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Normal Iodine Uptake and Anoxia Resistance Accompanying Apparent Hypometabolism in Hereditary Obese-Hyperglycemic Syndrome.*† (19865)

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The hereditary obese-hyperglycemic syndrome of mice is a recessive Mendelian entity characterized by an adult weight up to 3 to 4 times the normal, sterility(1), high blood sugar levels and glucosuria associated with insulin resistance(2), atrophy and ulcers of the skin, enlarged islets of Langerhans(3), increased food intake and modified food choices (4), decreased spontaneous activity(5), relatively low oxygen consumption(6), and a number of atypical reactions to hormonal and dietary treatments(7). The obese animals also show decreased oxidation of administered acetate and an increased conversion of acetate to fatty acids(8). The possible relation of hyperglycemia to a primary biochemical block has been discussed(6). Its etiological significance as regards hyperphagia has also been examined(9,10). Of special relevance to the study reported here are the following observations: the total basal oxygen consumption of obese mice is not higher than that of the non-obese animals, in spite of the fact that they weigh twice or 3 times the non-obese average(6). On a body surface basis, the basal metabolic rate of the obese animals can be calculated as 40 to 50% below normal. The low oxygen consumption of the obese animals is accompanied by normal fasting respiratory quotients, somewhat elevated non-fasting respiratory quotients(7). Obese animals are unusually sensitive to thyroxine from the standpoints of increased oxygen consumption, weight loss and toxicity(7). Serum and tissue cholesterol levels are high(6,7). As noted above, there is decreased spontaneous activity(5). These findings could be construed as suggesting hypothyroidism. On the other hand, the histological picture of the thyroid of obese animals is normal(3). Administration of thiouracil to non-obese animals, although it decreases their oxygen consumption, fails to reproduce any part of the obese-hyperglycemic syndrome(7). Finally, neither hyperphagia nor insulin resistance are generally associated with hypothyroidism.

Because of the conflicting lines of interpretation with respect to thyroid function in these obese mice, it appeared of importance to directly assess the physiological status of the thyroid by determination of radioactive iodine uptake. It also seemed of interest to compare metabolic rates of obese and non-obese animals on a basis more independent of body size. The propriety of comparing metabolic rates on a body surface basis when dealing with animals of widely different fat content has been questioned in a previous study(6). The anoxia method(11-14) which compares the relative degree of dependence of animals on oxygen tension has been shown to be de-

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TABLE I. Uptake of Radioactive Iodine by the Thyroid Gland of Obese and Non-Obese Mice.

Exp. No.	Exp. animal	Body wt	Interval after inj. (hr)	I^{131} uptake (% of inj. dose)
1	Non-obese (7)	20-30	18	4.7±1.1
	Obese (7)	38-58		5.7±1.6
2	Non-obese (7)	22-28	30	14.8±5
	Obese (7)	28-50		12 ±2.2

Figures after ± signs are stand. dev.

pendent on metabolic rates. For example, thyroxine decreases, while thiouracil increases the resistance to anoxia of normal animals.

Methods and results. Fourteen young obese animals, and 14 controls of the same age and sex distribution were used in the iodine uptake determinations. The animals had been maintained on a diet of Purina Lab Chow, in individual cages at constant temperature. All animals were given a single intraperitoneal injection of one microcurie of carrier-free I^{131}. The mice were kept in raised cages to prevent access to feces. Eighteen or 30 hours after injection, the mice were anesthetized with ether, exsanguinated, and the thyroid glands were carefully dissected out and freed of extraneous tissue with the aid of a binocular microscope. The glands were digested in 1 ml 2N NaOH, diluted to a convenient volume, and aliquots were counted with a thin mica end window Geiger-Muller counter.

The uptake of radioactive iodine by the thyroids of the obese and non-obese mice is shown in Table I. It will be seen that there is no significant difference in the radioactive uptake of the thyroids of the two groups of mice.

Ten animals, 5 obese and 5 non-obese of the same age and sex distribution were used in the anoxia test. They were confined in a closed container (desiccator). The carbon dioxide produced was fixed by a solution of concentrated alkali. All animals, whether obese or non-obese, died between 92 and 100 minutes after the beginning of the experiment. Within this interval, no difference in duration of survival attributable to obesity could be observed. Average survival was 96 minutes for both groups.

Discussion. The results of the radioiodine uptake experiment constitute additional and fairly conclusive confirmation of the normalcy of thyroid function in these obese animals. The anoxia test, similarly, suggests that active tissues, in both obese and non-obese animals, are equally dependent on oxygen tension and have presumably comparable metabolic rates. These results therefore confirm histological evidence(3) as well as the interpretation of the negative results of thiouracil administration to non-obese animals(7). High cholesterol levels are difficult to interpret in the presence of diabetic-like conditions. Sensitivity to thyroxin is not necessarily related to hypothyroidism.

Finally, the results of the anoxia test bring additional evidence to support the contention that relating metabolic rates to either body weight or body surface when comparing obese and non-obese animals is meaningless. The protein and water contents of obese and non-obese are similar. The excess weight carried by obese mice can be accounted for to the extent of about 90% by fat(15). The fact that this increase in body weight or in body surface is accompanied by no increase in oxygen consumption, and that the anoxia test indicates that active tissues have comparable metabolic intensities in both groups, simply testifies to the almost complete metabolic inertia of depot fat in this syndrome.

Summary. In the hereditary obese hyperglycemic syndrome of mice, radioactive iodine uptake is normal. Similarly, the anoxia test reveals no difference in dependence on oxygen tension between obese and non-obese mice. The significance of these findings is discussed with respect to the etiology of the syndrome, and to the extension of the concept of basal metabolic rate to obese animals.

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Application of Perfused Rat Liver Preparation to Isotopic Study. (19866)

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It seems a reasonable assumption that an isolated liver forming bile is a living liver. Such a preparation lends itself to many useful studies. Many apparatus and methods for perfusing the isolated liver of the rat have been used. A particularly good method emphasizing bile production has been developed by Brauer and coworkers(1). The authors have presented evidence, in addition to bile production, that the liver is viable during perfusion. This recent paper appeared subsequent to the completion of the present study. A perfusion apparatus that performs reasonably satisfactory has been made in this laboratory and adapted to the investigation of liver physiology in relation to radioactive materials. Gallium^{72} citrate was used in preliminary experiments.

General perfusion technic. The perfusion model, designed by one of the authors (M.B.), was fashioned in the shop of this laboratory from lucite. The essential parts comprising the apparatus are shown Fig. 1. They consist essentially of an oxygenation chamber, an artificial heart, a windkessel, which acts to convert a pulsatile into a constant flow, and an adjustable side reservoir. Polyethylene tubing is used for connections. About 90 ml of blood are required for operation of the present model. The artificial heart is driven by a variable stroke pump† set to deliver about 110 ml of air per stroke at a stroke rate of about 190 per minute. Blood flow from the portal vein cannula, when attached separately to the apparatus, has been measured as about 7.5 ml per minute. However, blood flow from the inferior vena cava during perfusion has been measured as about 2.5 ml per minute. The flow from the portal vein cannula is delivered under a head of constant

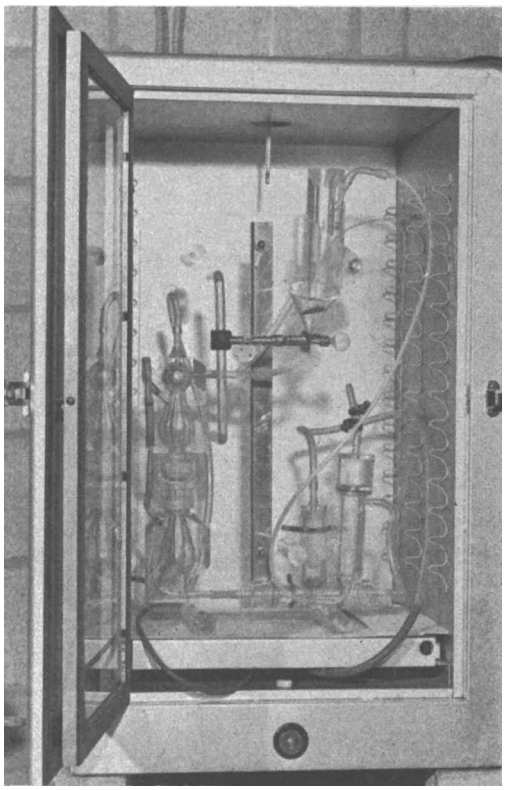

FIG. 1.

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