SYMPOSIUM: OBESITY

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Some Etiological Factors in Obesity

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Abstract

The frequent occurrence of obesity, which is associated with shortened life expectancy, has made the condition a main topic of research. Simple explanations, such as a reliable correlation between overeating and overweight, are incorrect for the majority of the severely obese. Obesity goes hand in hand with increased lipogenesis, decreased fat mobilization, and metabolic inertia of the triglycerides deposited, which may be related to genetic enzymatic and hormonal factors. From rat studies, one can speculate that fat deposition may be influenced by the individual's reaction to qualitatively different foodstuffs. Although no explanation is as yet possible for the metabolic inertia of depot fat in the obese, some evidence has accumulated which suggests studies of its molecular structure. The obese are capable of adapting to decreased intake more rapidly than normal persons; increased activity can be handled more efficiently than in normal persons, while the metabolic inertia of their triglycerides interferes with their mobilization. No way of overcoming this vicious cycle has as yet been found.

Introduction

TO DEFINE WHETHER or not a person is overweight is, in many instances, extremely difficult, because the opinions as to what constitutes overweight have varied historically, geographically, and esthetically. However, for the subsequent discussion, we do not have to be concerned about the borderline cases; only conditions with severe obesity, the etiology of which is not established, will be examined.

The main reasons for the interest in obesity are its association with shortened life expectancy and increased morbidity. Table I and II published by Dublin and Marks illustrate these points (1). The study included about 26,000 men 20 to 64 years of age, of whom 3,700 died during the period of investigation. It is quite obvious that the death rate of the 3 groups, separated according to height, increased steeply with the degree of overweight; a similar result was obtained in observations on females. In Table II are given statistically significant morbidity data in men 25 to 74 years of age. The relationship to vascular diseases and diabetes is now particularly important because of the frequent occurrence of these diseases in the Western World. Other examiners have pointed out the danger of overweight to hepatic functions (2), to the increased risk in pregnancy and after surgery (3). The question of whether obesity is a main cause of arteriosclerosis, or plays merely a supporting role in its pathogenesis has been discussed elsewhere (4). In any event, the fact that about one-fifth of the total population over 30 years of age in the Western World has varying degrees of overweight (5) has made it a major health hazard (6,7).

TABLE I

Increase in Mortality Rate Over Standard Risks of Men Rated as Overweight According to Height and Weight Groups (ages 20–64 years)[a]

Degree of overweight (% of normal weight)	Short	Medium	Tall
Less than 30	43%	33%	56%
30–39	48	48	77
40–49	88	63	172
50–59	90	180	126
60–74	166	182	

[a] After L. I. Dublin and H. H. Marks. *Mortality Among Insured Overweights in Recent Years,* Recording and Statistical Corporation Press, New York, 1952.

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TABLE II

Statistically Significant Deviations in Causes of Death Among Men Rated for Overweight (25–74 years)

Cause of death	Differences (%) compared to expected incidence
Heart disease (coronary)	+42
Cerebral hemorrhage	+59
Chronic nephritis	+91
Liver and gallbladder cancer	+68
Diabetes	+283
Liver cirrhosis	+149
Appendicitis	+54
Gallstones	+106
Ulcer (stomach and duodenal)	−37
Suicide	−22
Car accidents	+31

Classification of Obesity

The attempts to classify obesity have not been too successful. Gradually it has become apparent that the hypothalamus is the most frequent site of damage in cases in which central nervous system lesions are associated with obesity. It has been possible to produce obese animals by surgical or chemical (gold thioglucose) damage to the hypothalamus and these animals have been a source of important studies. Endocrine disorders (hyperadrenocorticism, some cases of hyperthyroidism, and cases of adenoma of the pancreas) are associated with obesity. Since their relation to fat deposition has been repeatedly discussed (8), and since these cases constitute only a small fraction of the obese, we will not discuss them further.

Among the pronounced cases of obesity with unknown etiology, the physician is often impressed by women with slender hands and feet but extremes of fat deposition over the breasts and abdomen. Other females have enormous fat accumulations on thighs and upper arms with relatively little fat on the body itself. Weight reduction unfortunately usually does not materially affect their extremities. In men, fat deposition is frequently most pronounced in the abdominal region, often producing apron-like extensions. Such men often have spindly legs. If these features are also accompanied by somnolence and cyanosis, one speaks of the Pickwickian type of obesity.

Environmental Factors

In discussions of pathogenesis, attempts have been made to distinguish environmental causes of obesity from inborn defects of metabolism. We will follow this approach and will first discuss so-called environmental factors although we will later try to point out that the division is somewhat artificial.

a) *Socioeconomic Factors.* It has been said that any labor-saving device will increase fat deposition in many people. Brozek et al. (9) demonstrated that the fat content of white-collar workers was higher than that of laborers even though both groups had the same average heights and body weights.

b) *Psychiatric Aspects.* A great deal has been heard about psychiatric aspects of obesity and it is probably true that some people try to drown their frustrations in overeating. Familial influences also are at work in that early identification with the eating habits of the parents could be a factor in the condition (10). However, we agree with Dole (11) that overeating is probably not an important parameter in many cases of severe obesity. Furthermore it does not seem to be certain that marked degrees of overweight have been increasing in the United States despite the rapidly changing socioeconomic conditions (5); this is a further reason why I am inclined to agree with Stunkard (12) that the psychiatric aspects have been unduly overrated in pronounced obesity.

c) *Food Intake.* Not only the amount but also the type of food ingested is intimately related to the amount of fat deposited after the intake of a fixed number of calories. Acceptance of this fact is still handicapped by strict adherence of many examiners to the theories of the German school of nutritionists of the late 19th century. This school introduced the isodynamic principle which claims that protein, carbohydrates and fat can isocalorically replace each other in the diet. Therefore fat deposition was thought to be mainly influenced by caloric intake and no allowance was made for the possible influence of qualitatively different foodstuffs on adaptive changes during food restriction.

An undertaker in London, William Banting, first noted about one hundred years ago that carbohydrate restriction led to best results in reducing diets. This has often been corroborated; thus Kekwick and Pawan (13) demonstrated that a diet containing 1,000 calories led to more rapid weight losses when it was mainly composed of fat and protein rather than carbohydrate. On the other hand, unlimited access to a high fat diet leads in rats to high body weights (14,15). The effects of the restriction of fats and proteins has been studied by their effects on lipogenesis in the fat depots in vivo. It was found that carbohydrates stimulate and fats depress lipogenesis (16). The influence of various fats on body weight, food consumption, life span and other parameters in rats was studied, and some of the results have been reported before (17).

Carefully selected, matching groups of male rats of the Columbia Sherman strain were placed on the complete, purified diet given in Table III. The fats were used either fresh or after 40 hr of aeration of 60C at an airflow of 1 liter/min. Body weights were taken at least once monthly; weekly food intakes were determined at intervals of one to three months. The food intakes given in Table IV constitute the average intakes of the determinations after the animals were over 200 days old. The studies with cottonseed and olive oils and beef and chicken fats have been completed. Those with butter, lard, and corn and soybean oils have been going on for one year.

The animals reached their maximum weights at widely different times. In the statistical interpretation of the results two groups were formed from the rats fed each diet according to whether they attained their maximum weight early or late for their group. Table IV gives averages for these groups of life span, maximum weight, age when maximum weight was attained, and food intake.

Table IVA shows that, among rats reaching their

TABLE III

Composition of the Purified Diet

	%		%
Casein	30	Salt mixture, USP XIII[a]	3.5
Dextrose	44	Calcium carbonate	0.5
Cellulose	2	Fat	20

	mg/kg		mg/kg
Choline dihydrogen citrate	1000	Folic acid	2.5
Inositol	1000	Biotin	.025
p-Aminobenzoic acid	300	Ascorbic acid	25
Nicotinamide	100	Vitamin K	10
Thiamine · HCl	2	a-Tocopheryl acetate	50
Pyridoxine · HCl	4	Free a-Tocopherol	10
Ca pantothenate	10	b-Carotene	5
Vit. B_{12} (.1% trituration)	5	Vitamin D_2	.5
Riboflavin	4		

[a] This salt mixture contains virtually no iodine.

maximum weight late, various fats influenced the animals' life span in that there were significant differences among some of the groups. There were distinct associations between weight and life span. Comparisons of Table IVA and B shows that the earlier attainment of maximum weight was associated with significantly shortened life span. This would not be particularly important if the weight gain of the groups had been curtailed by their shorter life span. Actually, however, in most groups, there was little or no differences in the maximum weight attained by the "early" and "late" groups. Therefore it appears that the animals which gained weight faster died earlier. This is in agreement with McCay's studies (18) in which a longer life span was noted when the development of higher body weights was delayed by restricted feeding. This can also be concluded from the fact that, among the rats reaching their maximum weights later (Table IVA) those fed oxidized cottonseed oil reached the highest weights and had the shortest life span. The opposite was true for those fed fresh beef fat.

Although there were highly significant differences in the food intakes of the various groups, no positive associations between food intake and maximum weight were noted. The rats fed fresh beef fat (Table IVA) had, on the average, the highest food intake and the lowest maximum weights.

The data for the animals which reached their maximum weights earlier (Table IVB) are, in general, in agreement with those of Table IVA, but the differences are less pronounced. The sequence of the groups in Table IVA and B were similar to the extent that the same four groups were contained in the upper and lower parts of Tables IVA and B. Again it is noticeable that early attainment of maximum weight was associated with shortened life span. Again there were significant differences in food intakes of the groups but no positive relationship to weight or life span.

These studies showed that the type of fat ingested influenced body weight and life expectancy and that higher weight was associated with a shorter life span. These general conclusions are in good agreement with observations on humans. Whether or not the conclusions as to the desirability of specific natural fats can also be applied to humans remains to be seen.

We have previously reported (17) that the average weights of the groups fed the various fats was approximately 500 g after 10 months of feeding. In Table V are given the percentages of the heavier animals in each group (weighing 600 g or more). The results (Table V) are given in two parts, because the animals described in Table VB were studied two years after those given in Table VA. Otherwise, conditions were kept as similar as possible as to selection of the rats and their distribution into groups. The second experimental series was kept in the same room under the same conditions as the first.

In the first series (Table VA) the number of rats with weights of at least 600 g was significantly higher among those eating fresh cottonseed oil than among those fed olive oil or chicken fat (P less than 0.01). In the second series feeding of soybean oil was associated with the highest incidence of heavy rats. A chi-square calculation (using Yates' correction) comparing the animals fed fresh lard with those fed fresh soybean oil gave a P of less than 0.05. At a later age, there were many heavy rats among the groups fed corn oil. In view of these results, one may speculate

TABLE IV

Influence of Dietary Fat on Life Span, Maximum Weight Attained, Age when Maximum Weight Was Reached, and Food Intake in Rats on a Purified Diet Containing Different Fats (± Values are Standard Errors)

A

Late [a] attainment of maximum weight

Fat	No. in group	Age at maximum wt (days)	Life span (days)	Maximum weight (g)	Food intake g/week
FBe	7	702±46.1	809±26.4	616±40.1	116±7.2
OOO	11	653±21.6	787±26.7	629±26.6	97±2.0
FCh	7	680±29.4	786±17.8	663±34.0	95±3.3
OCh	8	634±24.6	755±13.3	649±29.5	100±5.7
OBe	7	616±40.4	754±17.5	645±26.7	111±6.4
FCSO	11	649±33.6	734±37.1	707±35.7	107±3.8
FOO	11	629±16.4	713±18.1	660±18.1	101±2.4
OCSO	11	567±21.8	663±26.6	710±25.6	107±1.7

B

Early [a] attainment of maximum weight

FCh	7	474±29.2	706±43.0	618±20.9	105±5.7
OOO	11	478±17.9	694±20.0	611±23.2	92±2.7
OCh	8	487±42.3	652±34.8	593±41.4	99±10.0
FBe	7	449±32.8	641±76.4	659±39.8	125±6.0
FCSO	10	375±10.3	637±36.4	681±24.8	104±2.0
OCSO	11	400±31.8	591±54.4	614±34.8	107±2.2
OBe	7	419±25.8	586±53.4	625±27.4	119±5.9
FOO	11	418±24.4	560±50.4	595±18.3	97±2.1

The prefix F stands for fresh and O, for oxidized fat; Be, beef fat; Ch, chicken fat; OO Olive oil; CSO, cottonseed oil.

[a] Members of each group were ranked according to the age at which they attained their maximum weight and divided into two equal groups.

that linoleate promotes the deposition of excess body fat. This is supported by studies of Jacquot et al. (19) which showed that mobilization of depot fat in the rat is more difficult if it contains a high level of linoleate. Oxidation was associated with statistically significant differences compared to the fresh fat only in the case of butter, where feeding of the oxidized material was associated with fewer heavy animals.

In a study by Barboriak et al. (20) in which corn oil, cottonseed oil, coconut oil, Crisco, lard and butter were fed to rats at a level of 60% in the diet, it was found that lard and Crisco produced the heaviest average weights.

From the standpoint of human obesity it is of interest that fat deposition differs with different dietary fats, but it cannot be taken for granted that the same fats will promote similar results in humans and rats. The circumstance that only some of the rats achieved high weights may deserve attention. Genetic factors may be at work and this speculation is supported by the fact that selective breeding has produced strains of rats with high and low efficiency of food utilization (21). It could be in line with present trends in genetics if one were to assume that some animals have an anlage to develop obesity when subjected to the proper stimulus. Inasmuch as the necessary stimulus probably varies from animal to animal, the separation of environmental from "inborn" factors as well as the attempt to contrast "simple" obesity with "metabolic" obesity are oversimplifications.

TABLE V

Number and Percentage of Heavy Male Rats (600 g and Over) in Groups Fed Various Fats for 45 Weeks After Weaning

A

Experiments during 1962

Dietary fat	Fresh	Oxidized
Cottonseed oil	17/33=52%	9/33=27%
Olive oil	3/33= 9%	0/33= 0%
Chicken fat	0/20= 0%	4/20=20%
Beef fat	6/20=30%	5/20=25%

B

Experiments during 1964

Corn oil	5/19=26%	9/20=45%
Soybean oil	10/20=50%	10/20=50%
Butter	13/34=38%	4/34=12%
Lard	7/36=19%	4/16=25%

Inborn Defects

Inborn defects related to obesity have been noted in these overlapping general areas: a) heredity, b) adaptation to food restriction, c) metabolism of adipose tissue, d) metabolic changes possibly related to enzymes.

a) *Heredity.* The question of whether obesity in humans has a genetic background is of considerable practical importance. Although it is a common experience that fat parents often have fat children, it has been claimed by some that this may be due to early identification wtih the parents or by learning their eating habits, rather than due to genetic factors; but the frequent occurrence of constitutional types associated with obesity can hardly be due to environmental influences (22).

A number of human diseases have been unquestionably linked to genetic disturbances of lipid metabolism. Nieman-Pick and Tay-Sachs diseases are recessively inherited disturbances associated with phospholipid accumulations based upon the absence of enzymes necessary for phospholipid catabolism. Similarly explained are Gaucher's disease (cerebroside accumulation) and Schüller-Christian disease (cholesterol deposits). There are some rare conditions in man with abnormally high triglyceride accumulation, the genetic character of which has been established: monstrous infantile obesity; congenital hypoglycemia due to lack of alpha cells; sex limited steatopygia in Hottentot women. Studies in twins suggest that there may be a genetic factor in the more common forms of obesity (23), and Tepperman (24) has tried to give some biochemical background to this theory.

Further support for genetic influence in obesity was obtained in animal studies. Genetically obese strains were noted in mice, rats, dogs, and pigs. A yellow strain of genetically obese mice, originally observed by Danforth (25) is characterized by hyperglycemia, sterility, diabetes and reduced life span. Inasmuch as this syndrome is quite similar to that observed in many obese humans, it is of importance that the disease has been shown to be caused by a recessive mendelian gene (26). On the basis of these facts, various authors have assumed that excessive triglyceride deposition in humans may often be related to a genetic aberration of some enzyme systems (23).

b) *Adaptation to Restricted Food Intake.* Gradually a large body of evidence has accumulated proving that the mammalian organism is able to adapt its utilization of food to previous experiences in food intake; in general, the response to food restriction is a more efficient utilization of the food available. It has been shown that obese people given a restricted intake first lose weight but soon are able to maintain their lower weight on the reduced intake (27). In studies of the energy requirements of soldiers for simple tasks, it became evident that there were wide variations in energy utilization (28,29). Of considerable interest for the understanding of obesity are the observations that obese childern in an English orphanage ate less than their nonobese mates (30) and a similar observation for obese girls (who may, however, have been less active) (31).

Swift and French (32) noted in rats that reduction of their food intake to less than one-half of their freely chosen intake first produced weight loss followed by weight maintenance at the lower level and finally renewed weight gains. Quimby (33) found that rats gradually maintain their weights on roughly 30% less than their freely chosen intake. We confirmed this (34) and noted that the animal's capacity for adaptation is also influenced by the kind of food offered. The animals needed more of a high-carbohydrate diet than of diets high in protein or fat to maintain weight equilibrium (35). The type of fat influenced the results in that a larger amount of a diet containing saturated medium chain triglycerides (MCT) was necessary to permit weight maintenance, than of one containing lard. When the diet contained a highly oxidized fat, no reduction of the requirements for weight maintenance occurred (36).

An important contribution was made by Jacquot's group (37), who found that periodic withdrawal of food from rats led to a greater weight increase and nitrogen retention than in the controls, when the same amount of food was offered. Rats fed ad libitum were more damaged as a consequence of food withdrawal than animals with previous experience of food withdrawal. In Heggeness' studies, caloric restriction was followed by enhanced lipid accumulation ad libitum feeding (38).

Tremolieres et al. (39) found that the processes of adaptation to food withdrawal are different in obese and nonobese persons. The obese show a more rapid and intense reduction in caloric expenditures than normal persons placed on a low caloric diet. Kekwick and Pawan (40) reported that obese persons convert carbohydrate to fat more easily than normal individuals.

The constant variations of the adaptive state in relation to food intake are a corollary of the dynamic quality of all metabolic processes. One should remember that the composition of the diet influences the adaptive state and that the obese are capable of adaptation to low food intake more easily than normal persons.

c) *Adipose Tissues.* The embryonal development of adipose tissues suggests that these tissues form a system of specific organs responsible for fat synthesis and mobilization (40). Some of the properties of the adipose tissues lend themselves to speculations about some possible metabolic changes in obesity. Neutral fat is a major constituent of the body; fat people die, on the average, sooner; obese people live longer if they reduce their body fat and keep their weight down; underfed animals have, relatively, little fat and have a long life expectancy; the neutral fat of old people and old animals increases more steeply than any other tissue. It is therefore evident that there exists a correlation between high neutral fat content and shortened life expectancy.

The studies of Schoenheimer and Rittenberg (42) with labelled fat showed that dietary fat is deposited in adipose tissue before it can be utilized, even when the amount of dietary fat is small; only fat from depots is oxidized. A large part of the dietary carbohydrate is converted to fatty acids (43), and the main site of fatty acid synthesis can now be assumed to be the fat cell within the adipose tissue (44), where fatty acid synthesis had first been described by Shapiro and Wertheimer (45).

Hormonal influences are involved in the synthesis and mobilization of fatty acids within the adipose tissues. In some fashion, all hormones seem to contribute to these processes. Easily demonstrable is the stimulating action on fatty acid release by adrenalin in vitro and in vivo (46). It is probably of considerable interest that Raulin and Launay have shown that the in vitro release of fatty acids under the in-

fluence of epinephrina is not random but that linoleate is preferentially retained by the tissues (47). On the other hand, insulin has been shown by Hausberger and Hausberger to enhance both fatty acid and triglyceride synthesis (48).

The influence of insulin on fat deposition is apparent because humans with pancreas adenoma are fat, and congenitally obese mice have hypertrophic, insulin-producing islets of Langerhans (8). Yet there is some mystery to the hormonal influence on lipogenesis and fat mobilization because most patients with diabetes are obese, and this discrepancy between hypoinsulinism and fat deposition is not well explained.

The fact that fatty acids are arranged by the adipose tissues into triglycerides having a characteristic structure (49) has perhaps not been sufficiently appreciated. One may ask whether Schoenheimer and Rittenberg's results could be explained by the necessary conversion of dietary fatty acids into triglycerides of a characteristic structure. Raulin and Launay's studies would support such a speculation. Could this be an explanation for the observation of Salcedo and Stetten (50) that the deposition of dietary fatty acids was normal in genetically obese mice but the metabolism of the resulting triglycerides was retarded, and for the report by Leboeuf et al. (50) that the action of epinephrine and insulin on adipose tissue was reduced in genetically obese mice? Therefore one would like to know whether the adipose tissues of genetically obese mice are made up of triglycerides with structural arrangements which reduce their metabolic turnover and thus favor their accumulation. This may have to be the case without changes in the over-all fatty acid composition of the adipose tissues since the absence of such changes in human obesity has been pointed out by Hirsh et al. (52). Differences in structural arrangements may also suggest explanations for the different effect of hormones on triglycerides from various parts of the body (46) and for the fact that the fat accumulations of various parts of the body respond quite differently to reducing diets.

d) *Enzymes.* Evidence has accumulated suggesting that obesity is related to enzymatic defects. Haagensen (53) has reported that the phosphorylase activity of the adipose tissue of obese persons is several times that of normal ones. Mayer (8) noted that congenitally obese mice have a high liver glycogen turnover and high levels of liver phosphorylase. Adaptive enzymatic changes leading to suppression of fatty acid release have been repeatedly demonstrated in starvation (54–56). Even if these changes were not accentuated in obesity they would counteract the effort of the obese to shed their fat by reduction of intake.

There are other metabolic differences between normal and obese persons. A striking difference in nutritional ketosis was found by Kekwick and Pawan (40). Normal persons develop marked hyperketonemia, hyperketonuria, hypoglycemia, and a pronounced negative nitrogen balance a few days after the sustained intake of a 1,000 calorie diet containing 90% fat. The obese showed little ketosis, essentially normal blood sugar levels, and little loss of protein. They appeared to be able to convert fat to carbohydrate more efficiently than normal persons.

The urine of obese persons maintained on a carbohydrate low, reducing diet contained a polypeptide the injection of which in mice produced weight loss and fat depletion (57). The presence of increased amounts of a substance in the serum of obese persons preventing diuresis in rats has repeatedly been reported (58–60).

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