This review focuses on animal studies that examine the role of dietary fat in obesity. It is evident from animal experiments that the percentage of energy derived from fat in the diet is positively correlated with body fat content. With few exceptions, obesity is induced by high-fat diets in monkeys, dogs, pigs, hamsters, squirrels, rats, and mice. The mechanisms responsible for this correlation between body fat and dietary fat content are not clear. It has been proposed that a high-fat diet produces hyperphagia, which is solely responsible for the increased body fat content. However, several studies in various rodent models showed that increased body fat content still results when the hyperphagia is prevented. This suggests that some metabolic effects of high-fat diets, independent of hyperphagia, may also be contributing to the obesity induced by high-fat diets. It is also clear from animal studies that genetic factors significantly modulate the body's response to diets high in fat-derived energy. In contrast with the animal studies, studies in humans that have examined the relation between dietary fat content and body fat are inconclusive. The limitations of cross-sectional studies, the lack of controlled feeding trials, and the importance of genetic variation in response explain the absence of conclusive evidence. The lessons learned from animal models point to dietary fat as one potentially important component in the etiology of human obesity. Additional comprehensive studies are warranted to determine the role of dietary fat in the etiology of human obesity.

KEY WORDS Obesity, animal models, humans, environment, dietary fat, hyperphagia, genetic predisposition, monkeys, pigs, dogs, hamsters, squirrels, rats, mice

INTRODUCTION

It is still unclear whether the amount and type of dietary fat consumed influences the amount of body fat in humans. The epidemiologic studies relating to this issue have significant methodologic limitations and interpretive difficulties, as reviewed by Seidell (1) in this supplement. One can essentially pick and choose among the different epidemiologic studies to identify those that support a particular view. The experimental literature in humans indicating that acutely increasing the amount of fat in the diet leads to both metabolic (2) and behavioral (3) changes favoring deposition of fat is more convincing than the epidemiologic findings. However, these findings certainly do not prove a causal relation between dietary fat and obesity in humans because the experiments were of relatively short duration.

To facilitate our interpretation of the literature in humans, it may be helpful to consider the results from studies in animal models. As reviewed below, many studies have characterized the role of dietary fat in obesity in experimental animals. High amounts of dietary fat are clearly associated with increased body fat content, and the data describing dietary obesity induced by high-fat diets in rodent models are comprehensive. The major issues from the animal literature are 1) the mechanisms by which high amounts of dietary fat promote the accumulation of larger body stores of lipid and 2) the role of genetic variation in determining the body's response to manipulations of dietary fat amounts. These issues are presented below along with a summary of the data supporting the hypothesis that the amount of fat in the diet is correlated with body fat content in numerous species.

DIETARY FAT AND OBESITY IN MONKEYS, DOGS, PIGS, HAMSTERS, AND SQUIRRELS

The purpose of this summary is to highlight the more informative studies in different species, excluding ruminants, to provide an overview of the experimental findings relating dietary fat to body fat content. Although there are data describing the metabolic responses to increased dietary fat in ruminants, these data are not reviewed here because the digestive processes in ruminants are very different from those in humans and other omnivores and it is not clear whether it is appropriate to extrapolate data from ruminants to nonruminants.

Monkeys

Spontaneous obesity and overweight have been noted to occur in several species of nonhuman primates, most notably in macaque and rhesus monkeys. The related literature was reviewed by Kemnitz (4). Obesity in captive monkeys generally occurs in adults and is under the control of a variety of factors,
especially food availability and social status. About 10–15% of macaque and rhesus monkeys in captivity will become spontaneously obese with aging when maintained on a relatively low-fat (<10% of energy), ad libitum diet. Spontaneous obesity also was observed in “wild” monkeys that were contained on an island at a higher than normal population density through the provision of food (4). Thus, limitation in physical activity arising from caging appears not to be a serious factor in producing spontaneous obesity in monkeys. Obesity is less common in monkeys in their natural environment, probably because of limited food availability and selection pressures from predators.

The standard laboratory biscuit fed to captive monkeys is low in fat (<10–13% of energy from fat). It is not clear whether this percentage is significantly different from that of energy from lipid ingested by monkeys in the wild. The foraging strategies of wild monkeys of different species vary considerably and therefore the food sources and macronutrient composition of their diets also are variable. Although it is possible that the incidence of spontaneous obesity in captive monkeys is due in part to the higher fat content of the commercial diets, it is more likely that the availability of energy is a more important factor.

There are numerous controlled dietary studies in primates in which dietary fat content and composition have been manipulated to examine the effects on lipid metabolism and indexes of atherosclerosis. However, there are only a few long-term studies in primates in which energy intake or body composition was carefully measured. In one such study, in which a high-fat diet was fed ad libitum to captive squirrel monkeys starting at weaning (5), the effect on body fat content was profound. The monkeys were fed either semipurified diets containing 21% to 31% of energy from fat or commercial monkey biscuits containing 13% fat. At age ≈4 y the animals were killed and their body compositions determined. The monkeys fed high-fat diets had body fat contents that, on average, were about fourfold higher than those of monkeys reared on the lower-fat commercial biscuits (30% body fat compared with ≈7% body fat, respectively). The energy intakes were directly and linearly correlated with rate of growth in these animals. One confounder of this study was that the semipurified high-fat diets also contained significant amounts of sucrose, which could have partly driven the hyperphagia observed in the group fed the high-fat diet because squirrel monkeys avidly consume sucrose solutions. Therefore, although this study is not ideal because the diets varied in components other than dietary fat, it is suggestive that a higher level of dietary fat is associated with a much higher level of body fat in squirrel monkeys. Of interest is the observation noted by this group that cebus monkeys did not become obese when consuming the semipurified high-fat diets, suggesting significant heterogeneity of response among monkey species.

In a short-term feeding study by Jen (6), male rhesus monkeys were fed a high-fat diet (50% of energy) for 6 wk and dramatically increased their energy intake (60% above baseline) and rate of weight gain (240% above baseline). Body composition was not assessed in this study.

In baboons, exposure to high-density, high-fat diets during the preweaning period by way of manipulation of the bottle feeding formulas led to a significant increase in body fat content at age 5 y (7). However, this was sex-specific, with only the female baboons showing an effect of early overfeeding. These studies support the notion that manipulating nutrition during an early critical period can have significant and permanent effects on later body composition.

Thus, it appears that spontaneous obesity occurs with a relatively low frequency in captive monkeys fed a low-fat diet. Although limited, data from at least two species (rhesus and squirrel monkeys) indicate that a high-fat diet is associated with increased energy intake and, when maintained over a long period of time, an increase in body fat content.

**Dogs**

It has certainly been noted that obesity is a significant problem among companion animals, especially dogs, with 25–44% of pet dogs being obese (8). A significant amount of veterinary literature has addressed the treatment of obesity in companion animals, along with the incidence and treatment of obesity-related diseases in dogs. However, little is actually known regarding the etiology of obesity in pet dogs, although it is often attributed to low levels of physical activity and highly palatable diets. It has been observed that specific breeds present at veterinary clinics with obesity more frequently than others (9). Therefore, genetic predisposition may be an important factor in the etiology of obesity in dogs as well as in other species.

Romsos et al (10, 11) completed two controlled feeding trials in dogs in which they studied the effects of dietary fat. They showed that higher levels of dietary fat are associated with increased body weight and body fat content. In one study (10), they systematically varied the amount of protein and carbohydrate in six different diets that were fed to dogs for 8 mo. The highest-fat diet contained 76% of energy from fat, the intermediate-fat diets contained 55% and 38% of energy from fat, and the lowest-fat diet contained just 13% of energy from fat. The highest-fat diet was aphysiologic, however, because it contained 0% of energy from carbohydrate. The largest effects of the fat manipulation were seen in those diets with intermediate-fat contents. At the end of the 32-wk study, fat-free mass did not differ with fat intake; however, the dogs fed the intermediate-fat diets contained significantly greater amounts of body fat (3.1 and 3.5 kg lipid) compared with the dogs in the low-fat diet group (1.9 kg lipid). In a similar study (11), two groups of dogs were fed semipurified diets containing either 51% or 23% of energy from fat for 25 wk. The two diets contained similar amounts of protein. At the end of the controlled feeding period, the dogs fed the higher-fat diet had consumed 13% more energy than those fed the lower-fat diet, and they had ≈5.8 kg body fat whereas those fed the lower-fat diet had 4.3 kg body fat.

In more recent studies, Rocchini et al (12) supplemented the normal daily ration of commercial dog food with cooked beef fat such that the total energy from fat was >70%. This procedure resulted in rapid body weight gain in the dogs and presumably an increase in body fat, although body fat content was not measured directly in these animals.

The results from studies conducted in dogs suggest that increased dietary fat content is associated with greater body fat accumulation. The magnitude of this effect may be strain dependent.

**Pigs**

Pigs generally respond to increased dietary fat by increasing their body fat. For example, Pond et al (13) fed both genetically obese and lean castrated male pigs a low-fat diet and the same diet supplemented with beef tallow (11% by weight) and dried egg yolk (1%) for a 16-mo period beginning at age 7 wk. The animals were initially fed ad libitum for 4 mo and were then
maintained on 1.82 kg diets daily until age 16 mo. Restricted feeding of pigs is important in nutrient manipulation studies because pigs will become markedly obese with low-fat diets when given ad libitum access to food. Back fat thickness was not affected by diet in the genetically obese pigs; however, in the lean pigs back fat thickness was 4.4 cm in the high-fat diet group and 3.5 cm in the low-fat control group. In a similar study by Diersen-Schade et al (14), young pigs were given liberal access (=90% of ad libitum intake) or restricted access to soy-oil or beef-based diets containing 40–50% of energy from fat, or given a conventional diet containing ~8–9% fat. With restricted energy intake, the pigs fed the high-fat diets had body fat contents approximately fourfold higher than those of pigs fed the low-fat diets. With liberal access to food, the effect on body fat of the high-fat diets was even greater. Earlier studies in both young and growing pigs also found that increasing dietary fat increased fat accumulation (15, 16).

Hamsters

Several species of hamsters display profound dietary obesity when fed diets containing high levels of dietary fats. Borer (17) showed that supplementation of a normal laboratory diet with sunflower seeds resulted in dietary obesity without consumption of more energy. Similarly, Wade (18) and Hamilton and Wade (19) showed that feeding a high-fat diet to golden or Syrian hamsters results in profound obesity. In Syrian hamsters, a 12-wk period of high-fat feeding of a nondefined diet [one part vegetable shortening and two parts powdered rodent feed (#5001; Ralston Purina, St Louis)] resulted in a three- to fourfold increase in selected adipose depot weights compared with control animals fed the rodent feed alone. In Syrian hamsters, high-fat diets were associated with prolonged hyperphagia. In contrast, carcass lipid content was doubled and protein content was increased ≈16% in golden hamsters that had been fed the high-fat diet. However, this occurred in the absence of hyperphagia. Therefore, in hamsters, as in rats and mice (discussed below), hyperphagia may not be necessary for a high-fat diet to promote increased adipose tissue lipid deposition.

Squirrels

Several studies have been completed characterizing the response to dietary fat in ground squirrels. Faust and Mrosovsky (20) showed that a high-fat diet [sunflower seeds, condensed milk, and liquid Ensure (Ross Laboratories, Columbus, OH)] provided as supplements to rat pellets (Ralston Purina) and fed over a period of 12mo resulted in an ≈40–70% increase in adipose depot weights in Richardson’s ground squirrels. The squirrels were maintained on an intermediate-duration photoperiod so that they did not develop the torpor that results from short photoperiods. In a similar study by Dark et al (21), golden-mantled ground squirrels were fed a high-fat diet composed of one part vegetable oil and two parts powdered rat feed (Ralston Purina). Control animals were fed the low-fat rat feed diet only. After ~6 mo of feeding the diets to juvenile ground squirrels, hibernation was induced by placing the squirrels in the cold, and food was then removed. The animals were killed after 3 consecutive days of euthermia following ~3 mo of hibernation. After terminal arousal following hibernation, body fat was approximately doubled in juvenile squirrels fed the high-fat diet compared with those fed the low-fat diet. Interestingly, in the adult animals there was no affect of a similar dietary manipulation.

Summary

Overall, the data from studies in a variety of mammals including nonhuman primates, dogs, pigs, hamsters, and squirrels support the notion that increased amounts of dietary fat are associated with greater body fat content. There also is evidence from these species that there is heterogeneity in the response to dietary fat between different strains or among different species in the same family. For example, body fat content appears to increase in squirrel monkeys fed a moderately high-fat diet, but not in cebus monkeys. Some strains of dog present at veterinary clinics with spontaneous obesity more frequently than others, and this is not solely the result of the popularity of specific breeds. Also, one species of hamster becomes hyperphagic when fed a high-fat diet and becomes markedly obese, whereas another species fed a similar diet does not become hyperphagic and yet still becomes obese. These findings of a positive association between dietary fat amounts and body fat and of genetic heterogeneity in response are supported by studies in rodents.

DIETARY FAT AND OBESITY IN RATS AND MICE

There is extensive literature characterizing responses to high-fat feeding in rodents, and several reviews have been published that focus on this and other dietary manipulations producing obesity, primarily in rats (22, 23). Overall, high-fat diets produce a consistent and significant increase in body fat content that is dependent on the amount of fat in the diet and the duration of feeding.

The earlier studies by Mickelson et al (24) in rats and by Fenton and Carr (25) and Lemonnier (26) in mice generally used diets that were extremely high in fat contents with 70–80% of total energy derived from fat. These diets resulted in prodigious obesity but the physiologic relevance of such extremely high-fat diets can certainly be questioned. Many subsequent studies showed a consistent and pronounced increase in the body fat content of rats fed moderate concentrations of dietary fat (27–31). Usually, hyperphagia is induced (relative to a low-fat dehydrated diet) in these studies but not always (reviewed later in this article). Hyperphagia might be an important mechanism by which high-fat diets promote obesity. Some studies have been performed with so-called “cafeteria” diets that provide a mixture of commercially available supermarket foods consumed by humans (32, 33). The rats gain weight rapidly and can become quite obese on this fare, and they tend to select and consume a high proportion of energy from fat (34). It has been suggested that rats actually become more obese with cafeteria diets than with high-fat diets, indicating perhaps a greater hyperphagia arising from the food variety. However, this has not been studied systematically.

One consideration in these studies is the composition and formulation of the control low-fat diet against which the effects of high-fat diets are compared. Usually, the control diet is a powdered or pelleted dry diet containing fat as <15% of energy. There are certainly palatability issues, as well as the effects of the other macronutrients on metabolism, that must be considered when making such comparisons. For example, there is considerable evidence that sweet-tasting diets (with sucrose or sucrose combined with saccharin) promote hyperphagia and obesity in rats (35–37). Usually these manipulations provide the sucrose in solution in combination with a pelleted diet, and the animals avidly consume the sucrose solution and do not adequately com-
pensate for the energy derived from the sucrose solution by decreasing their intake of the pelleted low-fat diet.

It is also evident that rats will chronically consume more energy when the diets are hydrated either as gels (36) or in solution (38) compared with similar diets in powdered or pelleted form. However, this effect is found primarily with high-carbohydrate diets and to a lesser extent with high-fat diets. These studies also showed that liquid diets promoted greater body weight gain when fed over long periods of time, compared with powdered or pelleted dry diets. Similar studies by JC Smith (personal communication, 1997) showed that liquid formulations containing higher amounts of fat but the same amount of sucrose also lead to greater energy intake and higher body weights (although body fat was not determined). Thus, increasing fat content, even in liquid formulations, is associated with increased energy intake and body weight gain in rats.

It is clear that there are palatability issues involved in determining total daily energy intake, and one must be careful when varying dietary content in concluding that manipulation of specific macronutrients affects energy balance and body adiposity. However, it is also clear that, despite these caveats, increased dietary fat in liquid or solid form also promotes both hyperphagia and increased body fat accumulation in rats.

**Dose-response relation between dietary fat and body fat content**

In rats, there is a clear relation between the age of the rat when an obesity-producing diet is initiated, the duration of the diet, and the degree of body fat increase. That is, the earlier an obesity-producing feeding regimen is begun, the greater the effect on the final body fat content (39), and the longer the duration of an obesity-producing diet, the greater the increment of body-weight gain and presumably body fat. These studies have been reviewed by Sclafani (40). The implication of these results is that obesity-producing diets may have a gradual, continuous effect on body fat and therefore the duration of exposure to the diet is an important variable. Furthermore, there may be no plateau effect of dietary manipulations that promote obesity. Thus, feeding a high-fat diet to experimental animals may not result in rapid accumulations of body fat that then plateau. Instead, there may be a gradual, steady accumulation of body fat that might decelerate as extremes of body fat content are achieved, but weight gain may never plateau. There is no information from human studies to determine whether the duration of exposure to a high-fat diet is an important factor in controlling body fat accumulation.

There are few studies examining the association between the concentration of dietary fat and the final amount of body fat achieved over a fixed interval of feeding. Two more recent studies in rats and mice can be used to show that dietary fat and body fat content are correlated. For example, West et al (41) showed in AKR/J mice that increasing dietary fat content from 15% to 30% to 45% of energy resulted in a linear increase in body fat content after 12 wk of access to these diets under ad libitum feeding conditions. Similarly, Boozer et al (42) showed that, under a restricted feeding paradigm, when rats were fed different concentrations of dietary fat, their body fat content was positively correlated with the concentration of dietary fat.

These results are similar to the findings by Edozien and Switzer (43), who evaluated the effect of dietary fat concentrations at 5%, 11.9%, and 21.1% (by weight) as well as the variation in concentrations of protein on growth and carcass composition in rats. However, the effects of varying dietary fat on body fat content were much smaller than the effects described above. This might be attributable to the energetic dilution of the 21.1% fat diet with significant amounts of fiber to make all of the diets isoenergetic in this experiment.

Overall, these results suggest that the relation between the amount of dietary fat consumed and body fat content could be linear, with no threshold effect. Thus, there may not be a certain fat intake at which the risk for increasing body fat content becomes markedly apparent. Again, there is no evidence from human studies that the association between the amount of dietary fat consumed and body fat content, if it exists, is linear and continuous. An understanding of the relation between the amount of dietary fat consumed and body fat content in humans has important public policy implications for diet recommendations and deserves further study in human populations.

**Dietary fat compared with excess energy as promoting lipid storage**

It is not clear whether the correlation between the amount of dietary fat consumed and body fat content in animals is attributable to the ingestion of more energy during high-fat feeding or to some metabolic features of high-fat diets that promote lipid storage independent of any effects on the amount of energy consumed. In rodents, high-fat diets generally promote the ingestion of more energy than do low-fat diets. However, this relative hyperphagia induced in rats by high-fat feeding is transient and generally decreases during the first 4–5 wk of exposure to the diet until it approaches control intakes (44). The mechanism responsible for the hyperphagia induced by high-fat feeding is not clear. It could be related to issues of palatability or to other post-ingestive metabolic consequences of the high fat content.

There are reports of high-fat feeding leading to obesity in the absence of hyperphagia. For example, as discussed above, Wade (18) found that a high-fat diet led to increased body fat in the golden hamster without overfeeding. In addition, a limited number of studies in rats showed the same phenomenon (45). In these studies, the animals were allowed ad libitum access to the high-fat diets but did not express the normal hyperphagia observed with high-fat feeding in many other studies. These results suggest that hyperphagia is not necessary for obesity induced by high-fat diets, although hyperphagia is usually observed with high-fat diets.

Several recent studies have attempted to examine the relation between dietary fat content and body fat content under conditions of restricted access to energy. In a recent report by Boozer et al (42), one group of rats was fed a low-fat diet, whereas three other groups were fed the same amount of energy each day but were fed diets containing higher concentrations of dietary fat. There was a clear dose-response function with a higher proportion of energy from fat associated with a significantly greater body fat content assessed by adipose depot weights. In our own laboratory (unpublished observations, M Chavez and DB West, 1997), we examined the response of AKR/J mice (a strain that markedly increases body fat content when fed a high-fat diet) to a high-fat diet when they were prevented from expressing the normal hyperphagia observed with high-fat feeding. After 8 wk of high-fat feeding, the AKR/J mice prevented from expressing the normal hyperphagia contained amounts of body fat equivalent to amounts in AKR/J mice allowed ad libitum access to the high-fat diet. This
occurred even though the mice prevented from hyperphagia consumed 12% less energy over the 8-wk period. One criticism of this kind of study is that restriction of access to energy often results in an altered pattern of feeding such that the total daily energy intake is achieved in fewer meals and the normal circadian pattern of feeding is disrupted. It has been reported that feeding by gavage two meals containing the same amount of energy as normally consumed ad libitum results in a significant increase in body fat content in rats (46). This could be one factor in the above-mentioned results. Therefore, the role of meal feeding in the restricted-fat feeding studies described above should be investigated.

Although this area certainly deserves significantly more attention, it is clear in the rodent models that diets high in fat result in a greater deposition of carcass lipid and that hyperphagia is not necessary for this to be observed. Obviously, if an animal is depositing more energy as fat, but consuming the same amount of energy, then some alteration of energy expenditure must occur if normal lean tissue growth is to be maintained. This could be accomplished by several mechanisms in rodents including reduced physical activity and a modification of basal metabolic rate through as yet undescribed mechanisms.

Modulation of body fat by dietary fat in rodent models of simple genetic obesity

At the writing of this brief review, all of the genes responsible for obesity in the well-characterized Mendelian models of rodent genetic obesity have been cloned. These include the agouti (47), ob (48), db (49), fat (50) and tub (51, 52) genes in the mouse. The well-known fatty (fa/fa) rat gene is likely to be a homologue of the mouse db mutation, but the specific mutation producing the obesity in the fatty rat has not yet been described.

All of these single-gene mutations result in massive obesity, and the limited number of studies examining dietary modulation suggest that the primary defect is metabolic and that even though all of these rodent models are hyperphagic, hyperphagia is not necessary for the expression of obesity. For example, studies in both the ob mouse (53) and the fatty rat (54) indicate that lifelong postweaning energy restriction to the dietary intake of lean littermates results in stunted growth, but the animals remain massively obese. Only a few manipulations of dietary fat composition have been completed in these models. For example, Vasselli et al (55) showed that increasing the dietary fat content of the diet fed to Zucker fatty rats had a significant effect on adult body fat content. However, this effect was moderate compared with the effect of the recessive mutation. In that study, the effect of the recessive mutation was to increase retroperitoneal adipose depot weight nearly 10-fold above that of lean control animals, whereas the high-fat diet in the obese animals approximately doubled depot weights compared with genetically obese animals fed a low-fat diet. Similar studies in the ob mouse (56) also showed a modulating effect of high-fat diets. Thus, the massive obesity caused by these genetic defects can only be modulated by dietary fat intake.

Polygenic models of obesity and dietary fat

Polygenic models of obesity have been described in rodents, primarily mice, including New Zealand Obese mice (57), KK mice (58), and Wellesley mice (59). New Zealand Obese mice are bred for high body-weight and obesity, and the degree of body fat can be increased by a high-fat diet (60). Similarly, the KK mouse is bred for large body size and the obesity in this strain tends to be moderate. Wellesley mice are actually first-generation hybrids generated by breeding C3H mice and I strain mice. The body fat content in Wellesley mice also can be increased by increasing dietary fat content. The genetic basis for the obesity in these models is unknown, but it is assumed to be polygenic in nature. It is of interest that the amount of body fat can be significantly modified by dietary fat in several of these mouse models of moderate genetic obesity. It suggests that dietary fat by gene interactions may be important in these models, unlike in the single-gene models of obesity in which the effects of dietary manipulations are modest compared with the gene effects.

Differences among strains in the ability of high-fat diets to promote obesity have been described in both rats and mice. For example, Levin and Sullivan (28) have showed in an outbred line of Sprague Dawley rats that there was a marked variability in susceptibility to dietary obesity induced by a diet moderately high in fat. In a survey of seven strains of rats, Schemmel et al (31) noted that the Osborne Mendel strain was very sensitive to obesity induced by a high-fat diet, whereas the S5B/Pl strain was very resistant. In a similar study in mice, West et al (27) noted in a survey of nine mouse strains that there was a continuous range of sensitivity to dietary obesity, with some strains markedly increasing body fat content while being fed a moderately high-fat diet and other strains showing no sensitivity to obesity induced by a high-fat diet. Another study by this group established that the differences in body fat with the feeding of different diets were due to variations in the dietary fat content and not the carbohydrate content and that body fat content was only weakly correlated with cumulative energy intake (41). These observations in rodents suggest that there may be genetic factors that either protect animals from dietary obesity or predispose them to obesity when placed in an environment in which high amounts of dietary fat are available.

The role of gene by dietary environment interactions in obesity

Although it is likely that there are gene by dietary environment interactions affecting which individuals become obese, this has not been extensively studied. There are now several models of polygenic obesity in mice that are being characterized for genetic susceptibility to dietary obesity. Fisler et al (61) described a backcross between F1 animals (derived from Mus spretus × C57BL/6J) and C57BL/6J mice in which the animals show a remarkable range of body fat content. They have mapped at least four genetic loci that control body fat content or individual adipose depot weights in this cross (62). These genetic loci are called mobil–4 for multigenic obesity loci.

West et al (27) identified strains of mice that are differentially sensitive to obesity resulting from high dietary fat, with the AKR/J strain among the most sensitive and the SWR/J strain among the least sensitive. When these two strains were intercrossed and either the F1 mice backcrossed with SWR/J mice or the F1 mice intercrossed to generate an F2 population, the body fat phenotype segregated and quantitative analyses suggested that it was under the control of a minimum of three to four genetic loci (63). Further genetic mapping studies have now identified six genetic loci (63–65), named Dol–6 for dietary obesity loci.

In a similar study, York et al (66) observed that CAST/Ei and C57BL/6J mice differed in their sensitivity to obesity induced by a high-fat diet, with the CAST/Ei strain resistant to dietary obesity and...
the C57BL/6J strain sensitive to dietary obesity. Preliminary mapping studies have identified a locus on chromosome 15 that controls body fat content, with suggestive linkage on chromosome 7.

These studies are certainly preliminary, but they clearly show that the strain differences noted for both spontaneous obesity (Mus spretus × C57BL/6J) and obesity induced by a high-fat diet (AKR/J × SWR/J and CAST/Ei × C57BL/6J) are due to genetic differences and that these traits are under polygenic control in each of these crosses. Furthermore, identifying the chromosomal location of the genes controlling these phenotypes is a first step toward identifying and characterizing the genes that mediate these strain differences in body fat content (67). Once these genes are characterized in mice, further studies will aim to determine whether the same genes or the same metabolic pathways are involved in the genetic control of body fat content in humans.

EXTRAPOLATION OF FINDINGS FROM ANIMAL STUDIES TO HUMANS

One must always be cautious when using experimental findings in one species to make predictions regarding the control of physiology or metabolism in another species. This is certainly true when attempting to extrapolate findings from animal studies of dietary fat and obesity to the human population. However, it is compelling that, in virtually all species in which it has been studied, there is a general positive association between the amount of dietary fat consumed and the amount of body fat. This is true for monkeys as well as for many other mammals. This observation might be explained by the common problem shared by most nonhuman mammalian species, ie, the difficulty in obtaining enough energy to maintain adequate amounts of lipid stores that will protect the animal from starvation during periods when energy is less abundant. Generally, food sources in the wild for most terrestrial mammals are not high in fat; this is certainly true for nonhuman primates, for whom the ecology has been well described. Therefore, we might speculate that mechanisms have evolved to maximize the efficiency of both energy utilization in general and the storage of ingested fat as lipids in adipose depot stores specifically. This is essentially a modification of the thrifty gene hypothesis originally proposed by Neel (68, 69). Under normal feeding conditions of a relatively low-fat diet and low food abundance, body fat content will be low. However, under conditions of an abundance of high-fat food sources, these thrifty genes will cause excess adipose lipid deposition and a greater risk for the development of obesity-associated diseases.

One explanation for the failure to detect a strong association between dietary fat intake and body fat content in human epidemiologic studies may be the presence of genetic heterogeneity. The studies in rodents described above suggest that different strains within a species vary in the amount of fat accumulated when the animals are fed diets high in dietary fat, and that this is under genetic control. If the response to dietary fat in human populations is also under genetic control, and some individuals carry susceptibility genes whereas others carry resistance genes, then this would weaken any association between dietary fat and body fat content in cross-sectional studies of human populations. Bouchard et al (70) clearly showed in studies in human twins that the change in body fat stores in response to overfeeding is highly heritable. It is likely that in humans, as well as in rats and mice, the response to dietary fat is also under genetic control. The role of genetic heterogeneity in determining the response to dietary fat, along with the difficulties in accurately and reliably assessing dietary intakes in humans and the inaccuracy of body mass index as a measure of body fat (71), may explain overall why the cross-sectional epidemiologic data do not support a strong association between dietary fat and body fat in humans. Long-term human feeding trials, in which the diets are prepared and supplied to the subjects and accurate measures of energy metabolism and body composition are used, would go far in resolving this controversy.

Several questions remain to be answered in animal studies of the relation between dietary fat content and body fat content. One issue is the role of hyperphagia during high-fat feeding in promoting the accumulation of additional adipose tissue lipid stores. Studies suggest that the hyperphagia is not necessary but may be an important factor in the overall effect of dietary fat on energy metabolism. It is also not clear whether there are threshold effects for the influence of dietary fat intake on body fat accumulation. The available animal studies are limited as reviewed above. This issue may be of particular importance in humans because it might influence general dietary intake recommendations. Finally, the relative role of genetic factors in determining the response to varying amounts of dietary fats is an important area for future work. The studies at this point suggest that there are important genetic factors modulating response to diet. The identification and characterization of these genetic mechanisms would help further our understanding of the role of dietary fat in obesity as well as in obesity-related diseases.

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