It is reasonable to suggest a possible mechanism of quinidine action in converting cardiac arrhythmias. It is now generally accepted that digitaline nativelle causes a depletion of intracellular cardiac potassium, and alters the concentration of other intracellular electrolytes such as sodium and calcium(6). The results of this study reveal that intramuscular quinidine gluconate produces in the rabbit intracellular hyperpotassemia, and possibly intracellular hyponatremia. (Other electrolytes such as Mg, Ca and Mn were not studied.) Therefore, quinidine gluconate may effect its action via intracellular enzyme systems which are either stimulated or inhibited by alteration in sodium, potassium or other trace metals. This possibility is being studied actively at present.

Conclusions. *1.* 32 rabbits were injected intramuscularly in the gluteal region with 0.12 g of quinidine gluconate twice daily and 21 rabbits were similarly injected daily with 0.3 mg digitaline nativelle for 5 days and 10 days respectively. *2.* A gain in intracellular cardiac potassium as expressed in liters of intracellular water was observed in the quinidine treated animals (from 108 to 124 mEq). A loss in intracellular cardiac sodium from 13.6 to 6.8 was also observed. *3.* The mechanism of digitoxin toxicity and its reversal by quinidine is discussed. It is suggested that one of the actions of quinidine may be to reverse the ionic flow of sodium and potassium (and perhaps other ions) in cardiac muscle which occurs in digitoxin toxicity.

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Oxidation of Specifically Labeled Glucose by Rat Adipose Tissue.* (22567)

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Recent studies have indicated that the rate of glucose utilization *in vitro* by adipose tissue of the rat is greater than that of liver(1,2). The extensive lipogenic activity of adipose tissue implies the occurrence of rapid glycolysis(3), but does not exclude other pathways of hexose metabolism. Considerable evidence for the extraglycolytic breakdown of glucose in hepatic and other tissues is available, although accurate quantitation of its role in carbohydrate metabolism has been hampered by both technical and interpretative difficulties(4). Using one of the more direct experimental approaches to this problem (5), the oxidation of C^{14} glucose substrates, labeled in the first and sixth positions, has been studied in liver and testicular adipose

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TABLE I. Oxidation of Glucose-1-C^{14} and Glucose-6-C^{14} by Adipose Tissue and Liver. From 200 to 600 mg of tissue were incubated for 3 hr in 6.0 ml of buffer containing about 1 μc of the appropriate substrate.

Condition of animals			Adipose tissue			Liver		
			$C^{14}O_2$ yield* from		C-6†	$C^{14}O_2$ yield* from		C-6†
			G-1-C^{14}	G-6-C^{14}	C-1	G-1-C^{14}	G-6-C^{14}	C-1
Normal:	(2)‡		.72	.10	.14	.37	.20	.54
	(3)		.63	.07	.11	.29	.18	.62
	(2)		.53	.11	.21	.27	.23	.85
	(1)		.45	.12	.27	.40	.28	.70
Fasted:	(1)	18 hr	.27	.10	.37	—	—	—
	(1)	18	.27	.11	.41	—	—	—
	(1)	18	.27	.14	.52	—	—	—
	(3)	24	.16	.10	.63	.34	.27	.80
	(3)	48	.12	.08	.67	.27	.16	.60
	(3)	96	.19	.11	.58	.19	.09	.47
	(3)	192	.20	.11	.55	.16	.10	.63
Diabetic§:	(1)		.30	.11	.37	—	—	—
	(1)		.22	.12	.55	—	—	—
	(1)		.20	.10	.50	.10	.07	.70
	(2)		.11	.07	.63	.06	.04	.67
	(1)		.08	.04	.50	—	—	—
Cortisone-treated:								
mg/kg / day × days		30 × 2	.22	.02	.11	.18	.14	.78
		42 × 6	.15	.11	.73	.41	.25	.61
		40 × 8	.21	.08	.40	.46	.28	.61
Insulin-treated diabetics:								
Units‖ / Doses	Hr¶	BS**						
198/1	3.5	35	.18	.08	.44	.22	.20	.91
170/1	3.5	67	.17	.06	.35	.15	.14	.93
100/2	18	57	.96	.09	.09	.41	.31	.76
190/3	42	41	.92	.05	.05	.84	.34	.40
177/4	75	61	2.20	.20	.09	—	—	—

* Radiochemical yield $= \frac{\text{counts recovered as } CO_2/100 \text{ mg} \times 100}{\text{counts in substrate}}$. † $\frac{C^{14}O_2 \text{ from glucose-6-}C^{14}}{C^{14}O_2 \text{ from glucose-1-}C^{14}}$.

‡ No. of animals used in parentheses. Cortisone and insulin experiments done on individual rats. § Listed in order of increasing severity of diabetes. Lowest non-fasting blood sugar at sacrifice was 185 mg %, highest was greater than 600 mg %. ‖ Total insulin units/kg given in No. of doses indicated. ¶ Time from first insulin inj. to sacrifice. ** Blood sugar determined at sacrifice.

tissues from normal, fasted and hormonally manipulated rats.

Materials and methods. Male Wistar rats weighing between 200 and 400 g were fed on a stock Purina Chow diet unless otherwise indicated. Diabetes was induced by the intraperitoneal injection of alloxan monohydrate in animals fasted 48 hours and was permitted to progress untreated for at least 3 weeks. Protamine zinc insulin and cortisone, when administered, were given subcutaneously; the last injection was given 3 to 4 hours before sacrifice. Blood glucose levels were determined by the method of Durham *et al.*(6). The rats were sacrificed by a sharp blow on the head, exsanguinated and the required tissues immediately removed to ice-cold saline. Tissues from 1 to 3 animals were pooled in each flask. Stock solutions of the substrates (glucose-1-C^{14} and glucose-6-C^{14} obtained from the National Bureau of Standards) were prepared in saline and adjusted so that a final concentration of 100 mg% resulted in each flask. The incubations were carried out at 37°C as previously described(1). Radioactivity of the evolved carbon dioxide was determined according to Entenman *et al.*(7).

Results. The results, summarized in Table

I, indicate that the oxidation of carbon 1 of exogenous glucose is much more rapid than that of carbon 6 in normal adipose tissue, giving an average C-6/C-1 ratio of 0.18. Liver slices from the same animals exhibit significantly higher ratios, averaging about 0.68. On a wet weight basis, the rate of C-1 oxidation in adipose tissue is higher than that found in liver and, as previously indicated(1), this superiority is substantially amplified when the large difference in protein content between the tissues is considered. Even C-6 oxidation in adipose tissue is much greater than in liver when specific activity is related to nitrogen content. Prolonged starvation depressed the rates of C-1 and C-6 oxidation slightly in the liver, while their ratios remained normal. In adipose tissue, however, C-1 oxidation was significantly lowered after a short fast, while C-6 oxidation remained remarkably constant throughout the starvation periods studied, resulting in a rise of the C-6/C-1 ratio. Insulin deficiency, whether achieved by alloxan diabetes or cortisone administration, did not alter the ratio from normal in the liver, although a pronounced drop in oxidative rates of both labeled positions occurred in the alloxanized preparations. Again, C-6 oxidation by diabetic adipose tissues was relatively normal in magnitude, while the rate of C-1 oxidation varied inversely with the severity of the disease. In all instances, a significant elevation of the ratio is evident. Prolonged Cortisone administration also elevated the ratio by depressing the rate of C-1 oxidation. Administration of a massive dose of insulin (sufficient to cause coma within 3 to 4 hours) to diabetic rats fasted 24 hours, brought the hepatic rate of C-6 oxidation back to normal but failed to do the same for the C-1 oxidation, permitting the ratio to approach unity. However, the C-1 and C-6 oxidation rates and their ratios in adipose tissue appear similar to those of the diabetics. Gradual administration of insulin restored the normal rates of C-1 and C-6 oxidation in the liver and increased the C-1 oxidation above normal in adipose tissue, giving a significant depression of the latter's ratio.

Discussion. Although precise estimation of the fraction of glucose catabolized via the direct oxidative scheme in adipose tissue cannot be made from the data presented, it is obvious that under normal conditions it constitutes the major pathway of utilization. The shunt in adipose tissue appears to be very sensitive to starvation and the endocrine stresses which were imposed while glycolysis, as measured by the rate of C-6 oxidation, remained remarkably constant throughout. As a result, fasting, alloxan diabetes and cortisone treatment have the general tendency to reduce the total amount of glucose oxidized and permit glycolysis to account for a greater percentage of that which *is* catabolized. Insulin treatment of diabetics restored and enhanced both the total oxidative capacity of the tissue and the fractional importance of the shunt.

In the liver, the normal range of glycolytic participation in overall glucose metabolism was large enough to obscure small shifts in the quantitative significance of either pathway. While the total rates of oxidation seem to parallel the nutritionally and hormonally induced fluctuations in adipose tissue, no real change in the predominance of hepatic glycolysis is evident.

The significance of the relatively high rate of oxidation of glucose carbon 1 in normal adipose tissue may be intimately related to the extensive lipogenic capacity of that tissue. Lactating mammary gland tissue, in corelation with its stimulated fatty acid synthesis, has been shown to exhibit a low C-6/C-1 ratio similar to that of adipose tissue(8,9). Diabetic tissues usually demonstrate an elevated C-6/C-1 ratio(10) and a markedly decreased ability to synthesize fat. Hepatic lipogenic failure has been noted previously in insulin coma(11) and has been here shown to be associated with a C-6/C-1 ratio of practically 1. A tempting speculation arising from these and other correlations(12,13) is that lipogenesis is very sensitive to, or at least proceeds more readily with concomitant rapid oxidation of glucose carbon 1. While glycolysis appears to be a general prerequisite for lipogenesis(3), equally important reductive steps in the fatty acid cycle(14) must be considered in a complete evaluation of the proc-

ess. Two reactions of this cycle involve hydrogen transfers and the redox status of the enzymatic cofactors concerned may determine not only the extent but the direction (*i.e.*, synthesis or degradation) in which the cycle may turn. Recently, a specific requirement for triphosphopyridine nucleotide (TPN) in liver fatty acid synthesis has been demonstrated(15). If this system is operative in adipose tissue as well, then the availability of the reduced coenzyme (TPNH) would become a critical aspect of lipogenesis. The physiological appearance of TPNH, exclusive of the presence of transhydrogenase activity (16), is dependent on the activity of TPN-linked dehydrogenases, prominent among which are those involved in the phosphogluconate shunt. The presence of pyridine nucleotides (DPN and TPN) and their reduced forms in adipose tissue is currently under investigation.

Summary. The *in vitro* oxidation of glucose-1-C^{14} and glucose-6-C^{14} by liver and adipose tissues of the rat has been studied. 1) In adipose tissues from normal animals, the yield of $C^{14}O_2$ from glucose-6-C^{14} averaged about 18% of that obtained from glucose-1-C^{14}, indicating the extensive occurrence of extraglycolytic catabolism of glucose. Liver slices from these animals showed a corresponding $C^{14}O_2$ ratio of 68%. 2) Starvation (from 18 to 192 hours) depressed the $C^{14}O_2$ yield from glucose-1-C^{14} without affecting the yield from glucose-6-C^{14} in adipose tissues. Similar changes were seen in adipose tissues from alloxan diabetic and cortisone-treated animals. In all these cases, the C-6/C-1 ratio was significantly elevated above normal. In the liver, prolonged starvation (96 to 192 hours) lowered the $C^{14}O_2$ yields from both substrates without affecting their ratio. Marked depressions of $C^{14}O_2$ yields were seen in diabetic livers, but no changes in C-6/C-1 ratio were evident in these, as well as in livers from cortisone-treated rats. 3) Fasted diabetic rats responded to a massive insulin dose with typical symptoms of insulin coma. Adipose tissue oxidation rates of both substrates and their ratio remained characteristically diabetic while the liver ratio approached unity. Previous work indicates that hepatic lipogenesis is abolished under such conditions. Gradual administration of insulin to *ad lib.* fed diabetics resulted in a stimulation of $C^{14}O_2$ yield from glucose-1-C^{14} without affecting the yield from glucose-6-C^{14} in adipose tissue. Both $C^{14}O_2$ yields returned to normal levels in the liver with no change in ratio.

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