

Lipids in Human Health and Disease

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Introduction

The major nutritional cause of diseases in the United States is not the quality of the diet we consume but the quantity. Recommendations from previous RMC speakers who have addressed issues of diet and disease have a similar theme at the close of their presentation. In recommending approaches to reduce the risks of heart disease, McNamara (1985) stated "the population needs to lose weight, get more exercise. . . and normalize blood pressure." In making recommendations to reduce the risk of hypertension, Frank (1985) made the following comment "We should strive to control obesity. . ." While there were other recommendations to change the composition of the diet, evidence will be provided to show that weight control has a greater impact on reducing the risk of specific diseases. Information will be provided which indicates that for decreasing the risks of cancer and improving life expectancy, the quantity of food consumed is more important than the composition of food (assuming all essential nutrients are provided).

First, the role of lipids in normal health will be summarized, followed by a discussion of some of the diseases that have been associated with lipids and with obesity. The rest of the presentation will focus on the causes of different obesities found in man. Research on the different causes of obesity in man is aided by similar mechanisms in obese animals. These animal models may be useful in determining the most effective and safest approach to use in the long-term treatment of obesity.

Summary of Lipids in Health

In addition to the effect of palatability of foods, lipids contribute significantly to health. Some of the positive attributes of lipids are as follows:

Source of Energy

Lipids are a major source of stored energy. Approximately 90% of energy available for mobilization is found in adipose tissue lipids. In situations where food availability was cyclic, adipose tissue storage had tremendous survival value. Normal individuals have enough stored lipid energy to last over a month. Some massively obese individuals have enough stored energy to last almost a year.

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Reciprocal Meat Conference Proceedings, Volume 40, 1987.

Essential Fatty Acids

Dietary sources of essential fatty acids (i.e., linoleic acid) are required for normal growth and health (Duel et al., 1954). Normal pregnancy cannot be maintained without essential fatty acids. Rats fed a fat-free diet produce fewer young and those that are born die soon after birth. Infants receiving total parenteral nutrition for many weeks develop scaly skin lesions and poor wound healing because of inadequate essential fatty acid status (Alfin-Slater and Aftergood, 1980). Many of the beneficial effects of dietary linoleic acid can be explained by an increase in prostaglandin synthesis from this essential fatty acid.

The health benefits of fish oils has received much attention recently. Omega 3 polyunsaturated fatty acids from fish oils have been known for some time to have a lowering effect on serum lipids (Peifer et al., 1962). The low level of cardiovascular disease found in Greenland Eskimos appears to be caused by their high intake of fish (Bang and Dyerberg, 1980). In addition, dietary fish oils have been shown to inhibit the development of mammary, pancreatic and prostatic tumors (Carroll, 1986).

Cholesterol in Cell Development and Endocrinology

Cholesterol is an important intermediate in normal growth and development. It is the precursor for bile salts, steroid hormones and vitamin D-3. Cholesterol is a major structural component of plasma membranes as well as nuclear, mitochondrial and endoplasmic membranes of all cells.

Since cholesterol is synthesized by the body, it is not an essential nutrient. However, when cholesterol synthesis was blocked in vitro, fusion of myogenic cells (Horitz et al., 1978) and differentiation of neuronal cells (Maltese et al., 1981) were prevented. When cells were stimulated to proliferate, cholesterol synthesis was detected in the G-1 phase of the cell cycle and when cholesterol synthesis was blocked, DNA synthesis was inhibited (Chen, 1984). Cholesterol synthesis is an essential event in normal growth and development.

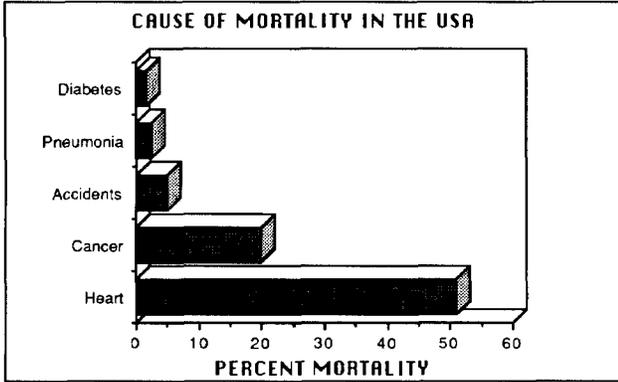
Summary of Lipids in Disease

It has been recommended that the lipid content of the US diet be reduced. The basis for this recommendation involves harmful events that occur when excesses of different classes of lipids accumulate in the body.

Lipids and Heart Disease

Cardiovascular disease is the number one killer in the United States (Figure 1) and serum cholesterol is the primary risk factor. While it is essential that cholesterol be made by

Figure 1



Causes of mortality in the U.S.A. (Adapted from McNamara 1985).

cells undergoing rapid proliferation, an excess of plasma cholesterol increases the risk of developing heart disease (McNamara, 1985). By lowering blood levels of cholesterol with the drug cholestyramine, it has been possible to reduce the risks of coronary heart disease (Lipids Research Clinics Program 1984). While this type of observation was used to recommend that dietary cholesterol levels should be reduced, a recent RMC invited speaker indicated that "no clinical trial, whether diet or drug, has shown a decrease in overall mortality" (McNamara, 1985). The drug lowering of serum cholesterol resulted in a decrease in deaths due to coronary heart disease (CHD) but was accompanied by an increase in non-CHD deaths.

It has been shown that altering dietary unsaturated and saturated fatty acid intake will influence the plasma cholesterol level. While this observation is not challenged, the efficacy in reducing mortality has been questioned. Part of the controversy is based on the potential negative effects of excessive intakes of polyunsaturated fatty acids. Unsaturated fatty acids have been linked to breast cancer (Cohen, 1985).

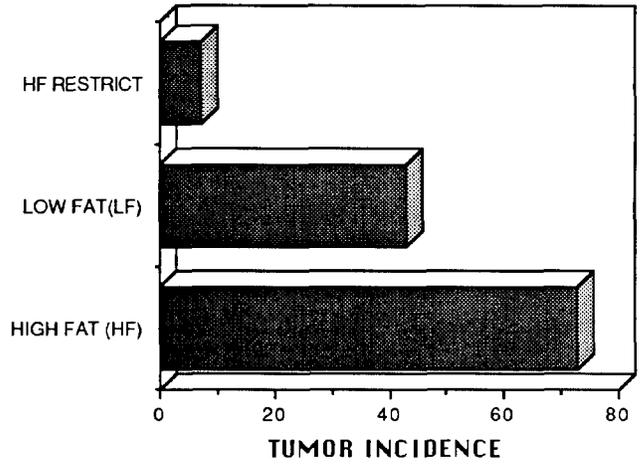
Lipids and Cancer

Dietary fat intake has been linked to specific cancers. Epidemiological and animal data support a role for unsaturated fatty acids in the development of breast cancer (Cohen, 1985). It has been shown that corn oil and safflower oil increase the incidence of mammary tumors in rats and that certain fats such as marine oils, olive oil, and medium chain triglycerides lack tumor-enhancing effects. It has been suggested that the tumor-promoting effects of certain fats may be linked to their linoleic acid content and the stimulation of prostaglandin synthesis (Cohen, 1985).

Mammary tumor incidence is influenced by the level of lipid in the diet and also the level of food intake (Pariza, 1986). In fact, the effect of fat in the diet can be largely reversed if the level of food intake is restricted (Figure 2). From these studies, it appears that the level of food intake, rather than the composition of diet, has the major impact on the development of this type of cancer.

Figure 2

EFFECT OF DIET ON MAMMARY CARCINOMA



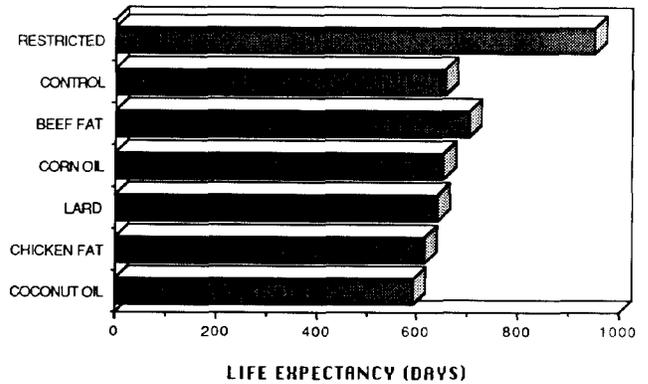
Effect of diet on mammary carcinoma (Adapted from Pariza, 1986).

Lipids and Longevity

There have been numerous animal studies that show an increase in longevity in rats subjected to energy restriction (McCay et al., 1935; Kaunitz and Johnson, 1972; Kritchevsky, 1979). The improvement in longevity is as high as 73%. The effects of dietary lipids were less impressive. Beef fat improved longevity over coconut oil by 18%, while corn oil and olive oil were intermediate in their ability to increase life expectancy (Figure 3). Energy restriction and the control of body weight gain have a far greater impact on longevity than any change in the lipid composition of the diet (assuming all essential fatty acids are provided).

Figure 3

EFFECT OF DIET ON LIFE EXPECTANCY



Effect of diet on life expectancy (Adapted from Kritchevsky (1985) and Young 1985).

Importance of Obesity in Human Health and Disease

Obesity and Longevity

Obesity has been shown to have an adverse effect on longevity. The greater the degree of obesity, the greater the mortality ratio (Figure 4). Mortality ratios of extremely obese (morbid obesity) individuals have been reported to be as high as 1200% (Drenick, 1979). The primary cause of death in morbid obesity was cardiovascular disease.

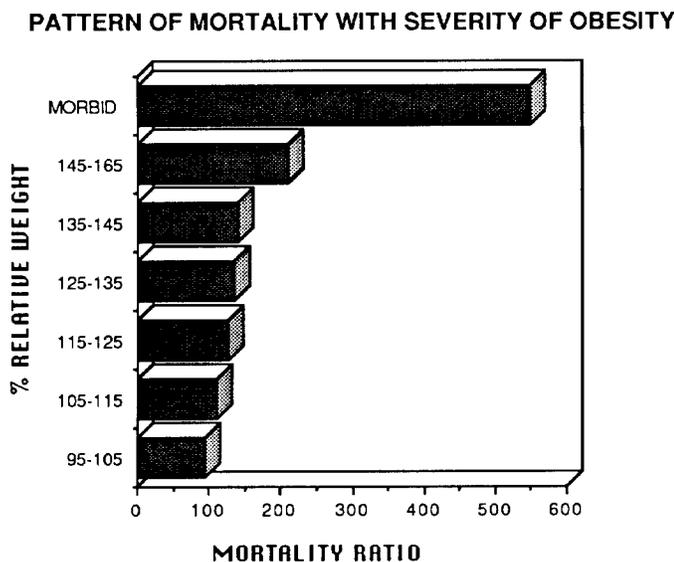
Obesity and Cardiovascular Disease

Obesity is associated with several risk factors associated with heart disease (Figure 5). Overweight individuals are more likely to have high blood pressure, total plasma cholesterol and triglycerides. In addition, the levels of HDL-cholesterol, which are usually associated with protection from cardiovascular disease, are lower in obese populations. However, some reports indicated conflicting relationships between obesity and cardiovascular disease (Barrett-Connor, 1985). However, a large population-based study of long duration and with follow-up data showed an increased risk of cardiovascular disease with severity of obesity, independent of other standard risk factors (Hubert et al., 1983). It appears that some of the original confusion in the literature may be caused by the observation that abdominal obesity is associated with an increased risk of heart disease, independent of total obesity (Bjorntorp, 1985).

Diabetes

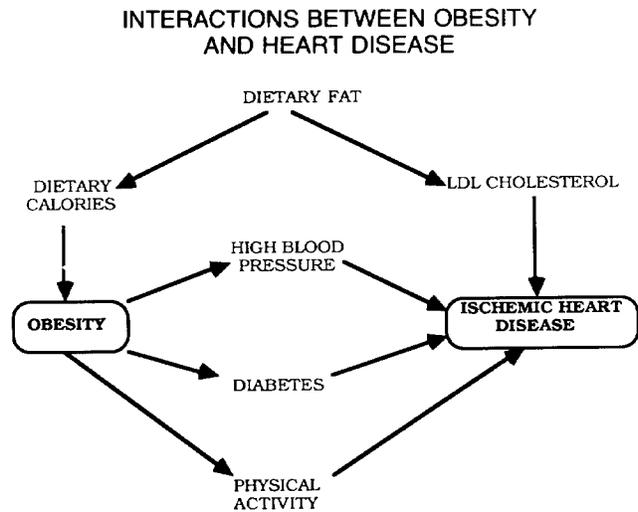
The clinical evidence that obesity is a special risk factor for diabetes is overwhelming (Hirsch, 1979; Van Itallie, 1985). The prevalence of reported diabetes is 2.9 times higher in obese individuals. In the 20 to 44 year age group, diabetes is 3.8 times greater in obese populations. Maturity

Figure 4



Effect of obesity on mortality.

Figure 5



Interactions of risk factors for heart disease as influenced by obesity.

onset diabetes is the type influenced by obesity. This form of diabetes affects 9.5 million of the 10 million people with diabetes. The biochemical abnormalities of maturity onset diabetes are reversible in 90% of cases by weight reduction.

Cancer

There is substantial evidence for an association between obesity and the risks of site-specific cancers. When compared to non-obese, obese had a higher mortality from breast cancer in postmenopausal women (Wallace et al., 1983). Obese males had higher mortality ratios for colorectal and prostate cancers (Garfinkel, 1985). Women with marked obesity showed the highest relative risks for endometrial cancer when compared with non-obese.

Other Medical Complications of Obesity

There are 26 known complications of obesity. In addition to those mentioned above, some of the more frequently encountered complications include: gallbladder disease, pulmonary function impairment, endocrine abnormalities, trauma to weight-bearing joints, gout, proteinuria, increased hemoglobin concentration and immunologic impairment (Bray, 1985).

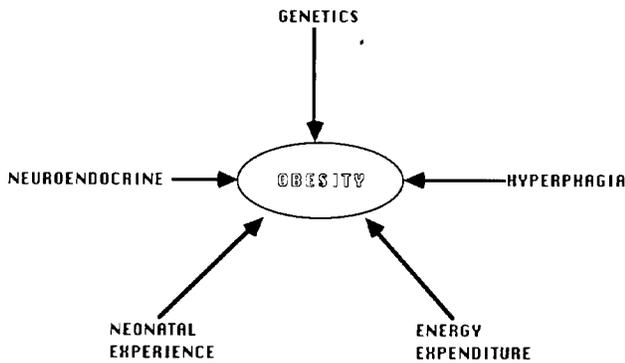
Causes of Obesity

While it is well recognized that obesity is a major health hazard, long term success in treatment of this problem has been rare. The reason for this failure is probably due to the fact that treatment approaches rarely take into account that obesity has multiple etiologies (Figure 6). The following is a discussion of some of the major events that predispose individuals to obesity.

Genetic Predisposition

Obesity has been found to be prevalent in some families. The child of one obese parent is more likely to be obese and

Figure 6
CAUSES OF OBESITY



Major causes of the development of obesity.

even more likely if both parents are obese (Garn and Clark, 1976). These observations do not provide an answer to the question "Was obesity an inherited trait or a learned eating disorder?" It is apparent that both are involved in the development of obesity.

Studies of identical twins have provided support for a genetic component in human obesities. The heritability of obesity using data from mono and dizygotic twins has been reported as high as .75 and .81 in two different studies (Borjeson, 1976; Stunkard et al., 1986). In the laboratory, there are several animal models of obesity that are caused by single gene mutations. These animals gained fat even when food intake was limited to that of a genetically lean control (Martin, 1976; Cleary and Vasselli, 1981). Genetic selection in domestic species has been used to alter the composition of animal products and increase productivity. Selection for fatness in pigs allowed for the estimation of heritability of this trait. Heritability of back fat in domestic pigs has been reported to be about .47 (Hetzer and Harvey, 1967). From these different observations, it is clear that genetics plays a key role in the predisposition to obesity.

Data of fatness in adopted children have been used to provide support for a role of environmental factors in the development of obesity (Garn, 1986). Adopted children show similarities in fatness to the adoptive parents, contrary to what is expected of a genetic predisposition. Family members still living together show synchronic fatness changes, they go up and down in fatness together. It is difficult to explain these changes in fatness to genes held in common, since mothers and fathers are unrelated. Environmental factors (i.e., eating habits) also play a contributing role in the development of obesity.

Hyperphagia

Over-eating relative to energy needs is a common form of obesity. It is clear that the mechanisms that normally regulate body weight "set point" are subject to error (Harris and Martin, 1984). Experimentally, the long-term regulation of body weight is demonstrated in over- and underfeeding experiments in which recovery of control body weight is

spontaneous. This has been demonstrated in human and animal models of body weight regulation. There appears to be a blood born factor produced when overfed which influences food intake and adipose tissue metabolism (Harris and Martin, 1986).

The brain is thought to be the main integrator of information about body fat status and the controller of food intake (Bray, 1979; Jeanrenaud, 1985 and Martin et al., 1986). A disruption in normal brain function in the areas that are involved in this regulation results in massive changes in body weight. Brain tumors that disrupt the hypothalamic areas involved in feeding behavior cause morbid obesities (Bray and Gallagher, 1975). An example of this was a 20-year old woman who developed hyperphagia and obesity in a relatively short period of time. It was later learned that a tumor had destroyed the ventromedial hypothalamus and was the primary cause of the obesity (Reeves and Plum, 1969).

Energy Expenditure

The role of energy expenditure in controlling body weight has received much attention. There are two main areas of investigation, physical activity and thermogenesis. The physical activity level of most Americans has decreased over the years as modern conveniences and labor-saving devices became available. It has been shown that this sedentary lifestyle leads to obesity. Most weight control programs include some form of increased physical activity to maintain a reasonable energy expenditure level as well as improve the circulatory system.

Abnormal energy expenditure, involving either basal metabolic rate or thermogenesis, has been implicated in some forms of obesity. It has been proposed that some forms of genetic and dietary obesities are caused by an abnormal energy expenditure by brown fat tissue. Efforts are being made to discover methods of stimulating thermogenesis in order to maintain energy balance.

Neonatal Metabolic and Nutrition Experience

Early exposure to high energy intakes has been shown to produce an increase in adipose cellularity. The greater number of fat cells are maintained throughout life and thereby produce a continuous burden on the individual to maintain normal lipid status. Children who are overweight are twice as likely as normal-weight children to be overweight as adults (Charney et al., 1976). It appears that the early introduction of solid foods and infant formulas that replace breast feeding are contributing factors to obesity in the first year of life (Kramer et al., 1985).

Even before birth, it is possible to influence the development of adipose cells. Infants born of mothers that experience gestational diabetes are larger and contain greater adiposity than infants from normal pregnancies (Bjorntorp et al., 1974). Maternal obesity during pregnancy creates a greater risk of macrosomia (Gross et al., 1980). There is also evidence that maternal weight gain during pregnancy can influence obesity in the offspring (Enzi et al., 1980). It appears that greater nutrient flux through the placenta to the fetus during the later stages of pregnancy is a stimulus for greater adipose cell development.

Endocrine-Neuroendocrine Abnormalities

There are a number of examples of abnormal endocrine or neuroendocrine function that lead to obesity (Bray, 1979; Dallman and Bray, 1986). These cases are usually relatively rare. However, their influence on obesity is quite remarkable. In most of the cases, if the endocrine imbalance was reversed, the obesity was reversed as well. One of the more characterized endocrine abnormalities of genetic origin is the Prader-Willi syndrome. It has many endocrine characteristics of the genetically obese Zucker Fatty rat (Figure 7). It has been proposed that both of these genetic abnormalities are caused by a brain disorder (Bray, 1979; Jeanrenaud, 1985; Martin et al., 1986).

Summary

It is clear that there are many dietary risk factors associated with disease. From the information available, food intake and weight reduction should have a far greater impact on the improvement of health in the general population than any wholesale change in the type of food consumed.

Obesity may be caused by a number of different mechanisms. Research which determines how these different mechanisms may be reversed should allow the development of a focused attack on the specific causes and not the symptoms of obesity.

Figure 7

A COMPARISON OF A GENETIC FORM OF HUMAN OBESITY (PRADER WILLY) WITH AN ANIMAL MODEL (ZUCKER FATTY RAT)

CHARACTERISTICS	PRADER WILLY SYNDROME	ZUCKER OBESE RAT
GENETIC ORIGIN	YES	YES
JUVENILE ONSET	YES	YES
FOOD INTAKE	ELEVATED	ELEVATED
HYPERGLYCEMIC	SOMETIMES	MILD
SERUM INSULIN	ELEVATED	ELEVATED
SERUM GROWTH HORMONE	DECREASED	DECREASED
STATURE	STUNTED	STUNTED
REPRODUCTION	IMPAIRED	IMPAIRED
LIFE SPAN	SHORTENED	SHORTENED

A comparison of a genetic form of human obesity (Prader Willi Syndrome) and an animal model of obesity (Zucker obese rat).

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