mazine metabolism. Other metabolic changes in the phenothiazine nucleus and dimethyl propylamine side chain are inferred by the presence of 4 glucuronide spots. The differences among these metabolites may be the result of hydroxylation at different positions of the nucleus accompanied by oxidation to sulfoxides and demethylation of the side chain.

Summary. Four polar, water-soluble metabolites of chlorpromazine were separated from urine by use of a cation exchange resin. These were shown to be glucuronides by release of free glucuronic acid and less polar, ether-extractable phenothiazines as a result of β-glucuronidase hydrolysis. Presence of enolic functions in these released phenothiazines was shown by their extractability from an acidic medium. Results strongly suggest hydroxylation of chlorpromazine and subsequent conjugation with glucuronic acid as an important route of chlorpromazine metabolism and detoxification in man.

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Metabolism of Propionate-1-C-14 in the Intact Mouse.* (25332)

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Previous *in vitro* studies indicated that adipose tissue may play an unique role in metabolism of propionic acid(1). It was noted, for instance, that incorporation of propionate-1-C-14 and propionate-2-C-14 into fatty acids of adipose tissue slices was 100 to 200 times the incorporation into fatty acids of liver slices. In contrast, total oxidation of propionic acid was comparable in both tissues. These results have led to a description of a new proposed metabolic pathway for fat synthesis in adipose tissue which includes propionate as a precursor(2). The present work was undertaken to determine whether this function of propionic acid in adipose tissue can be demonstrated in the intact animal, and whether this function is more pronounced in obesity.

Methods. Two groups of mice of the White Swiss strain were used: normal animals and animals made obese by injection of goldthioglucose(3). Both groups were fed *ad lib.* until time of experiment. Animals were injected intraperitoneally with 10 microcuries sodium propionate-1-C-14, in isotonic NaCl and were placed in all-glass, temperature-controlled metabolism cages with access to only water. CO_2 and urine were collected until time of sacrifice. Groups of animals (Table II) were killed by etherization at intervals up to 24 hours. The entire animal was immersed in alcoholic potassium hydroxide and heated overnight on a steam bath. Glycogen, fatty acids and non-saponifiable lipids were assayed

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TABLE I. Body Composition

Mouse	Total wt, g	Lean wt, g	g lipids/g lean wt (× 100)
Normal (24)*	31.4 ± .7†	28.7 ± .6	9.4 ± .9
Obese (16)	44.3 ±1.7	35.8 ±1.4	24.4 ±2.9

* No. of animals. † Stand. error of mean.

for total amount and radioactivity as described previously(4).

Results. Comparison of body composition of the 2 experimental groups is shown in Table I. Obese mice averaged 40% higher in total weight than the normal. Although this weight gain was due in part to increase in tissue other than adipose, the greatest weight gain was at the expense of deposition of fat.

Table II shows a balance study of the C-14 from injected propionate. Values in this Table are averages of from 3 to 10 animals/group. Total recovery of administered propionate-1-C-14 varied from 87 to 105%. The major part of radioactivity administered was collected as expired CO_2. Glycogen and nonsaponifiable lipids accounted for only negligible amounts of activity. Radioactivity recovered in urine and feces ranged from 0.2% at early intervals for individual mice to as much as 14% after 24 hours of collection.

A pronounced difference in conversion of propionate into lipids of obese and normal mice was noted. Five hours following injection, C-14 recovered as fatty acids in obese mice was 10.4% of administered activity compared to a value of 2.3% in the normal group. At 16 and 24 hours, there was less difference between the 2 groups: 4% for obese and 3.2% for normal at the former time, and 2.6% for obese and 2.0% for normal at the latter time.

These differences in fatty acid synthesis are shown graphically in Fig. 1. The data are expressed as lipid incorporation/gram lean body weight which more adequately represents metabolizing tissue for each group of animals (Table I). The curve for obese mice reaches

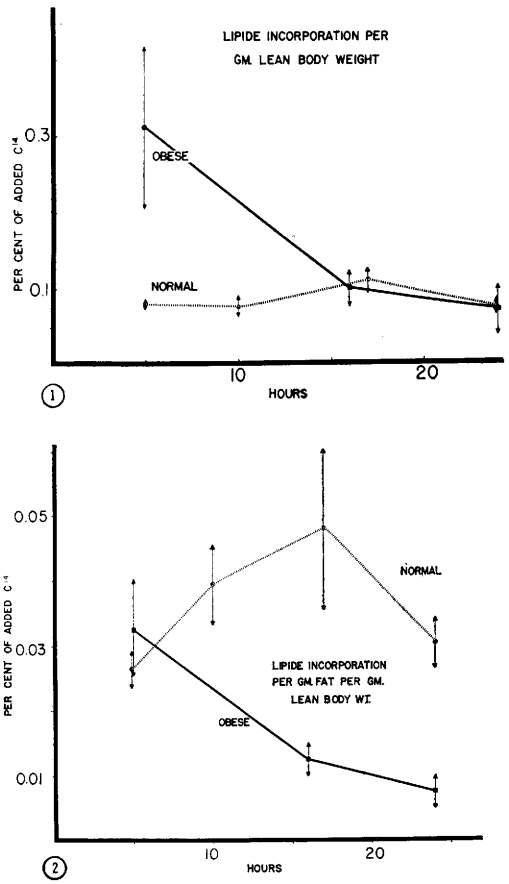

FIG. 1 and 2.

a peak value at an early period and obtains a value 3 times greater than obtained by the normal group. This activity falls off rapidly

TABLE II. Metabolism of Propionate-1-C-14 Balance Study. (10 μcuries of sodium propionate-1-C-14 in isotonic NaCl was inj. intraper. into each mouse. Total activity assayed as 4 × 10^6 cpm. Specific activity was 1 millicurie/millimole.)

Mouse	No. of animals	Interval after inj, hr	Avg C-14 recovered as CO_2	Glycogen	Urine & feces	Fatty acids	Total
			%				
Normal	10	5	95.4	.6	1.9	2.3	100.2
	3	10	91.2	.1	4.6	2.3	98.2
	7	17	92.2	.1	8.0	3.2	103.5
	4	24	89.6	.2	8.3	2.0	100.1
Obese	5	5	88.8	1.5	2.4	10.4	103.1
	5	16	93.2	.5	3.9	4.0	101.6
	6	24	90.9	.3	4.2	2.6	98.0

so that at 24 hours the 2 groups are at the same level. In spite of variations of weight as well as differences in degree of obesity achieved, the differences between the 2 curves are significant, as evidenced by the bar lines representing standard deviations of experimental points.

Fig. 2 shows a comparison of normal and obese activities expressed as lipid incorporation/g of fat/g of lean body weight. Here the normal curve rises to a higher value than the curve obtained from obese animal primarily because of smaller stores of fat/unit animal in the normal group.

Discussion. That slices of adipose tissue converted propionate to fatty acids at rates comparable to acetate conversion while liver was relatively inactive, led to the suggestion that propionate might be selectively synthesized into newly formed fatty acids by adipose tissue in the intact animal. By using the C-14 labelled compound, it was thought a measure of amount of adipose tissue could be made with a balance study. This should yield a measure of the degree of obesity by employing a metabolic criterion.

Our studies indicate that the aims described above might be achieved. By assaying expired CO_2, excreta, lipids and glycogen, essentially 100% of administered radioactivity from propionate was recovered. Of radioactivity not eliminated as CO_2, urine and feces, 90% remained in the fatty acid fraction (see Table II) with glycogen making up the difference. Thus, the difference in amount of radioactive propionate injected and that collected in CO_2 and excreta gives an estimate of labelled fatty acids in the intact animal.

Propionate has been shown to be a precursor for body fat synthesis in the whole animal. In the obese animal, up to 10% of the C-14 remained as labelled fatty acids 5 hours after propionate-1-C-14 was injected. This value might be higher at earlier intervals.

Fall of radioactivity after the 5 hour peak indicates the rapidity by which body fat may turnover. Recent work by Dole and others (5) has shown that the unesterified fatty acid fraction in plasma has half-times of only a few minutes. These components of plasma are derived from adipose tissue and are insensitive to fat ingestion but are extremely sensitive to such physiological changes as are brought about by administration of glucose, insulin or epinephrin, and to other determinants of carbohydrate utilization. Fasting represents another such determinant. The animals were not allowed food during the experiment. Such mild starvation might have altered turnover of fat stores differently in each group of animals. Similar type experiments with controlled dietary intake are the subject of future investigation.

Summary. Twenty-four normal and 16 obese mice were injected with radioactive propionate and the tag was followed into CO_2, non-saponifiable lipids, fatty acids, glycogen, urine and feces. Propionate is a precursor for body fat synthesis in the whole animal. Conversion of propionate to lipids was greater in obese than in lean mice.

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