The Obese Hyperglycemic Syndrome of Mice as an Example of "Metabolic" Obesity

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THE ASSIGNED subject of this report is the obese hyperglycemic syndrome and its genetic, metabolic and physiologic effects. To give a comprehensive review of this interesting syndrome would entail several chapters, considering the amount of information accumulated. It therefore, appeared to be more in keeping with the general character of this symposium to use this syndrome simply as a typical illustration of the concept of "metabolic obesity" as opposed to "regulatory obesity."

I have been asked on numerous occasions for a comprehensive list of research papers on studies of the obese hyperglycemic syndrome carried out in our laboratory; this list is presented separately as a bibliography, which also incorporates some of the more significant reports of studies made elsewhere on the subject. The references given in the text are for general references on the subject of obesity and are obviously by no means exhaustive nor even perhaps entirely representative. No effort has been made to document every statement in the references.

The development of the various forms of obesity can be considered from either the point of view of etiology or of pathogenesis. The etiologic approach has been developed at length in a previous review[1] in which genetic, traumatic and environmental factors were distinghished (Fig. 1). Obviously, such a distinction, although useful, necessitates a certain degree of oversimplification; in order for obesity to develop, there has to be permissive interaction of genetic and of environmental factors, or of traumatic factors with genetic and environmental background. However, this simplification provides a useful classification for singling out the characteristic element in the etiology. Table 1 is an adaptation of a table given in a more extensive review[2] which includes references for the different types cited.

My associates and I have also grouped obesities into two categories, these being regulatory and metabolic. We found that a general distinction could be made between regulatory obesities, in which the primary impairment is of the central mechanism regulating food intake, and metabolic obesities, in which the primary lesion is an inborn or acquired error in the metabolism of tissues, *per se*. In the first case, habitual hyperphagia may lead to secondary metabolic abnormalities. In the second case, peripheral metabolic dysfunction may in turn interfere with the proper function of the central nervous system. This difference has been demonstrated in our laboratory by comparisons between different types of obesity in mice.

Regulatory obesities are exemplified by the hypothalamic obesities induced either by surgical (stereotaxic) bilateral destructions in the ventromedial nuclei[3] or by extensive symmetrical destructions in the ventromedial area after administration of goldthioglucose.[4] Mice with these syndromes show hyperphagia and may gain up to four times their normal weights. Their rate of lipogenesis and cholesterogenesis (as measured by incorporation of radioacetate into hepatic and extrahepatic fatty acids and cholesterol, *in vivo* and *in vitro*) increases in proportion to the amount they are allowed to overeat. Fasting brings lipogenesis down to normal fasted levels. Their

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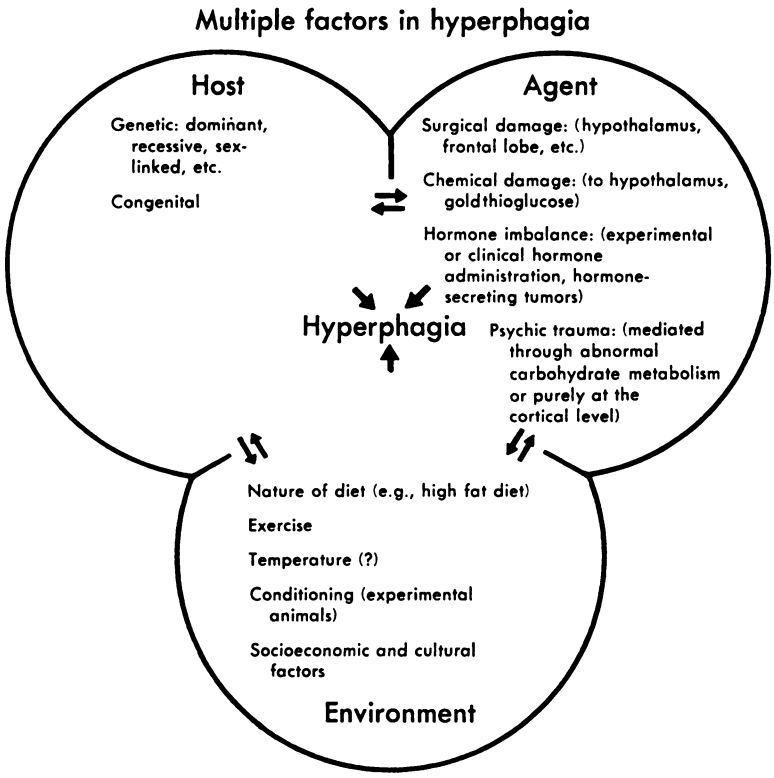

FIG. 1. A schematic view of constitutional (genetic and congenital), traumatic and environmental factors in the etiology of obesity. (From: MAYER, J. Etiology and pathogenesis of obesity.) *Postgrad. Med.*, 25: 631, 1959.

rate of absorption of glucose by the intestine increases, but this appears to be a secondary result of hyperphagia. When such obese animals are reduced by fasting, their body composition returns to normal as their weight returns to normal. Animals made hyperphagic by conditioning are also examples of regulatory obesity.

The situation in metabolic obesities such as the hereditary obese hyperglycemic syndrome or obesity due to grafting of ACTH-secreting pituitary tumors is in striking contrast to that in regulatory obesities (Table II).

The obesity of mice with the hereditary obese hyperglycemic syndrome is as extreme as that observed in mice of the hypothalamic types. However, their hyperphagia is usually less pronounced than the latter's, since their caloric surplus is partially due to their relative inactivity. In the first group of mice, either marked hyperglycemia already exists or it is readily elicited by the administration of growth hormone; whereas the hormone has little or no effect on the levels of blood glucose in normal littermates or in littermates made obese by hypothalamic lesions induced by stereotaxis or by administration of goldthioglucose. Mice with the obese hyperglycemic syndrome show marked hypercholesterolemia. In addition, they evince a variety of atypical responses to the administration of hormones. Although their means of "physical" defense against cold (such as pilo-erection and vasoconstriction) are intact, the animals are incapable of raising their metabolism when exposed to low temperatures and therefore die rapidly.

Mice with the obese hyperglycemic syndrome show considerably hypertrophied islets of Langerhans with increased numbers of both alpha and beta cells, increased pancreatic insulin and glucagon content and increased circulating insulin. The most recent findings concerning hormone concentrations support a previously postulated etiology of primary pancre-

TABLE I
Types of Obesity

In Mice

Genetic:
"Yellow" obesity, associated with coat color: heterozygous, dominant character; normal mating. "Hereditary obese hyperglycemic syndrome"; homozygous, recessive character associated with absence of mating. "NZO" obesity; homozygous recessive character, normal mating.
Of hypothalamic origin:
Spontaneous; surgically induced; induced by gold-thioglucose.
Of endocrine origin:
Caused by grafting of pituitary tumors secreting adrenocorticotrophic hormone.
Otherwise induced:
By high-fat diet.

In Rats

Genetic:
Associated with diabetes.
Of hypothalamic origin:
Induced by bilateral or unilateral lesions.
Of other central nervous system origin:
From frontal lobe damage.
Of endocrine origin:
From hypertrophy of adrenal cortical tissue; from prolonged treatment with protamine zinc insulin, or insulin with forced feeding; after thyroidectomy with hypothalamic lesions or with forced feeding.
Otherwise induced:
By immobilization; by high-fat diet; by conditioning.

In Dogs

Genetic:
In the Shetland sheepdog, recessive character.
Of hypothalamic origin:
Spontaneous; surgically induced; due to paraventricular degeneration caused by corticotrophin or cortisone.
Otherwise induced:
By immobilization

In Monkeys

Of hypothalamic origin:
Surgically induced.
Of other central nervous system origin:
Surgically induced by lesions of the thalamus.

In Farm Animals

Genetic:
In strains selectively bred for fat, in particular, pigs bred for lard.
Of endocrine origin:
Induced by castration and by estrogens in the fowl; by castration and implants of estrogens in male cattle.
Otherwise induced:
By immobilization in pigs, cattle and geese; by forced feeding in geese for production of foie gras.

In Man

Genetic:
A multiplicity of genes have been studied by Newman, von Vershuer, Bauer, Gurney, Rony, Angel and others; in congenital adipose macrosomia; in monstrous infantile obesity; associated with Laurence Moon Biedl syndrome; associated with hyperostosis frontalis interna; associated with von Gierke's disease; in familial hypoglycemosis (congenital lack of alpha cells).
Of hypothalamic origin:
In dystrophia adiposogenitalis, with discrete or diffuse hypothalamic injury; occasionally with panhypopituitarism and narcolepsy; Kleine Levin syndrome.
Of other central nervous system origin:
After frontal lobotomy; in association with cortical lesions, in particular, bilateral frontal lesions
Of endocrine origin:
With insulin-producing adenoma of the islets of Langerhans, with diffuse hyperplasia of the islets, and in association with diabetes; with chromophobe adenoma of the pituitary without hypothalamic injury; in Cushing's syndrome (hyperglycocorticoidism); from treatment with cortisone or adrenocorticotropic hormone; in the Bongiovanni Eisenmenger syndrome. In disorders of the reproductive system: gynandrism and gynism, aspermatogenic gynecomastia without aleydigism; male hypogonadism (sometimes with bulimia), postpuberal castration, menopause, ovarian disorder, paradoxical (Gilbert Dreyfus) disorder.
Otherwise induced:
By immobilization in adults and children; by psychic disturbance; by social and cultural pressure.

atic dysfunction, namely, increased secretion of insulin and probably increased secretion of glucagon. Such an etiology is supported by the fact that obese hyperglycemic mice show a six-fold increase in the rate of hepatic glycogen turnover and in hepatic phosphorylase activity. (Glucagon is known to activate hepatic phosphorylase activity.) Of particularly critical importance in the definition of metabolic obesity are the facts that in this syndrome, fasted rates of lipogenesis are increased over the fasted normal rates; fasting does not cause hyperketonemia; and reducing the animals to normal weight by underfeeding them does not bring body composition back to normal, but leaves them with a fat content still considerably greater than the normal fat content at the expense of non-fat tissues.

It is interesting to note that another type of genetic obesity in mice, also associated with hyperglycemia, has been described recently

TABLE II
Comparison Between Regulatory and Metabolic Obesities in Mice from the Same Litter

Object of Comparison	Obese Hyperglycemic Syndrome (Metabolic)	"Goldthioglucose Obesity" (Regulatory)
Etiology	Mendelian recessive	1 mg./gm. goldthioglucose
Pathology and mechanism	Pancreatic dysfunction, hyperplasia of islets of Langerhans, increased insulin and glucagon secretion.	Hypothalamic lesions: destruction of cells regulating intake in ventromedial area
Energy balance	Positive during moderate hyperphagia, moderate or small increase in O_2 consumption, activity is drastically decreased	Positive during considerable hyperphagia
Effect of type of diet	Maximum weight gain on high carbohydrate, less on protein, less or decreased on high fat.	Maximum weight gain on high fat diet, less on carbohydrate, decreased on high fat
Effect of weight reduction	Body composition remains obese: i.e. animal loses nitrogen as well as fat, but is still obese when weight is normal or below normal.	Brings body composition back to normal
Resistance to cold	Drastically reduced.	Normal
Blood glucose levels	Generally hyperglycemic; further increased by growth hormone, etc.	Normal
Total levels of blood lipids	Elevated	Elevated
Blood cholesterol levels	Elevated; further elevated by growth hormone, etc.	Normal
Effect of administration of hormones	Abnormal sensitivity to hyperglycemic effects of growth hormone, glucagon, etc. Increased resistance to insulin.	Normal
Mating behavior	Absent	Normal, though less frequent.
Lipogenesis *in vivo*	Increased with hyperphagia and increased during fasting. Fatty acids are broken down and resynthesized abnormally fast.	Increased with hyperphagia, normal during fasting. Normal fatty acid breakdown.
Hepatic lipogenesis *in vitro*	Increased with hyperphagia and increased during fasting.	Increased with hyperphagia, normal during fasting.
Adipose tissue metabolism	Glucose oxidation half of normal, impaired pyruvate metabolism	Glucose oxidation normal, pyruvate metabolism normal
Cholesterogenesis *in vivo*	Increased during fasting	Normal during fasting
Acetate pool and turnover	Increased pool; the rate of turnover was considerably increased	Normal
Liver glycogen turnover	Considerably increased	
Enzymatic activities	Increased liver phosphorylase	Normal phosphorylase
Intestinal absorption	Increased in proportion to increase in hyperphagia	Increased in proportion to increase in hyperphagia
Body composition and the size of specific organs	High body fat, decreased protein, cholesterol content increased with weight, enlarged liver, heart, pancreas, thymus, adrenals; decreased uteri, ovaries, brain.	High body fat, slightly increased protein; cholesterol content normal; enlarged liver, kidneys, ovaries and uteri
Retention of steroid hormones	Increased in proportion to increase in body fat	Increased in proportion to increase in body fat
Ketone levels of fed animals	Slightly increased	Slightly increased
Effect of fasting on levels of blood ketones	Decreased	Normal elevation of levels of blood ketones

by workers in New Zealand.[5] These "NZO mice" exhibit a syndrome which, in spite of certain resemblances, is different from the hereditary obese hyperglycemic syndrome. First of all, NZO mice mate and produce offspring in contrast to the mice we used which were obtained by mating non-obese carriers of the obese gene or by artificial insemination or ovum transplantation. Extensive metabolic studies have not yet been published by the discoverers of this syndrome but reaction of the levels of blood glucose to fasting appears quite

different in these animals. The usually high blood sugar levels in NZO mice may go even higher during fasting, instead of going down rapidly when food is withdrawn, as they do in mice with the hereditary obese hyperglycemic syndrome. In the NZO mice, low glucose values are observed during pregnancy, and very low values at parturition. Like the hereditarily obese hyperglycemic mice, the NZO mice show insulin resistance.

Mice made obese by grafting ACTH-secreting tumors evince a number of metabolic abnormalities. Levels of blood glucose are high in some of the animals. The blood sugars of all such mice show a remarkable stability under fasting conditions. Levels of liver glycogen also remain higher than normal under fasting conditions, doubtless reflecting more active gluconeogenesis because of increase in circulating corticosteroids. Hepatic glucose-6-phosphatase activity is increased while phosphorylase activity is normal, unlike the finding in the obese hyperglycemic syndrome.[6] As in other forms of metabolic obesity (and characteristic of the class), the rate of lipogenesis in these animals during fasting is greater than that in normal animals during fasting.[7,8] When these animals are reduced to normal weight, their fat content is still much higher than normal,[9] which is a typical characteristic of metabolic obesities. Another difference between regulatory and metabolic obesities is that the animals with the metabolic obesities tested thus far fail to show the normal rise in blood ketones which accompanies starvation.

Behavioral studies also emphasize the difference between regulatory and metabolic obesities in mice. Regulatory and metabolic types react differently to different diets. Similarly, the association with pathologic conditions differs between the two classes. This has been analyzed, in terms of the complex interrelationships between various types of obesity and diabetes, in a recent review on hyperglycemia.[10]

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