end of the experiment; concurrently, it may be noted, no rise in the rate of ketone formation has taken place. On the contrary, there was a measurable drop in the ketonemic level.

May it be reiterated that the amounts of intravenously supplied glucose were identical in Experiments II and III (Table II); only the duration of the injection differed. In Experiment II, because of a shorter duration, hypoglycemia was allowed to develop during the latter part of the fever, a factor that invariably increases the rate of hepatic glycogenolysis,[15] while in Experiment III hypoglycemia was avoided by a safe margin throughout the entire experiment, so that the liver had not to be pressed into service to provide for the augmented carbohydrate need of the extrahepatic tissues.

Summary. Artificial hyperthermia in man increases ketosis. This, according to available evidence, is due to an increased rate of ketogenesis in the liver. Our observations on human subjects are in accord with the findings of previous investigators, who demonstrated on perfused liver, on liver slices and on living animals, that an inverse relationship exists between the glycogen content of the liver and the rate of ketone formation. The data presented indicate, moreover, that an increased rate of hepatic glycogenolysis *per se* suffices to increase ketosis, without any appreciable diminution of the glycogen reserves of the liver. An increased ketonemia in artificial fever can be entirely forestalled by the continuous injection of glucose so as to ensure the maintenance of blood sugar at hyperglycemic levels, a condition which enhances glycogen deposition in the liver and at the same time prevents an increase in the rate of glycogenolysis.

11780

Changes in Ketonemia and Ketenuria During Hypoglycemia.

MICHAEL SOMOGYI.

From the Laboratory of the Jewish Hospital of St. Louis, Mo.

Artificial fever, as we reported, causes a substantial rise in ketonemia. Our experimental data indicated that an increase in the rate of hepatic glycogenolysis in itself suffices to accelerate the formation

[15] Somogyi, M., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 51.

of ketone bodies, irrespective of the glycogen content of the liver.[1] If this concept is correct, then hypoglycemia, which in general entails an increased rate of hepatic glycogenolysis, should cause a rise also in ketonemia.

In an inquiry whether or not this is the case, we studied subjects known to develop spontaneously moderate degrees of hypoglycemia during post-absorptive periods. In 3 cases in which hypoglycemia was frequent in the morning hours, we actually found elevated ketone contents in blood samples taken before breakfast. But in these instances one cannot preclude the possibility that the glycogen stores of the liver may have been greatly depleted during the night, due to the possible persistence of the hypoglycemic state over periods of several hours.

This uncertainty was eliminated in experiments in which the subjects were fed 100 g of glucose in the morning, thus providing fresh glycogen reserves for the liver. Individuals with inclination to spontaneous hypoglycemias as a rule develop such states several hours after glucose feedings, and thus one can observe the concurrent changes in blood ketones. Two examples of such experiments are presented in Table I. The subject in the first of the 2 (Case A) was a student, in the second (Case B) a middle-aged woman. In each case 100 g of glucose were given in the morning, and the subjects were at complete rest throughout the experiments. As may be noted in both cases, the blood ketones showed a transitory decrease during the first 3 hours after the ingestion of glucose, but began to rise in the fourth hour, at the time when hypoglycemia had developed. At the end of the fifth hour the ketone body content of the blood had risen to 3.0 and 1.2 mg %, respectively, a level that is well above the normal (0.3 to 1.0 mg %).

TABLE I.
Increase in Ketonemia After Hypoglycemia During Glucose Tolerance Tests.

Hr after ingestion of 100 g of glucose	Subject A Mg in 100 cc of blood		Subject B Mg in 100 cc of blood	
	Glucose	Ketones*	Glucose	Ketones*
0	66	—	75	0.40
1	131	0.81	—	—
2	81	0.57	80	0.28
3	68	0.44	62	0.31
4	53	0.48	49	0.16
5	66	3.00	78	1.22

*Expressed in terms of β-hydroxybutyric acid.

[1] Somogyi, M., and Kirstein, M. B., PROC. SOC. EXP. BIOL. AND MED., 1940, 45, 640.

TABLE II.
Ketonuria Due to Spontaneous Hypoglycemia ("Hyperinsulinism"?).

Day and hour of observation 1938	Excreted in urine: Glucose g	Ketone bodies mg %	Ketone bodies mg/hr	Nitroprusside test	Remarks
Feb. 3 and 4					At 9:30 p.m. hypoglycemic symptoms, 40 g glucose given. Symptoms persisted, blood sugar at 10:30 p.m. only 65 mg%. At 11:00 p.m. 50 g glucose given, at 11:30 hypoglycemic reaction marked, 40 g glucose given, followed by 180 g more (part intravenously) to 3:30 a.m., when relief from hypoglycemic symptoms was evident.
5:00 p.m.- 9:30 p.m.	0	....	....	—	
9:30 " -11:30 "	0	10	2.5	+	
11:30 " -12:30 a.m.	0	37	28	+++	
12:30 a.m.- 3:30 "	0	....	....	+	
3:30 " - 6:30 "	0.4	....	....	—	
Feb. 16 and 17					Listless since 2:30 p.m., at 5:45 p.m. marked hypoglycemic symptoms; 25 g glucose given, followed by meal containing 100 g available glucose. At 10:40 p.m. hypoglycemic reaction, blood sugar 48 mg%. At 11:00 p.m. 35 g glucose given, patient asleep. At 8:00 a.m. breakfast containing about 70 g available glucose.
2:30 p.m.- 9:30 p.m.	0	....	....	—	
9:30 " - 4:00 a.m.	0	....	....	—	
4:00 a.m.- 8:00 "	0	24	13	++	
8:00 " -10:00 "	0	13	4.6	++	
Feb. 26 and 27					At 11:30 a.m., just before lunch, hypoglycemic reaction. Lunch given, containing 100 g available glucose. Patient listless, asleep 2:00 p.m.
10:30 p.m.- 8:30 a.m.	0	....	....	—	
8:30 a.m.- 2:00 p.m.	0	....	....	+	
2:00 p.m.- 4:30 "	0	420	546	++++	

A more illustrative case, a young woman with a serious derangement in her carbohydrate metabolism, has been under our continual observation during the last 2 years. Her blood sugar frequently dropped to 30 mg % and even lower, occasionally causing unconsciousness, at variable hours of the day or night. At a time when this condition confined her to the hospital for several months, we found that hypoglycemic periods were often accompanied by ketonuria. In view of the fact that she received 300 g of carbohydrates daily in her food, and in addition to this large amounts of glucose during hypoglycemic attacks, the ketonuria was altogether inconsistent with the current concepts of ketogenesis, antiketogenesis and ketolysis.

Of numerous instances of hypoglycemia accompanied by ketonuria in this case, 3 examples are presented in Table II; the only reason for

selecting these particular periods is that ketonuria during these is demonstrated not only by the customary qualitative test but also by quantitative estimation. It is evident from our data, without much comment, that protracted hypoglycemic conditions may persist and can entail ketonuria despite carbohydrate intake that is far beyond the measure normally consumed.

When hypoglycemia persists during the administration of glucose, practically all of the glucose is deposited as glycogen in the peripheral tissues, while at the same time glycogen breakdown in the liver continues at an increased rate. When hepatic glycogenolysis is accelerated, the formation of ketone bodies is also increased.[1] The observations on February 3 and 4 clearly show this relationship. It may be noted that ketonuria ceased only after the hypoglycemic attack had subsided; as indicated by a slight glycosuria at the end, the large amounts of injected glucose eventually led to hyperglycemia, and at the same time the qualitative test for acetone became negative. The third period (February 26 and 27) in Table II is noteworthy in this respect, that it shows that ketonuria due to hypoglycemia may develop to serious dimensions. The excretion of ketone bodies rose to more than 0.5 g per hour due to the fact that in this instance hypoglycemia was not combatted as vigorously as in the preceding 2 periods.

Summary. Hypoglycemia, either induced by hyperglycemia or occurring spontaneously ("hyperinsulinism"?), is frequently accompanied by ketosis (ketonemia and ketonuria). Increased rates of formation of ketone acids, known to occur in the liver, are coincident with increased rates of hepatic glycogenolysis.

11781

Effect of Sulfanilamide on Wound Healing.*

MAX TAFFEL AND SAMUEL C. HARVEY.

From the Department of Surgery, Yale University School of Medicine, New Haven, Conn.

Bricker and Graham[1] reported that sulfanilamide had an inhibitory effect upon the healing of stomach wounds in dogs. Their deter-

*Aided by a grant from the Fluid Research Funds of Yale University School of Medicine.

1 Bricker, E. M., and Graham, E. A., *J. A. M. A.*, 1939, **112**, 2593.