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Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals.

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We described[1] experiments on dogs which show the frequent occurrence of hyperglycemia as the aftermath of hypoglycemia in the postabsorptive state. We had previously made the same observation on diabetic and nondiabetic human subjects. The phenomenon attained particular interest because it explains the familiar extreme fluctuations of the blood sugar level in insulin-treated severe diabetics that perplexed investigators since the advent of insulin. An understanding of the nature of these fluctuations made possible a satisfactory clinical management of such cases.

The extent of the compensatory hyperglycemia in nondiabetic subjects is moderate so that its existence assumed significance only in the light of our observations on diabetic patients. The phenomenon was found to occur in numerous nondiabetic individuals in the course of the conventional glucose tolerance test. In the majority of healthy persons, as is known, the hyperglycemia that obtains for a period of about one hour or 90 minutes after the ingestion of 100 gm. of glucose, recedes close to the postabsorptive (fasting) level at the end of about 2 hours. An hour later, *i. e.*, 3 hours after the intake of sugar, a hypoglycemic dip (5 to 20 mg. %) below the fasting level frequently occurs, and in another hour the fasting level is restored.

Individual variations and deviations from this course, however, are frequent. In many instances directly after the hypoglycemic phase a secondary hyperglycemia appears before the fasting level is reëstablished. It is this phenomenon with which we are concerned. To illustrate it, we present the results of 23 glucose tolerance tests performed on nondiabetic individuals. The first 14 of these cases exhibit distinct secondary hyperglycemic levels at the end of 3 hours after the ingestion of glucose, the rise above the fasting values ranging from 8 to 29 mg. %. This hyperglycemia is preceded by a hypoglycemic drop at the end of the second hour. In the remaining 9 cases given in Table I, marked hyperglycemia was observed at the end of the fourth hour; in a few of these cases

[1] Somogyi, M., Weichselbaum, T. E., and Heinbecker, P., PROC. SOC. EXP. BIOL. AND MED., 1937, **32**, 65.

hyperglycemia was present at the end of the third hour but increased further during the fourth. The greatest rise in this group was 33 mg. % above the fasting level.

TABLE I.
Response to Glucose Tolerance Tests in Nondiabetic Subjects Showing Secondary Hyperglycemia.

No. of case	Time after ingestion of 100 gm. of glucose (hours)					Secondary rise above fasting level
	0	1	2	3	4	
	Mg. true sugar per 100 cc. of blood.					
1	88	90	60	96	74	8
2	70	80	64	79	—	9
3	92	139	70	103	—	11
4	91	158	83	103	102	12
5	86	90	84	98	—	12
6	93	138	88	109	84	13
7	77	97	82	93	—	16
8	76	97	57	93	73	17
9	67	91	65	85	83, 57*	18
10	82	142	83	101	81	19
11	82	122	80	101	—	19
12	86	132	72	109	89	23
13	80	110	84	105	81	25
14	83	176	98	112	92	29
15	93	104	74	88	98	5
16	79	119	107	81	89	10
17	90	133	93	96	101	11
18	73	107	76	82	85	12
19	80	136	89	83	93	13
20	90	116	112	78	105	15
21	81	138	124	80	99	18
22	86	149	131	97	105	19
23	82	108	93	87	115	33

*Five hours after the ingestion of glucose.

It may be noted that in some of the cases no actual hypoglycemia is recorded, that is to say, the blood sugar dropped only to or near the fasting level, yet a hyperglycemic after-effect ensued. A substantial and relatively rapid drop of the blood sugar from hyperglycemic levels apparently sufficed in these instances to elicit a subsequent rise, without the necessity of attaining a true hypoglycemia. It is likely also that in some instances the hypoglycemic stage has been missed since blood sugar determinations were carried out only at hourly intervals.

That hyperglycemia is in general a physiologic response to hypoglycemia, is indicated by the fact that it occurs independently of the causes that are responsible for the hypoglycemia. Thus in experiments on dogs hyperglycemia was observed as a response to hypoglycemia in the course of glucose tolerance tests, and also as the aftermath of hypoglycemia that was produced by the injection of

small doses of insulin.[1] Again entirely different experimental conditions are at work in bringing about the so-called "arbeitshyperglykemie." This phenomenon occurs during strenuous physical exertion performed in the postabsorptive state. A rapid initial drop of the blood sugar under these conditions is followed by a rise above the fasting level. Similarly in artificial fever, with rising body temperature, hypoglycemia frequently sets in and is promptly followed by hyperglycemia (unpublished observations made in this laboratory).

The blood sugar level, therefore, seems to be the primary factor that influences the equilibrium of the reversible enzymatic reaction, glycogen $\rightleftarrows$ blood sugar, in the liver. One must postulate on this basis that hypoglycemia, in order to produce a hyperglycemic aftereffect, causes a shift in the balance of the reaction by increasing its velocity in the direction of glycogen breakdown (to the right) relative to the reaction velocity in the direction of glycogen formation. (Hyperglycemia causes a reversal of this relationship.)

The accommodating capacity of the enzymatic reaction, *i. e.*, its elasticity and quickness of response to changing blood sugar levels, exhibits considerable individual variations. In many normal individuals and experimental animals the glycogen breakdown, when stimulated by hypoglycemia, proceeds at an increased rate only until the normal postabsorptive sugar level had been restored, the process slowing down in time to avoid an overstepping of this limit. This course represents the regulatory system at its best, in that it provides maximum stability in the readjustment of the blood sugar level. In other healthy subjects and animals, however, the enzymatic glycogen breakdown, once stimulated, maintains an accelerated pace for some time after it has satisfied the demand, producing a transitory hyperglycemia of moderate degree. The cases in Table I belong to this group. We interpret this as an expression of a slight degree of inefficiency of the regulatory system, conducive to a mild form of instability in the readjustments of the blood sugar level. A more pronounced instability is exhibited in a third group, where hyperglycemic and hypoglycemic phases alternate repeatedly before the final readjustment takes place. Examples of this condition are cases No. 1, 6, and 9 in Table I and the 3 cases in Table II.

We have found that these differences in the response to glucose tolerance tests do not by any means represent accidental variations that may occur in the same individual from one day to another. On the contrary, a given person responds to repeated tolerance tests with the same type of curve (provided, of course, that no essential

TABLE II.
Repetition of Glucose Tolerance Tests Shows Consistency in Type of Response.

No. of case and date of test	Time after ingestion of 100 gm. of glucose (hours)					Secondary rise above fasting level
	0	1	2	3	4	
	Mg. true sugar per 100 cc. of blood.					
1. July 7	76	97	57	93	73	17
July 10	81	134	78	92	55	11
2. Feb. 11	81	65	73	88	69	7
Apr. 11	76	70	78	86	64	10
3. Nov. 23	94	119	88	106	88	12
Nov. 26	87	105	80	111	—	24

change has taken place in his dietary regimen and physical condition). It appears, therefore, that the type of response of nondiabetic persons to glucose tolerance tests expresses characteristic individual qualities. A few examples, given in Table II, show that individuals in whom a glucose tolerance test indicated lability of the regulatory mechanism, exhibited a similar type of response when the test was repeated.

In the diabetic condition hypoglycemia exerts the same effect upon the hepatic enzyme system as in the nondiabetic, but in a greatly exaggerated degree. The difference between the processes in the normal and in the pathological condition is quantitative rather than qualitative. In diabetes (irrespective of its etiologic causes, and aside from the influence of the muscle tissues upon the blood sugar level) the prevalence of hyperglycemia attests to a dislocation in the balance between the 2 opposite enzymatic processes in the liver, in the sense that the rate of glycogen breakdown materially outstrips the rate of glycogen formation. If in addition the stimulating effect of hypoglycemia is superimposed upon such an unbalanced enzyme system, it is understandable that the ensuing compensatory swings will be far greater than in the nondiabetic, resulting in excessive hyperglycemia and glycosuria.

Our experience has convinced us that the wide fluctuations in the blood sugar and the progressively increasing instability of diabetic patients are the direct results of the administration of excessive doses of insulin over a long period of time. (In this relation we define as an excessive dose any amount of insulin that causes hypoglycemia.) In our experience adequate reduction of the insulin dosage in conjunction with a liberal dietary regimen eventually restores such patients to a greatly improved stability. This will be shown in forthcoming clinical reports.

Summary. 1. In numerous healthy individuals and normal experimental animals hypoglycemia entails hyperglycemia in the post-absorptive state, irrespective of the experimental conditions which initiated the hypoglycemia. The phenomenon is interpreted as the result of a delay in the adjustment between the reaction velocities of glycogen breakdown and glycogen formation in the liver. 2. In the diabetic the same physiologic process takes place on a greatly magnified scale. Hypoglycemias, caused by overdoses of insulin, entail in the diabetic patient excessive degrees of hyperglycemia and glycosuria. Recurrence of this sequel over considerable periods of time progressively increases the instability of the patient and aggravates the disease.

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Vitamin C Saturation—Kidney Retention after an Intravenous Test Dose of Ascorbic Acid.

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Following the observation that Vitamin C was not uniformly absorbed from the intestinal tract it was natural that the intravenous route of administration should be adopted for the test dose* and for therapy when utilization by the oral route was unsatisfactory. This method of studying the Vitamin C saturation of the body was described by the authors,[1, 2] using 1000 mg. doses and later by others[3, 4] with smaller dosage. When the 1000 mg. test dose in 10 cc. of physiologic solution of sodium chloride was given intravenously the normal urinary excretion during the 24 hours following was found to be not less than 500 mg. In deficient states the body uses more of the vitamin and the excretion is less. In saturated states the excretion may be markedly increased. Fever and the use

* The ascorbic acid used was supplied through the courtesy of Merck and Company, Rahway, N. J.

1 Wright, Irving S., *Am. J. Med. Sci.*, 1936, **192**, 719.

2 Wright, Irving S., Lilienfeld, Alfred, and MacLenathen, Elizabeth, *Arch. Int. Med.*, 1937, **60**, 264.

3 Ralli, E. P., Friedman, G. J., and Kaslon, M., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 52.

4 Finkle, Philip, *J. Clin. Invest.*, 1937, **16**, 587.