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SUMMARY OF A WORKSHOP

FETAL AND INFANT NUTRITION, AND SUSCEPTIBILITY TO OBESITY

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Washington, D.C.

Committee on Nutrition of the Mother and Preschool Child

FOOD AND NUTRITION BOARD
NATIONAL RESEARCH COUNCIL
NATIONAL ACADEMY OF SCIENCES

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NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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SUMMARY OF A WORKSHOP
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Introduction

Growing concern about early childhood obesity and its possible association with later obesity prompted the Committee on Nutrition of the Mother and Preschool Child, Food and Nutrition Board, to sponsor a workshop to review the current state of knowledge on prenatal and early postnatal determinants of obesity and to identify areas in which further research is needed for clarification of the processes of adipose tissue development. Because the subject of obesity involves many disciplines and an all-inclusive conference would be unwieldy, this workshop was limited to the basic biomedical issue of the growth of adipose tissue, its measurement and significance. The underlying question was whether there are periods of adipocyte tissue increase in early life that predispose to the various types of obesity in adolescence or adulthood.

GROWTH AND DIFFERENTIATION OF ADIPOSE TISSUE

Growth of fat cells has been better defined in laboratory animals, particularly rats and guinea pigs, than in humans. E. M. Widdowson and M. R. C. Greenwood opened the workshop by reviewing pertinent animal data. At birth, body fat of the human comprises approximately 16 percent of body weight; of the guinea pig, 10 percent; and of other species studied, 1-4 percent. The percent of fat seems to be unrelated to newborn maturational level of the species or to the length of gestation. Some animals with little body fat at birth deposit fat rapidly just after birth. Intrauterine growth retardation does not seem to be accompanied by a reduction in the percentage of body fat in experimental animals although there is suggestive evidence that this may be the case in human newborns considered small for gestational age.

Undernutrition of the guinea pig during pregnancy results in intrauterine growth retardation, with the offspring small in size and low in total body fat. However, fat as a percent of body weight is not appreciably different from that of larger offspring of well-nourished mothers. Overnutrition during fetal life results in greater size but not a greater percent of body fat or glycogen stores. After birth, undernutrition of the pigs delays growth and fat deposition; if undernutrition is severe there may be a reduction of body fat. Upon refeeding, growth is resumed but the degree of catch up growth is less in animals undernourished for the longest period of time. During rehabilitation, fat is rapidly deposited, with increase in cell size, but without measurable increase in cell number.

Growth of adipose tissue in rats follows the pattern known to occur in most other tissues: a period of rapid cell division (hyperplasia) during which DNA polymerase and thymidine kinase activity are high, followed by a period of combined proliferation and enlargement of cells, and finally a period when only cell enlargement is observed (hypertrophy). Critical periods of cellular increase vary from site to site early in the postnatal period and the exact timing of the growth stages in adipose tissue and susceptibility to environmental influences, however, continue to be controversial. In the genetically obese rat DNA polymerase and thymidine kinase activities are elevated beyond weaning, suggesting a fundamentally different pattern of fat cell proliferation in the obese.

In addition, adipose tissue lipoprotein lipase activity appears to be associated with the lipid-filling stage of adipose tissue development. The onset of increased lipoprotein-lipase activity per adipocyte and predominant localization of lipoprotein lipase activity in the stromal-vascular fraction of tissues during early postnatal development supports the hypothesis that a "bed of preadipocytes" is formed during the postnatal hyperplastic growth phase of the tissue which becomes filled with lipid as a result of lipoprotein lipase provision of free fatty acids for triglyceride synthesis.

Dr. Knittle discussed relationships of adipocyte number and size in obese children, and changes in these patterns with weight reduction. Obese children show a different pattern of development from nonobese children in the number and size of fat cells. Obese children attain at age two levels of fat cells comparable in size to those of nonobese adults; subsequently, increase in fat stores occurs almost exclusively by increases in fat cell number. Nonobese children display little growth in adipose tissue mass from age two until 10 to 12 years of age; at that time cell size and number increase to adult levels. Weight reduction is accompanied by a decrease in cell size, but not cell number.

Evidence from experiments measuring glycerol release of adipocytes in response to epinephrine suggests that obese individuals have altered lipolytic activity compared to nonobese individuals; this response also occurs after weight reduction of obese subjects. The exact mechanism of altered lipolysis is unclear, but its etiology may be related to genetic or early dietary factors.

GENETIC DETERMINANTS

Physiologic and genetic factors in obesity were discussed by R. F. J. Withers, S. M. Garn, and D. L. Coleman. Frequent reference to heritability estimates of fatness has been made in the literature, based on comparisons of parent-child pairs, twins, and siblings. Nevertheless, typical heritability estimates neglect any environmental-genetic interactions, and describe only the proportion of phenotypic variance contributed by the additive component of genetic variance. In light of substantial evidence of genotype-environment interaction, heritability estimates contribute little information that is meaningful to an understanding of the genetics of obesity. Data that may be analyzed using quantitative genetic models would be most helpful in this regard. Noninvasive measures of insulin, lipids, and enzymes are possible examples. These data could give insight into genetic markers associated with obesity, and consequently, the genetics of the obese state.

Parent-child, and sibling correlations in skinfold thickness approximate 0.25, irrespective of sex. There is striking similarity between correlations in skinfold thickness for children and their adoptive parents, with corresponding correlations for children and their biological parents. That social factors and shared environment are important in obesity is further seen in evidence of assortative mating for fatness of individuals, and of adoptive "siblings" tending toward similarities in fatness. Moreover, length of living together seems related to degree of similarity in fatness between spouses.

Genetic determinants of obesity, appetite, and diabetes, have been studied in certain strains of mice, particularly in relation to the satiety centers of the hypothalamus. Based on parabiotic experiments of genetically obese, genetically diabetic, and normal mice, it is suggested that the obese mouse is unable to produce sufficient satiety factor to regulate its food consumption, whereas the diabetic mouse produces this factor, but cannot respond to it. It appears that the diabetic mouse has excess insulin secretion very early in life prior to any hyperphagia or development of obesity, while in the genetically obese mouse, enlarged fat cells and other signs of obesity precede hyperinsulinemia.

ADIPOSE TISSUE DEVELOPMENT AND SOMATIC GROWTH

Measurement of body fat and relationship of adiposity to somatic growth were discussed by A. F. Roche, S. M. Garn, and P. E. Heald. Measurements of subcutaneous fat thickness by roentgenograms and by caliper skinfolds correlate at a level of 0.8 to 0.9 at various body sites. The variation from site to site and from age to age in compressibility of skinfolds creates some errors, possibly related to skin tension, vascularity, and tissue content of water and connective tissue. Nevertheless, of the available methods for measuring subcutaneous fatness, skinfolds measured by calipers are relatively valid, most easily used, noninvasive, and therefore, appropriate for mass studies. In children the best sites for skinform measurements are the triceps, anterior chest, and subscapula. Anterior chest skinfold measurements are meaningful for most ages, but are not often used.

Skinfold thickness increases in both sexes in early infancy followed by a decrease in the post-infancy period. Females then have a steady increase to middle age, with subsequent decrease. In males, skinfold measurements indicate a decrease in fat during early childhood, a temporary increase in early adolescence, and thereafter, an increase at a slower rate than in females.

There is still no convincing evidence that the obese child becomes an obese adult; correlations of weight, weight gain, or skinfold measurements at birth or in the first year with comparable measures at ages 7 to 16 years, have rarely been found to be as high as 0.25.

Based on evidence from the Ten State Nutrition Survey, "obese" children (at or above the 85th percentile) and "lean" children (at or below the 15th percentile) differ in a number of characteristics. Obese children, by these criteria, tend to be taller for age and to have greater lean body mass than lean children. Obese children also tend to be more skeletally mature, including advanced epiphyseal union, than nonobese; and obese girls attain menarche earlier than lean girls. Obese children are more likely to have higher hematocrit, hemoglobin, and serum cholesterol values.

Obese adolescents also are relatively taller and have greater lean body mass. These youths are relatively advanced in skeletal age, and tend to be advanced in maturational age determined from secondary sex characteristics. There is some evidence that individuals who are fat during adolescence tend to have greater transverse bone dimensions, and because of their earlier maturity, may attain somewhat shorter stature as adults. The effect of weight reduction in obese children and adolescents, particularly as it may be associated with possible restriction in growth and maturational progress, is not known.

VULNERABLE OR CRITICAL PERIODS OF GROWTH

Vulnerable periods in brain growth and somatic growth were discussed by Dr. Dobbing. A review of current theories concerning vulnerable periods of somatic growth indicates that a vulnerable or "critical" period of somatic growth exists during which subsequent growth is sensitive to nutritional insult. This vulnerable period, which occurs at different times in different animals, seems closely related to the period of peak velocity weight growth of the brain but not to the period of peak somatic growth. In humans, this vulnerable period probably extends from mid-gestation until well into the second postnatal year. Most of the evidence of a vulnerable period for somatic growth is based on animal studies and concerns undernutrition and growth restriction rather than obesity. Nevertheless, the notion of the existence of critical periods in growth that may affect subsequent development may have many more general implications.

NUTRITIONAL INFLUENCES

The effects of nutrition during the fetal period, infancy, and childhood were summarized by J. Metcoff, P. Rosso, G. P. Ravelli, W. B. Weil, Jr., and S. J. Fomon. Effects of maternal nutrition on human fetal growth and development have been studied by means of multiple regression analyses of a number of maternal variables recorded during pregnancy. These variables include leukocyte enzymes (PFK, G6PDH, PK) and metabolites (ATP, ADP), plasma nutrients (carotene, copper, zinc, choline), 19 plasma amino acids, pregnancy weight gain, smoking, and education. Multiple linear combinations of these variables were significantly correlated with newborn weight and length, and head circumference in 75 mother-baby pairs after adjusting for maternal body size, age, parity, race, and the infant's sex and gestational age. This multivariate approach allows consideration of many variables as predictors of pregnancy outcome, and may prove useful in understanding factors contributive to fetal growth and development.

In rats the peak velocity of fetal growth is correlated with the peak of transport across the placenta of major nutrients such as glucose and amino acids. In contrast, during maternal malnutrition in the rat, the placental transport of glucose and amino acids per g of fetal tissues is lower than in well-fed controls and the expansion of blood volume and deposition of maternal stores are reduced. In the human, the maximum rates of expansion of blood volume, deposition of maternal stores, and placental growth precede by several weeks the maximum rate of fetal growth. Thus, maternal factors that precede the rate of fetal growth may

influence the total influx of nutrients to the fetus. These relationships support the theory that there is a critical period during which availability of nutrients influence fetal growth and development; this period occurs during the last 15 weeks of gestation in humans.

Unusual epidemiologic data have come from the measurements of 19-year-old males in Holland whose mothers had been subjected to food shortages during World War II. An acute food shortage lasting for six months was followed by two years of food rationing. Weights and heights of males born in famine cities and outside famine areas were evaluated relative to the stage of intrauterine development at the time of the acute shortage. When the shortage occurred in the middle of pregnancy, there was a significant increase in the number of young men who were obese at 19 years of age. However, when the shortage occurred late in pregnancy, fewer males than expected were 20 percent or more above their ideal weight for height at 19 years. It may be speculated that undernutrition in mid-pregnancy interfered with development of normal hypothalamic set points and in late pregnancy limited replication of adipocytes.

A prospective study of growth of formula-fed and breast-fed infants indicated that at 112 days of age, formula-fed babies were significantly longer and heavier than those that were breast fed. However, when the same individuals were examined at eight years of age, there were no differences between those breast-fed, and those formula-fed as babies. Correlations of weight-height ratios at 112 days of age with those at eight years were significant (0.4) for formula-fed babies, but were not significant (0.1) for breast-fed babies. Moreover, a re-evaluation of published data on the later effects of early infant feeding suggests no real difference in later weight related to type of milk fed or to early or late introduction of semisolid foods. Thus, these data do not support the hypothesis that fat infants become fat children. There may be need, however, to distinguish between moderate and extreme obesity.

Discussion and Recommendations

It is clear that there is a lack of unanimity regarding definition and classification of obesity. Obesity in the broadest sense is a clinical presentation characterized by excessive fatness; however, there is no consensus as to what constitutes excessive fatness, or how this adiposity is to be measured. The obese state has no unique etiology; it is highly varied as to age of onset, general health, endocrine or metabolic status, and innumerable psychosocial and behavioral concomitants. Any meaningful definition or classification of obesity is therefore difficult to formulate but, nonetheless, is badly needed.

Unfortunately, little is known with certainty regarding the natural history of obesity. To answer many questions related to the development of obesity, longitudinal data are mandatory, but scarce. The effects of childhood eating patterns or rapid changes in weight during childhood on subsequent development of obesity are unknown. Longitudinal investigation of factors associated with normal and abnormal prenatal fat deposition are required. There is only presumptive evidence from cross-sectional studies that individuals who are obese as infants or children become obese adults. Serial investigations of fat cellularity in the first two years of life, and from 8 to 16 years, periods of apparent adipocyte proliferation, may help to identify individuals who may become obese later.

Better and more complete descriptions are needed of normal growth and development of adipose tissue. Proper evaluation of obese individuals is impossible without knowledge of the normal course of development. In this and in other aspects of obesity research, animal studies have much to contribute. Animal studies provide models allowing experimental manipulation, and can provide insight into the nature and timing of nutritional and other events associated with obesity. Many investigations of biochemical or enzymatic indicators associated with adipose tissue metabolism, or of prenatal development of adipose tissue, are often only practicable with experimental animals.

Regarding genetic factors in human obesity, there is little evidence that fatness is genetically controlled, only that fatness is familial. This lack of evidence may be due in part to the use of inappropriate methods in the analyses reported. Heritability estimates from a study of paternal half sibs would enable the separation of the genetic and environmental components of phenotypic variance. Quantitative genetic analyses, however, provide the most promise for understanding the genetics of obesity.

Obesity is not simply a biomedical problem, but is inextricably associated with behavioral, psychological, and social factors. Further, in many instances it is impossible to discern whether many of the psychosocial factors are primary or secondary to the obese state. Clearly, there is need for research regarding not only the biological, but also the behavioral and social factors involved with obesity.

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