.

AMERICAN INDIAN SETTLEMENT OF NORTH AMERICA

The high prevalence of NIDDM among many American Indians, who before the 1900s lived in widely different environments, suggests that the susceptible genotype was selected during an event in the remote past common to most American Indians, i.e., before or during the initial settlement of North America (12). It is widely held that the settlement of North America began near the end of the Pleistocene, thousands of years ago, and involved three separate migrations of Asian hunter-gatherers into Alaska: Paleo-Indian, Na-Dene or Athapaskan, and Aleut-Eskimo (15,16).

The Paleo-Indian migration may have occurred during the late Wisconsin glacial period (after ~23,000 yr ago) when hunter-gatherers crossed the now-submerged Bering land bridge (an 1800-km-wide land mass that extended from Saint Lawrence Island to the Diomede islands, connecting Asia and North America) (17). The route south through the interior of Canada was blocked until only ~12,000 yr ago by the occlusion of the Canadian continental glaciers (18). Shortly afterward, the Paleo-Indians were able to move south into what is now Montana and the rest of North America through a narrow ice-free tundra corridor that opened between the retreating continental glaciers (19; Fig. 1). The Na-Denes or Athapaskans may have migrated from Asia into Alaska ~10,000 yr ago, just before the Bering land bridge was submerged by rising sea levels (20). However,
America -4500 yr ago (20). They have since remained in the northern latitudes, where they developed an economy that can be used productively (22-25). In high-latitude highly seasonal environments, which have numerous species but fewer individuals per species, hunter-gatherers specialize and forage among a wide range of species and camp in such a way that foods can be brought back to camp as they are found by foraging parties. The result is a largely sedentary life-style with large campsites that are somewhat removed from any single food source.

Examining the archaeological record of the early Paleo-Indians (~11,000 yr ago), two life-styles are seen. The first is a generalist life-style that is evident throughout much of temperate North America. Most of these sites are campsites to which food was evidently returned by foraging parties, and some campsites even have evidence of housing, implying a relatively sedentary life-style (29,30).

However, in low elevations from Wyoming to Arizona and Texas, a second specialist life-style is evident. Small campsites near big game kills are seen. These camps were evidently being moved from one big game kill to another as if they were in the high arctic (31-38; Figs. 2 and 3). This settlement pattern is not only anomalous in the Upper Paleolithic (from ~40,000 to 10,000 yr ago), it is not what would be expected given what is known about hunter-gatherers living today.

What could have caused this articlike pattern of camping near game kills in the temperate latitudes for this group of specialist Paleo-Indians? Modern arctic hunter-gatherers provide clues. For instance, Eskimos today might move their camp to the site of a caribou kill to allow the entire group, including women and children, to take part in processing the game. Although other foods, such as an occasional ptarmigan (an arctic game fowl), are available and are included in the diet, it is crucial that the single food item that is sufficiently abundant to support the group (i.e., caribou) be quickly and efficiently processed. Like the Eskimo, these Paleo-Indians were moving their camps from one big game kill to another because big game (e.g., bison) was considered crucial to their survival, and the whole group took part in processing the game.

Why would big game be so crucial to the survival of this group of early Paleo-Indians? Like hunter-gatherers in temperate latitudes today, they should have relied more on the numerous species of small game and plant foods around them.

Because big game species are less diverse than small game species from one environment to another, big game would remain familiar prey as the Paleo-Indians moved south along the Rocky Mountains. However, new species of smaller game and plant foods would have been encountered as the Paleo-Indians moved from the tundras near the Canadian glaciers to the forests and parklands south of Montana. The change in smaller game and plant foods was too abrupt to allow for a gradual adaptation, leading to this unusual temperate-latitude reliance on big game (39). The other generalist Paleo-Indians, who moved east and west along the ice margins, did not have to adapt to a radical change in environment. Consequently, big game hunting was not as crucial to these Paleo-Indians as it was to the specialist Paleo-Indians.
Although big game is a high-risk resource even when it is abundant, many species, e.g., horses, camels, and mammoths, were becoming extinct throughout North America at this time (~11,000–10,000 yr ago). However, the specialist Paleo-Indians continued to rely on the only remaining big game species, the bison, for several hundred years, even though these animals were not as numerous as they would later become (17). Thus, the extinction of most species of big game did not cause these Paleo-Indians to abandon their reliance on large game. This reliance ended hundreds of years later as the specialists, who were no longer camping near big game kills, learned to hunt smaller game and process plant foods efficiently.

**THRIFTY GENOTYPE AND NIDDM**

The result of this big game reliance would have been frequent but short-lived food shortages as the specialist Paleo-Indians extracted the food energy from one kill and then waited for the next fortunate hunt. Due to the lack of preservation, little evidence of the use of plant foods by these Paleo-Indians has been found. However, it is likely that carbohydrates were included in the diet and could have prevented outright starvation during these periods of food shortage (40). A thrifty genotype metabolism, such as proposed by Neel (41; see below), could have allowed a survival advantage during these alternating periods of feast and famine.

Because certain Paleo-Indians, i.e., the Pimas, now have
a sedentary life-style and a constant food source, their thrifty genotype may now be disadvantageous and lead to obesity and NIDDM. In contrast, the Athapaskans, Aleuts, and Eskimos, who either remained in high latitudes or migrated south after the glaciers had retreated, did not experience the sudden change in environment that confronted these Paleo-Indians. Consequently, in the former group, the thrifty-genotype metabolism would not have conveyed as much survival advantage as in the Paleo-Indians.

A major feature of NIDDM in both white and Indian populations is insulin resistance in muscle, which is primary and antedates the onset of the disease (42–45). However, this resistance is not sufficient to produce the symptoms of NIDDM. Concomitant decreased insulin secretion is also necessary (43,44). Both population surveys and prospective studies of prediabetic Pima Indians indicate that insulin resistance predates the onset of NIDDM (5,46). Also, studies of glucose metabolism indicate that the major site of insulin resistance is in muscle (47).

To explain the presence of NIDDM genes in all populations, Neel (41) first postulated that a thrifty genotype existed that had a selection advantage as hunter-gatherers fluctuated between feast and famine. As he first proposed, the thrifty-genotype metabolism would not have conveyed as much survival advantage as in the Paleo-Indians. When placed in a laboratory environment can contribute to NIDDM in a food-abundant environment.

Most likely, in the obese form of NIDDM such as is seen in Pima Indians, multiple genes are involved, and thus, the basic cellular mechanism of insulin resistance remains unknown. Studies of the insulin receptor in tissues of typical NIDDM patients have revealed defects, but these defects have been relatively small and are believed to be secondary to the metabolic alterations of this disease (54). Therefore, the receptor abnormalities are probably not the primary defect in NIDDM. More likely is that cellular signaling events that occur after the insulin binds to its receptor cause the insulin resistance. Recent studies focused on postreceptor mechanisms in muscle such as the activation of glucose transport or glycolgen synthesis (55) or insulin-receptor tyrosine kinase antagonists (Sbraccia et al., this issue, p. 295). Defects in either of these steps in muscle glucose metabolism could explain in part the impaired glucose metabolism seen in Paleo-Indians and other groups with NIDDM.

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