TABLE 1

GRAMS OF DIETS I, II, AND III EATEN BY OBESE AND NONOBESE MICE

Obese animals			Nonobese animals		
Diet I (high protein)	Diet II (high carbohydrate)	Diet III (high fat)	Diet I (high protein)	Diet II (high carbohydrate)	Diet III (high fat)
1.12 ± 0.555*	1.96 ± 0.644	1.73 ± 0.379	1.42 ± 0.634	2.49 ± 0.828	0.56 ± 0.396

* The figures following ± signs represent standard deviations.

TABLE 2

DAILY AVERAGE TOTAL CALORIES CONSUMED AND PERCENTAGES DERIVED FROM PROTEIN, CARBOHYDRATE, AND FAT BY OBESE AND NONOBESE MICE

Obese animals				Nonobese animals			
Total cal	Protein	Carbohydrate	Fat	Total cal	Protein	Carbohydrate	Fat
25.48 ± 5.31*	19.98 ± 4.08	27.80 ± 8.30	52.22 ± 6.59	20.44 ± 4.37	26.40 ± 9.17	44.81 ± 16.1	28.78 ± 8.35

* The figures after the ± signs represent standard deviations.

three diets in proper amounts: choline, thiamine, pyridoxine, riboflavin, niacin, calcium pantothenate, *p*-aminobenzoic acid, α-tocopherol, and inositol. These diets were placed in separate 10-cc beakers disposed on the inside of V-shaped racks, with a slit opening allowing the animals to eat but preventing them from either spilling or contaminating the diet. Food and water were given *ad lib*. Food cups were weighed daily. The animals were on experiment an average of 18 days. The results, in grams, of diets I, II, and III eaten by obese and nonobese animals daily, as well as total average daily food intakes, are given in Table 1. Total daily calories, as well as percentage derived from carbohydrate, protein, and fat, are given in Table 2.

It will immediately be apparent that very marked differences were found between obese and nonobese animals. First, evidently, obese animals ate significantly more than nonobese animals ($P = 0.03$). Although the average difference of 5 cal/day between obese and nonobese animals may not appear sufficient to account for the differences in weight observed, it may be useful to recall that in 30 days a difference of 5 cal daily, with a maximum thermochemical efficiency of 24% (*3*), could represent up to 4 g of depot fat alone. If the difference in body composition comprises proteins and associated water, the difference in body weight could in theory run up to four times this value. Second, there were equally marked differences in the proportion of the calories derived from fat, protein, and carbohydrates. The obese animals ate proportionately more fat ($P < 0.0001$), less protein ($P = 0.03$), and less carbohydrate ($P = 0.007$) than the nonobese animals, with the differences in fat and carbohydrate particularly striking. These in turn led to two important considerations. First, the increase in fat and decrease in carbohydrate intake could be easily correlated with the "glucostatic" theory of the regulation of food intake (*4*). Second, the type of diet selected by the obese animals was reminiscent of diets restricted in carbohydrate often used in the dietary management of diabetes. Both suggestions have been actively explored, and the question of diabetes is considered in another note published in this journal.

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Hereditary Diabetes in Genetically Obese Mice

Jean Mayer, Margaret W. Bates, and Margaret M. Dickie

Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, and *Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine*[1]

The preceding note (*1*) has described the development of a strain of mice presenting a high proportion of hereditarily obese animals and their genetic constitution. It has been shown how the obese animals, placed on a "free-choice" diet, chose a "diabeticlike" regimen, whereas the nonobese animals chose a more normal distribution of nutrients. These results led to an investigation of the carbohydrate metabolism of these animals. It may be indicated at the outset that such a study presented special difficulties on two counts. First, this being a new strain of mice, experimental animals are still produced in limited numbers; second, glucose determinations by the Somogyi-Nelson

[1] The portion of the work done in the Department of Nutrition, Harvard School of Public Health, was supported in part by grants-in-aid from the National Heart Institute, of the National Institutes of Health, USPHS; the Milbank Memorial Fund, New York; and the Nutrition Foundation, Inc., New York. The portion of the work done at the Roscoe B. Jackson Memorial Laboratory has been aided by a grant from the National Cancer Institute.

TABLE 1

BLOOD SUGAR LEVELS

Obese mice				Nonobese mice			
Normal	Fasting	400 IU/kg insulin	20 IU/kg insulin	Normal	Fasting	400 IU/kg insulin	20 IU/kg insulin
197	148	231	273	79	125	Lethal	Lethal
	88	224	318	141	112	"	"
291	119		298	88			
155				127			
217							

method necessitate individual blood samples of 0.2 or 0.4 ml for duplicate determinations (*2, 3*). Such amounts can be taken safely from mice only once every three weeks, which seriously limits experimental possibilities. Urine collections, although presenting no special difficulties per se, are made more delicate by the small size of the samples.

A study was made of blood glucose levels of obese and nonobese animals under various experimental conditions, as well as of normal urine glucose levels. The animals used were housed in individual, screen-bottomed cages and fed water and pellets *ad lib*. The results are given in Table 1 on an individual basis because of the limited number of animals used. The figures demonstrate that fed obese animals have a high blood sugar level (generally above 200 mg%) whereas nonobese animals presented a blood sugar level of the order of 110 mg. The effect of fasting was next studied—a 4-hr period was used. It is evident from the results that the blood sugar level of obese animals is much more sensitive to fasting than that of the nonobese animals, as it drops 50–60%, whereas that of the nonobese animals does not change appreciably during this interval. This result, incidentally, is in agreement with the "glucostatic" scheme of the regulation of food intake, which sees food intake conditioned by the *variations* in the blood glucose level (*4*). More remarkable, it was found that all obese animals belonging to this strain were insulin-resistant. High (20 IU/kg) and massive (400 IU/kg) doses of insulin ("Iletin," Lilly) were administered to the obese animals. No convulsions or deaths were observed with those doses. The blood sugar levels 1 hr after injection are recorded in Table 1. The obese, diabetic mice were found to be as a rule totally unaffected, and conserved extremely high blood sugar on doses that would kill normal animals in a short time. On the other hand, the nonobese mice present a normal insulin sensitivity. Obese and nonobese animals seem to be quite responsive to the administration of epinephrine. Blood sugar values 1 hr after administration of 1 mg/kg of adrenaline were of the order of 500 mg%.

Obese animals normally present a glucosuria of the order of 3 g%.

These observations lead to the following important conclusions: First, for the first time the existence of hereditary diabetes, clearly independent of environmental influences, has been established. Second, an obvious link between pathology of carbohydrate regulation and obesity is evidenced in these animals. They thus furnished a striking illustration to the glucostatic theory of the mechanism of the regulation of food intake. Finally, these animals are useful subjects for the elucidation of insulin-resistant diabetes. Metabolic and biochemical studies are being continued.

Histological and pathological data concerning obese and nonobese animals will be published in the near future (*5*). Three results may be stated already: first, both obese and nonobese animals generally present enlarged islets of Langerhans; second, as compared to other strains, the liver of obese animals is characterized by an abnormally low glycogen content, and the liver of nonobese animals presents a definitely higher glycogen content; finally, obese mice frequently present ulcerative lesions not unlike the decubitus ulcers sometimes seen in obese diabetic humans.

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Significance of Endogenous Cholesterol in Arteriosclerosis: Synthesis in Arterial Tissue[1]

M. D. Siperstein,[2] I. L. Chaikoff, and S. S. Chernick

Division of Physiology,
University of California School of Medicine, Berkeley

Recent concepts of the pathogenesis of arteriosclerosis have stressed the importance of dietary cholesterol in the development of this lesion. Evidence that this sterol is synthesized by many tissues in the animal body is accumulating, however. The early balance experiments of Schoenheimer and Breusch (*1*) on mice fed cholesterol-free diets left no doubt that animals can synthesize cholesterol, and this conclusion has been amply confirmed in the isotopic studies of Bloch and his associates (*2, 3*). The latter demonstrated that surviving liver slices can convert acetate to cholesterol and, according to Srere *et al.* (*4, 5*), this conversion can also be carried out by the adrenal cortex, kidney, testes, small intestine, and skin. It thus becomes of some importance to evaluate the significance of this endogenously synthesized cholesterol in the development of atheromata. Experiments designed to do so are in progress in this laboratory. This paper reports the ability of the artery to synthesize cholesterol.

The chickens used were mature male White Leg-

[1] Aided by grants from the U. S. Public Health Service and the Life Insurance Medical Research Fund.

[2] Postdoctoral Fellow of the National Heart Institute, USPHS.