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For debate

The carnivore connection: dietary carbohydrate in the evolution of NIDDM

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Summary We postulate a critical role for the quantity and quality of dietary carbohydrate in the pathogenesis of non-insulin-dependent diabetes mellitus (NIDDM). Our primate ancestors ate a high-carbohydrate diet and the brain and reproductive tissues evolved a specific requirement for glucose as a source of fuel. But the Ice Ages which dominated the last two million years of human evolution brought a low-carbohydrate, high-protein diet. Certain metabolic adaptations were therefore necessary to accommodate the low glucose intake. Studies in both humans and experimental animals indicate that the adaptive (phenotypic) response to low-carbohydrate intake is insulin resistance. This provides the clue that insulin resistance is the mechanism for coping with a shortage of dietary glucose. We propose that the low-carbohydrate carnivorous diet would have disadvantaged reproduction in insulin-sensitive individuals and positively selected for individuals with insulin resistance. Natural selection would therefore result in a high proportion of people with genetically-determined insulin resistance. Other factors, such as geographic isolation, have contributed to further increases in the prevalence of the genotype in some population groups. Europeans may have a low incidence of diabetes because they were among the first to adopt agriculture and their diet has been high in carbohydrate for 10,000 years. The selection pressure for insulin resistance (i.e., a low-carbohydrate diet) was therefore relaxed much sooner in Caucasians than in other populations. Hence the prevalence of genes producing insulin resistance should be lower in the European population and any other group exposed to high-carbohydrate intake for a sufficiently long period of time. [Diabetologia (1994) 37: 1280–1286]

Key words Diet, diabetes, carbohydrate, protein, evolution.

Non-insulin-dependent diabetes mellitus (NIDDM) is one of the most common chronic conditions affecting the world's population. In the Pima Indians and Nauruans, the prevalence of NIDDM has reached epidemic proportions [1] while in other groups, such as the Australian Aborigines, the prevalence is several times higher than that of non-Aboriginal Australians. Eskimos, once thought to be resistant, are now developing diabetes in increasing numbers [2]. In fact, the European population and their descendents in other parts of the world may be the only group which does not have a high predisposition to NIDDM [3]. The major underlying metabolic characteristic is now known to be insulin resistance which precedes the onset of the disease and appears to be genetically determined [4–8]. Lifestyle changes are thought to be responsible for exposing the genetic predisposition to NIDDM although the specific factors involved are not known.

We postulate a critical role for the quantity and quality of dietary carbohydrate in the pathogenesis of NIDDM. Our hypothesis is that insulin resistance offered a survival and reproductive advantage dur-

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus. CHO, carbohydrate.

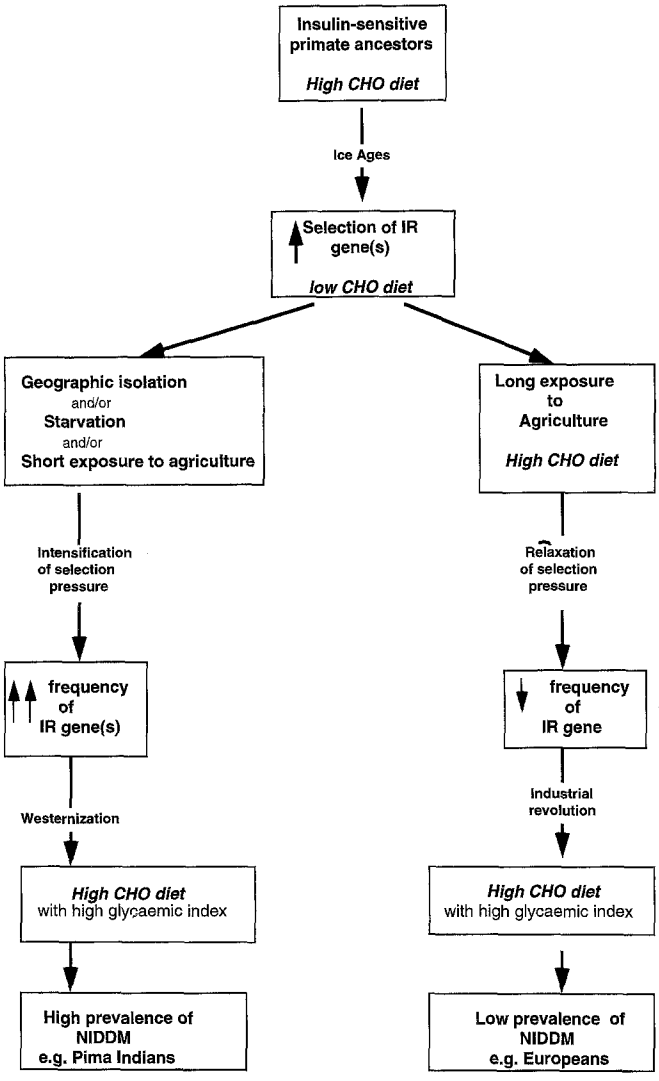

Fig. 1. The small quantity of carbohydrate in the diet of some groups during evolution is postulated to have acted as a selective force, increasing the proportion of people with the 'carnivorous' genotype, i.e., insulin resistance (IR). In certain groups of people, environmental pressures, such as starvation, further increased the proportion of people with the gene(s) for insulin resistance. In others, such as Europeans, the selection pressure was relaxed when agriculture increased the amount of carbohydrate (CHO) in the diet. Westernisation is associated with a high glycaemic index (GI), high-carbohydrate diet, which produces prolonged postprandial hyperinsulinaemia and leads to beta-cell exhaustion in those with IR. Hence, NIDDM will be more prevalent in populations with a high frequency of the IR gene(s)

ing the Ice Ages which dominated the last two million years of human evolution. During the Ice Ages, hunting of large game animals rather than gathering of plant foods was the principal source of food energy. The diet of many human groups was therefore low in carbohydrate and high in protein for most of the year. We propose that this carnivorous diet would have disadvantaged reproduction in insulin-sensitive individuals and positively selected for individuals with insulin resistance. Other factors, such as geographic isolation have contributed to further increases in the prevalence of the genotype in some population groups. But beginning about 10,000 years ago with the end of the last Ice Age and the development of agriculture, the selection pressure for insulin resistance (i.e., a low-carbohydrate diet) was relaxed in some groups. Agriculture first began in the Middle East and spread throughout Europe long before it was developed elsewhere. Hence the prevalence of genes producing insulin resistance should be lower in the European population and any other group exposed to high carbohydrate intake for a sufficiently long period of time. The hypothesis is summarised in Figure 1.

Our hypothesis hinges on four lines of evidence.
1. that during the last two million years of evolution, humans were primarily carnivorous, i.e., flesh-eating hunters consuming a low-carbohydrate, high-protein diet
2. that a low-carbohydrate, high-protein diet requires profound insulin resistance to maintain glucose homeostasis, particularly during reproduction
3. that genetic differences in insulin resistance and predisposition to NIDDM can be explained by differences in exposure to carbohydrate during the past 10,000 years
4. that changes in the quality of carbohydrate can explain the recent epidemic of NIDDM in susceptible populations.

The low-carbohydrate existence

For most of geological time, the world's climate was warmer and more homogeneous than it is today. Our pre-human ancestors who lived in Africa 2–4 million years ago enjoyed this warm, moist environment and gathered ripe fruits and berries from the tropical forests. Carbohydrate was an important part of their diet [9]. But about 2.5 million years ago, a severe Ice Age sent global temperatures plummeting and prompted the conversion of moist African woodland into much drier open savanna [10]. As the grasslands expanded, the tree cover shrank and forest-dwelling chimpanzees yielded to bipedal hominids who became increasingly carnivorous. *Homo habilis* who lived 2 million years ago was almost certainly a scavenger who supplemented a vegetarian diet with meat left over from predators' kills. *H. erectus* who lived 1.5 million years ago is known to have actively hunted [11]. There are many anthropologists who believe that hunting was the pressure that selected for the large brain of *H. sapiens* (i.e. "man the hunter") [12].

As one Ice Age followed another (nine in total during the last 700,000 years), hunting and fishing became a dominant way of life not just in high latitudes

but also in warmer environments. Ice Ages lock a large amount of water into ice caps, making the whole planet drier. Hence plant growth is mainly in the form of grasslands which only herbivores can utilise.

About 50,000 years ago, Neanderthal man was distributed from what is now Germany and France to parts of Russia, the Middle East and North Africa. They were cold-climate hunters of large game and subsisted primarily on game during the coldest periods [11]. Similarly, Cro-Magnon man who replaced the Neanderthals about 35,000 years ago, lived through the coldest of the Ice Ages on a high-protein diet. Their diets contained virtually no carbohydrate except minor amounts found in the liver or gut contents of animals and in seasonal roots and berries. Items that were gathered included nuts and shellfish but these contain little or no carbohydrate. The ancestors of the Australian Aborigines who arrived in Australia 40–50,000 years ago inhabited either coastal or well-watered inland areas, and led a hunting and shellfish-gathering existence [13]. Although seasonally and geographically variable, their diet was characteristically high in protein and low-to-moderate in carbohydrate [14].

Even during the inter-glacials, parts of the world remained cold (e.g., Arctic and sub-arctic regions) and continued to have little vegetation; human inhabitants maintained a hunting/fishing existence. Thus, the Eskimos are a modern-day example of a group whose historic diet was almost devoid of readily absorbable carbohydrate [15]. Similarly the Dogrib Indians of Northwest Canada have only recently incorporated any significant amount of carbohydrate in their diet [16].

Our hypothesis relates to both the quantity and quality of the carbohydrate in the diet. Berries and root vegetables would have supplied some carbohydrate, especially at lower latitudes and during inter-glacials, but probably not a great deal. Wild plants are fibrous and not as sweet as their cultivated equivalents. Much of the carbohydrate was therefore unavailable [17] and over half the available carbohydrate was in the form of fructose which elicits a small insulin response [18]. Root vegetables that grow in cool climates contain large amounts of inulin, a fructo-polysaccharide that is not digested and absorbed. Furthermore, the available glucose was absorbed very slowly in the presence of large amounts of fibre. In effect, any carbohydrate foods were low glycaemic index foods.

A low-carbohydrate, high-protein diet was therefore the nutritional 'backdrop' for some of the most important stages in human evolution. The actual amount of carbohydrate eaten has been estimated to range from as little as 10 g up to 125 g a day which contrasts with the present-day intakes of 250 to 400 g [9]. Only brief periods of 10,000 years or so were characterised by temperatures in which the earth was as warm as it is today and higher carbohydrate intake was feasible. The present interglacial, however, is unique because it corresponded to the advent of agriculture and the intake of large amounts of starch for the first time in human existence [19].

Agriculture began in the Near East and spread rapidly to Europe, resulting in an increase in the consumption of plant food, particularly of cereals which were high in starch [19]. Agriculture spread gradually throughout Asia and the Americas; Meso-Americans did not adopt agriculture until approximately 5,000 years ago and Pima Indians only 2,000 years ago [20]. Indeed, many Paleo-Indians continued to maintain an arctic-like hunter-gatherer lifestyle which featured a reliance on big game species as a major source of food [21]. Australian Aborigines never developed agriculture [13]. The early settlers of the Nauru and other Pacific atolls consumed a diet dominated by fish and coconuts, i.e., low in carbohydrate and high in protein [22]. Attempts to cultivate root crops were thwarted by drought, barren soils and natural phenomena such as hurricanes.

Metabolic consequences of a low-carbohydrate, high-protein diet

Our primate ancestors in the tropical forests of Africa evolved on a high-carbohydrate diet and the brain and reproductive tissues evolved a specific requirement for glucose as a source of fuel [23, 24]. But the Ice Ages which dominated human evolution brought a low-carbohydrate diet, and since the brain, the fetus and the mammary gland all had a specific requirement for glucose, certain metabolic adaptations were necessary to accommodate the low glucose intake. Many studies have shown that human metabolism adapts to a high-protein, low-carbohydrate diet. In acute experiments, a protein meal stimulates postprandial insulin and glucagon secretion without a commensurate change in plasma glucose [25–27].

Chronic ingestion of a low-carbohydrate, high-protein diet results in increased hepatic glucose production and decreased peripheral glucose utilisation, i.e., insulin resistance [28, 29]. Both the ability of insulin to inhibit hepatic glucose production and to augment tissue glucose disposal are impaired. The increased hepatic glucose production is the result of the high protein intake and is mediated through an increased carbon flux through the gluconeogenic pathway. Possible mechanisms include a mass action effect of increased concentrations of gluconeogenic substrates, or the increased glucagon level which stimulates gluconeogenesis, or the activation of a number of key enzymes in the gluconeogenic pathway. The decreased insulin-stimulated glucose disposal by peripheral tissues is largely due to the de-

crease in carbohydrate intake and the consequent hypoinsulinaemia [29].

Thus, a high-protein/low-carbohydrate diet can produce metabolic adaptation in the short term. The phenotypic expression of this adaptation is insulin resistance, both in the liver and the peripheral tissues. This provides a strong clue that insulin resistance is the mechanism for coping with a shortage of glucose but a surfeit of amino acids. While it is clear that some animals can survive on low-carbohydrate diets by developing insulin resistance, their ability to reproduce appears to be severely compromised. Female dogs fed a carbohydrate-free diet with 26 % protein became hypoglycaemic and ketotic towards the end of gestation and over a third of the puppies were stillborn [30–32]. We believe that reproduction is compromised because an insulin-sensitive animal cannot adapt sufficiently to the low dietary glucose supply to compensate for the extra demands for glucose during pregnancy.

The demand for glucose increases during pregnancy because the fetus and placenta oxidise glucose as a source of energy and the synthesis of glycoproteins and glycolipids requires preformed glucose. In fact, the materno-fetal unit utilises proportionately more carbohydrate than lipid as a fuel source compared to the non-pregnant state and fasting glucose levels fall late in pregnancy [33]. Interestingly, these changes in fuel utilisation are associated with a progressive increase in peripheral insulin resistance during all human pregnancies [34, 35].

Adequate synthesis of glucose from gluconeogenic amino acids may be accomplished if dietary protein is sufficiently high. For example, dogs are able to reproduce on a carbohydrate-free diet when the protein intake is as high as 50 % [31, 32]. This fits well with the evolutionary development of the dog as a hunter, since the body of prey would have supplied only a little available carbohydrate but large amounts of protein. The dog therefore falls halfway between a carnivore and an omnivore. In true carnivorous animals like the cat, gluconeogenesis is also more or less permanently "switched on" [36] with maximal gluconeogenesis occurring in the absorptive phase immediately following a meal. Carnivorous animals like the cat which have evolved and reproduce well on a low carbohydrate intake, appear to be genetically insulin resistant [36]. Moreover, they appear to develop NIDDM when exposed to a high-carbohydrate diet [37].

There is also an increased demand for glucose during lactation for the synthesis of lactose in milk. In rats, insulin resistance develops in muscle while the mammary gland becomes extremely sensitive in order to facilitate the preferential utilisation of glucose and other lipogenic precursors by the mammary gland [38, 39]. By analogy, very low-carbohydrate diets during human evolution may have selected for insulin-resistant females whose metabolism conserved glucose for fetal survival and milk production.

It may also be relevant that the average insulin-sensitive subject finds a low-carbohydrate, high-protein diet difficult to tolerate. Most studies have been prematurely aborted after a couple of weeks because subjects complained of nausea and weakness [28]. On the other hand, there is evidence that insulin-resistant subjects and genetically obese animals can tolerate a high-protein diet very well. In one study the subjects were actually individuals with NIDDM and the high-protein diet produced the most desirable metabolic profile of all four diets that were compared [40]. In other studies, the subjects were Australian Aborigines who adopted their traditional high-protein diet for several months [41, 42]. Lean Zucker rats could not adapt to a low-carbohydrate diet, while their genetically obese siblings could [43].

Hence, we propose that a more profound degree of insulin resistance or a different mechanism producing insulin resistance or both, is required to reproduce successfully on a low-carbohydrate diet. The genes/enzymes involved in dietary-induced insulin resistance may, therefore, be entirely different from those involved in producing an inherited insulin resistance which had reproductive advantages.

Differences in predisposition to NIDDM

Insulin resistance is now recognised as the earliest metabolic "defect" in those destined to develop NIDDM [44]. Our hypothesis proposes that this insulin resistance was the normal genotype for much of the world's population at the end of the last Ice Age. How then do we account for the relative insulin sensitivity and low prevalence of NIDDM in Caucasians? And how do we account for the extraordinary prevalence of NIDDM in groups like the Pima and Nauruans?

We believe that Europeans have the lowest incidence of diabetes because their diet has been high in carbohydrate for longer than any other population group. The amount of carbohydrate in European diets increased dramatically about 10,000 years ago with the advent of agriculture [11, 19]. The selection pressure for insulin resistance (i.e., a low-carbohydrate diet) was therefore relaxed first in Caucasians. Hence, we would expect the prevalence of genes producing insulin resistance to be lower in the European population and any other group exposed to high carbohydrate intake for sufficiently long. We know this is long enough to alter the frequency of a gene because lactase persistance during adulthood became the norm in this population over the same space of time [45, 46].

Relaxation of selection pressures has resulted in many features characteristic of humans. For exam-

ple, the use of weapons obviated the need for strong jaws and teeth for survival, and we gradually evolved our present mandibular structure. Relaxation of the selection pressure for insulin resistance is not the same as saying that insulin sensitivity became a selective advantage. Positive selection for insulin sensitivity might occur if high carbohydrate diets compromised reproduction in insulin-resistant populations. However, there is no evidence in the Pimas at present that fertility is reduced on high-carbohydrate, western diets.

We propose that further evolutionary pressures and geographic isolation produced populations which were particularly insulin-resistant. Both the Nauruans and Pima Indians are examples of geographically isolated populations in which genetic "bottlenecks" have diminished genetic diversity [47]. The Nauruans experienced severe human losses due to infectious disease, droughts and food shortage within the past century. Similarly, the number of Pimas was severely reduced by starvation after the arrival of Europeans in the 1860's. Starvation results in the same metabolic profile as that occurring with a low-carbohydrate, high-protein diet, i.e., increased gluconeogenesis and peripheral insulin resistance [48, 49]. Initially, hepatic glycogen is mobilised but subsequently gluconeogenesis from precursors such as endogenous amino acids, is increased. The oxidation of non-esterified fatty acids produced from lipolysis leads to suppression of glucose utilisation and oxidation via the glucose/fatty acid cycle [50, 51]. Hence, acute starvation in Pimas and Nauruans this century may have selected for those with a profound degree of insulin resistance that was determined by their genetic inheritance and therefore passed to their offspring.

O'Dea [14] and Wendorf and Goldfine [21] have also proposed that insulin resistance is a mechanism for coping with variable food intake during evolution. They invoke the thrifty gene hypothesis which postulates that cycles of food scarcity and abundance selected for individuals with mechanisms to increase the deposition of food energy as body fat for subsequent use during periods of food scarcity [52, 53]. However, specific mechanisms for coping with food scarcity, particularly of carbohydrate foods during pregnancy, were probably of more immediate survival advantage. These would include the ability to avoid severe ketosis and blunt the usual decline in plasma glucose which occurs with prolonged fasting or carbohydrate deprivation [51]. Insulin resistance may have been the mechanism which achieved this.

The quality of the carbohydrate

The agricultural revolution brought a sharp increase in the quantity of carbohydrate consumed. When the industrial revolution occurred in the 17th century, the *quality* of that carbohydrate changed. Until then carbohydrate had been eaten in a form which was slowly digested and absorbed, eliciting small postprandial insulin responses [54, 55]. Legumes and cereals which are coarsely ground or flaked are classed as low glycaemic index foods [56]. Similarly, many of the traditional carbohydrate foods of the Pima Indians, Pacific Islanders and Australian Aborigines have been shown to be low glycaemic index foods, producing relatively small increases in plasma glucose and insulin [57, 58]. Thus, although the carbohydrate content of the diet had increased as a result of agriculture, the beta cells were not unduly stressed.

However, the industrial revolution in the 17th century brought about significant changes to the milling of cereals which affected the rate of digestion and absorption of carbohydrate. Cereals began to be ground very finely by high-speed roller mills which removed almost all the indigestible material and increased the yield and palatability. The starch was thus made much more digestible and the postprandial glycaemic and insulin responses were 2 to 3 times higher compared to the coarsely ground flour or whole grain [55, 59]. At about the same time potatoes were introduced into western diets and they too have been shown to produce high glycaemic and insulin responses [56].

The modern high glycaemic index diet is therefore a relatively recent phenomenon which stresses the beta cells to a much greater extent than previous high-carbohydrate diets. The challenge is even more pronounced in individuals with insulin resistance such as Pimas and Australian Aborigines [60, 61]. Furthermore, high glycaemic index diets have been shown to worsen insulin resistance [62]. Only the carbohydrate staples of modern western diets require beta cells capable of secreting large amounts of insulin for a lifetime.

It would not be surprising therefore if many individuals did not have the beta-cell capacity to do this, considering the fact that humans did not need this ability in the past. Those who fail to sustain a high rate of insulin secretion will develop impaired glucose tolerance and eventually NIDDM [44]. Severely compromised beta-cell function (beta-cell 'exhaustion') is thought to represent the culmination of the effects of a genetic defect or other insult such as "glucose toxicity" or accumulated amylin deposits [63]. Hales and Barker [64] have proposed that the tendency to compromised insulin secretion is especially evident in individuals exposed in utero and in early life to sub-optimal nutrition.

Conclusion

Changes in the quantity and quality of carbohydrate are clearly evident across time and space and present a plausible explanation for differences in the predis-

position to NIDDM. The high-protein, low-carbohydrate diet was the nutritional backdrop for the last two million years of human evolution. It would be surprising therefore if our genotype did not change in important ways to accommodate this diet. Finally, we are not the first to suggest that an insulin-resistant genotype would have offered a survival advantage to specific populations consuming a low-carbohydrate, high-protein diet. O'Dea [14] and Wendorf and Goldfine [21] made similar observations for the Australian Aborigines and the Plains Indians of North America, respectively. Our hypothesis differs from theirs in that it recognises that most human groups were exposed to a high-protein, low-carbohydrate diet up until the end of the last Ice Age. Only our hypothesis explains the observation that insulin resistance is widespread in all human groups other than those of European descent.

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References

1. King H, Rewers M (1993) Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. Diabetes Care 16: 157–177
2. Schraer CD, Lanier AP, Boyko EJ, Gohdes DM, Murphy NJ (1988) Prevalence of diabetes in Alaskan Eskimo, Indians, and Aleuts. Diabetes Care 11: 693–700
3. Dowse G, Zimmet P (1993) The thrifty genotype in non-insulin-dependent diabetes. BMJ 306: 532–533
4. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L (1989) Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. New Engl J Med 321: 337–343
5. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR (1990) Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med 113: 909–915
6. Gulli G, Ferrannini E, Stern M, Haffner S, DeFronzo RA (1992) The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. Diabetes 41: 1575–1586
7. Osei K (1990) Increased basal glucose production and utilisation in nondiabetic first-degree relatives of patients with NIDDM. Diabetes 39: 597–601
8. Proietto J, Nankervis AJ, Triaiandes K, Rosella G, O'Dea K (1992) Identification of early metabolic defects in diabetes-prone Australian Aborigines. Diab Res Clin Prac 17: 21–26
9. Gaulin SJC, Konner M (1977) On the natural diet of primates, including humans. In: Wurtman RJ, Wurtman JJ (eds) Nutrition and the Brain, vol 1. Raven Press, New York, pp 1–86
10. Fagan BM (1992) People of the earth 7th ed. Harper Collins, New York
11. Garn SM, Leonard WR (1989) What did our ancestors eat? Nutrition Reviews 47: 337–345
12. Lee RB, DeVore I (1968) Man the hunter. Aldine, Chicago
13. Flood J (1992) Archaeology of the dreamtime. Angus and Robertson, Sydney
14. O'Dea K (1991) Westernisation, insulin resistance and diabetes in Australian Aborigines. Med J Aust 155: 258–264
15. Mann GV, Scott EM, Hursch LM et al. (1962) The health and nutritional status of Alaskan Eskimos. A survey of the Interdepartmental Committee on Nutrition for National Defence, 1958. Am J Clin Nutr 11: 31–39
16. Szathmary EJE, Ritenbaugh C, Goodby CM (1987) Dietary change and plasma glucose levels in an Amerindian population undergoing cultural transition. Soc Sci Med 24: 791–804
17. Kliks M (1978) Paleodietetics: a review of the role of dietary fiber in preagricultural human diets. In: Spiller GA, Amen RF (eds) Topics in dietary fiber research. Plenum Press, New York, pp 181–202
18. Crapo PA, Kolterman OG, Olefsky JM (1980) Effect of oral fructose in normal, diabetic and impaired glucose tolerant subjects. Diabetes Care 3: 575–581
19. Eaton SB, Konner M (1985) Paleolithic nutrition. A consideration of its nature and current implications. New Engl J Med 312: 283–289
20. Rea AM Historic changes in the Gila River Pima diet. In: Nabhan GP, Brand Miller JC (eds) Parallels in the evolution of Australian Aborigines and Pima Indians: diet, lifestyle and diabetes. University of Arizona Press, Tucson, in press
21. Wendorf W, Goldfine ID (1991) Archaeology of NIDDM. Excavation of the 'thrifty' genotype. Diabetes 40: 161–165
22. Prior IAM, Davidson F, Salmond CE, Czochanska Z (1981) Cholesterol, coconuts and diet on Polynesian atolls: the Pukapuka and Tokelau Island studies. Am J Clin Nutr 34: 1552–1561
23. Sokoloff L, Fitzgerald GG, Kaufman EE (1977) Cerebral nutrition and energy metabolism. In: RJ Wurtman, JJ Wurtman (eds) Nutrition and the Brain, vol 1. Raven Press, New York, pp 87–139
24. Frienkel N (1980) Of pregnancy and progeny. Diabetes 29: 1023–1034
25. Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P (1984) Effect of protein ingestion on the glucose and insulin response to a standardised oral glucose load. Diabetes Care 7: 465–470
26. Krezowski PA, Nuttall FQ, Gannon MC, Bartosh NH (1986) The effect of protein ingestion on the metabolic response to oral glucose in normal individuals. Am J Clin Nutr 44: 847–856
27. Schmid R, Schulte-Frohlinde V, Schusdziarra J, Neubauer J, Stegman M, Maier V, Classen M (1992) Contribution of postprandial amino acid levels to stimulation of insulin, glucagon and pancreatic polypeptide in humans. Pancreas 7: 698–704
28. Phinney SD, Bistrian BR, Wolfe RR, Blackburn GL (1983) The human metabolic response to chronic ketosis without caloric restriction: physical and biochemical adaptation. Metabolism 32: 757–768
29. Rossetti L, Rothman DL, DeFronzo RA, Schulman GI (1989) The effect of dietary protein on in vivo insulin action and liver glycogen repletion. Am J Physiol 257: E212–E219
30. Rosmos DR, Palmer HJ, Muiruri KL, Bensink MR (1981) Influence of a low carbohydrate diet on performance of pregnant and lactating dogs. J Nutr 111: 678–689
31. Kienzle E, Meyer H, Lohrie H (1985) Influence of carbohydrate-free rations with various protein/energy relationships on fetal development, viability of newborn puppies

and milk composition. Advances in animal physiology and animal nutrition 16: 78–99
32. Blaza SE, Booles D, Burger IH (1989) Is carbohydrate essential for pregnancy and lactation in dogs? In: Berger IH, Rivers JPW (eds) Nutrition of the dog and cat. Cambridge University Press, Cambridge, pp 229–243
33. Robinson S, Viira J, Learner J, Cahn SP, Anyaoku V, Beard RW, Johnston DG (1993) Insulin insensitivity is associated with a decrease in postprandial thermogenesis in normal pregnancy. Diabet Med 10: 139–145
34. Ryan, O'Sullivan MJ, Skyler JS (1985) Insulin action during pregnancy. Studies with the euglycemic clamp technique. Diabetes 34: 380–389
35. Buchanan TA, Metzger BE, Frienkel N, Bergman RN (1990) Insulin sensitivity and β-cell responsiveness to glucose during the pregnancy in lean and moderately obese women with normal glucose tolerance and mild gestational diabetes. Am J Obstet Gynecol 162: 1008–1014
36. MacDonald ML, Rogers QR, Morris JG (1984) Nutrition of the domestic cat, a mammalian carnivore. Ann Rev Nutr 4: 521–562
37. O'Brien TD, Hayden DW, Johnson KH, Stevens JB. (1985) High dose glucose tolerance test and serum insulin glucagon levels in diabetic and non-diabetic cats; relationships to insular amyloidosis. Vet Path 22: 255–261
38. Vernon RG (1989) Endocrine control of metabolic adaptation during lactation. Proc Nutr Soc 48: 23–32
39. Burnol AF, Loizeau M, Girard J (1990) Insulin receptor activity and insulin sensitivity in mammary gland of lactating rats. Am J Physiol 259: E828–E834
40. O'Dea K, Traianedes K, Ireland P, Niall M, Sadler J, Hopper J, De Luise M (1989) The effects of diet differing in fat, carbohydrate, and fibre on carbohydrate and lipid metabolism in type II diabetes. J Am Diet Assoc 89: 1076–1086
41. O'Dea K (1984) Marked improvement in carbohydrate metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. Diabetes 33: 596–603
42. O'Dea K, Spargo R (1982) Metabolic adaptation to a low carbohydrate-high protein ('traditional') diet in Australian Aborigines. Diabetologia 23: 494–498
43. Peret J, Bach AC, Delhomme B, Bois-Boyeux B, Canez M, Schirardin H (1984) Metabolic effects of high protein diets in Zucker rats. Metabolism 33: 200–207
44. DeFronzo RA, Bonadonna RC, Ferrannini E (1992) Pathogenesis of NIDDM: a balanced overview. Diabetes Care 15: 318–368
45. Simoons FJ (1981) Geographic patterns of primary adult lactose malabsorption. In: Paige DM, Bayless TM (eds) Lactose digestion. The Johns Hopkins University Press, Baltimore, pp 23–48
46. Kretchmer N (1981) Food: a selective agent in evolution. In: Walcher DN, Kretchmer N (eds) Food, nutrition and evolution. Masson, New York, pp 37–48
47. Serjeantson S, Zimmet P (1982) Diabetes in the Pacific: evidence of a major gene. In: Baba S, Gould MK, Zimmet P (eds) Diabetes mellitus: recent knowledge on aetiology, complications and treatment. Academic Press, Sydney, pp 23–30
48. DeFronzo RA, Soman V, Sherwin RT, Hendler R, Felig P (1978) Insulin binding to monocytes and insulin action in human obesity, starvation and refeeding. J Clin Invest 62: 204–213
49. Newman WP, Brodows RG (1983) Insulin action during fasting and refeeding in rat determined by euglycemic clamp. Am J Physiol 249: E514–E518
50. Sugden MC, Holness MJ, Palmer TN (1989) Fuel selection and carbon flux during the starved-to-fed transition. Biochem 263: 313–323
51. Youn JH, Buchanan TA (1993) Fasting does not impair insulin-stimulated glucose uptake but alters intracellular glucose metabolism in conscious rats. Diabetes 42: 757–763
52. Neel JV (1962) Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'? Am J Hum Genet 14: 353–362
53. Neel JV (1992) The thrifty genotype revisited. In: Kobberlong J, Tattersall R (eds) The genetics of diabetes mellitus. Academic Press, London, pp 283–293
54. Jenkins DJA, Wolever TMS, Jenkins AL, Jose RG, Wong GS (1984) The glycaemic response to carbohydrate foods. Lancet ii: 388–391
55. Heaton KW, Marcus SN, Emmett PM, Bolton CH (1988) Particle size of wheat, maize, and oat test meals: effects on plasma glucose and insulin responses and on the rate of starch digestion in vitro. Am J Clin Nutr 47: 675–682
56. Jenkins DJA, Wolever DJA, Jenkins AL (1988) Starchy foods and glycemic index. Diabetes Care 11: 149–159
57. Thorburn AW, Brand JC, Truswell AS (1987) Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor against diabetes. Am J Clin Nutr 45: 98–106
58. Brand JC, Snow J, Nabhan GP, Truswell AS (1990) Plasma glucose and insulin responses to traditional Pima Indian meals. Am J Clin Nutr 51: 416–420
59. Brand JC, Nicholson PL, Thorburn AW, Truswell AS (1985) Food processing and the glycemic index. Am J Clin Nutr 42: 1192–1196
60. Lillioja S, Nyomba BL, Saad MF, Ferraro R, Castillo C, Bennett PH, Bogardus C (1991) Exaggerated early insulin release and insulin resistance in a diabetes-prone population: a metabolic comparison of Pima Indians and Caucasians. J Endocrinol Metab 73: 866–876
61. Thorburn AW, Brand JC, O'Dea K, Spargo RM, Truswell AS (1987) Plasma glucose and insulin responses to starchy foods in Australian Aborigines: a population now at high risk of diabetes. Am J Clin Nutr 46: 282–285
62. Byrnes S, Denyer G, Brand Miller J (1994) Development of insulin resistance in rats after low amylose vs high amylose diets. Proc Nutr Soc Aust 18: 117
63. Granner DK, O'Brien RM (1992) Molecular physiology and genetics of NIDDM. Diabetes Care 15: 369–395
64. Hales CN, Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the trifty phenotype hypothesis. Diabetologia 35: 595–601