

# EFFECT OF INSULIN ON THE CONCENTRATION OF URIC ACID IN THE BLOOD

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In the past, opportunity to study the hypoglycemic state in human beings has been difficult to obtain. Before the introduction of the insulin hypoglycemia treatment of schizophrenia, the hypoglycemic state was considered to be dangerous and only a few observations were made by deliberately inducing this state in man. In January, 1937, the treatment of schizophrenia by the insulin hypoglycemia method was undertaken at the Rochester State Hospital. The patients were normal, physically, but had a functional mental disease; they thus provided an excellent chance to observe the effects of the injection of insulin and insulin hypoglycemia. The following study on the relation between the concentration of uric acid in the blood and the administration of insulin is a portion of the work done on the chemical changes accompanying hypoglycemia among these patients.

If one administers a large dose of insulin and allows hypoglycemia to develop, the concentration of uric acid in the blood drops markedly. The extent of the drop varies, but it may reach large proportions (Table I).

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Insulin hypoglycemia decreases the concentration of uric acid in the whole blood, serum, and plasma. The decreases differ, however, in the different components of the blood (Table II).

Table III shows the concentration of uric acid and sugar when insulin was not administered. These control studies, which do not show any significant spontaneous alteration in the concentration of uric acid in the blood, would seem to confirm the impression that there is a causal relationship between the administration of a large dose of insulin and lowering of the value for the uric acid in the blood.

These studies led to an inquiry into the question as to whether the ability of insulin to cause a drop in the value for the blood sugar, or some other property of insulin, is responsible for the change. To study this question a large dose of insulin was given to fasting patients. This dose was equal to or greater than the amount necessary to produce coma. Following this, sufficient carbohydrate to prevent the appearance of hypoglycemia was administered. The lowering effect of insulin on the blood sugar was counteracted by the giving of approximately 25 grams of chocolate

TABLE I

*Effect of injection of insulin on the concentration of sugar and uric acid in the blood in three cases of schizophrenia*

Date of analysis	Case	Units of insulin administered at 7 a.m.	Sugar*			Uric acid†			Maximal decrease in concentration of uric acid
			7 a.m.	9 a.m.	11 a.m.	7 a.m.	9 a.m.	11 a.m.	
			mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	per cent
1937									
Mar. 23.....	1	65	117.9	56.9	44.5	3.5	2.0	1.1	68.5
Mar. 24.....	2	100	100.0	55.5	25.0	4.4	4.0	3.6	18.2
Mar. 24.....	1	80	125.0	60.6	27.3	2.7	2.2	1.9	29.6
Mar. 29.....	2	80	117.0	51.4	29.2	4.8	4.0	3.1	35.5
Mar. 30.....	2	100	106.3	57.1	25.1	3.9	3.4	2.9	25.6
Mar. 30.....	3	90	96.6	53.3	24.7	3.4	3.0	2.5	26.5
Apr. 1.....	1	80	103.1	30.3	26.2	3.1	3.0	2.9	6.4
Apr. 1.....	2	100	90.9	28.9	21.7	3.5	2.9	2.8	20.0
Apr. 1.....	3	80	89.7	29.4	23.4	3.1	2.7	2.6	16.1

\* Determined by method of Folin (16).

† Determined by method of Folin (17).

TABLE II

*Effect of administration of 100 units of insulin \* on the concentration of uric acid and sugar in the blood in Case 2*

		Concentration			Maximal decrease in concentration of uric acid
		7 a.m.	9 a.m.	11 a.m.	
Uric acid	In whole blood . . .	mgm. per 100 cc. 2.0	mgm. per 100 cc. 1.4	mgm. per 100 cc. 1.3	per cent 35.0
	In plasma . . . . .	4.0	3.0	2.3	42.5
	In serum . . . . .	5.4	2.2	1.0	81.4
Sugar in whole blood . . .		106.3	35.7	30.4	

\* 100 units of insulin administered at 7 a.m., April 2, 1937.

TABLE III

*Concentration of uric acid and sugar in the blood when insulin was not administered*

Date of analysis	Case	Sugar			Uric acid			Maximal change in concentration of uric acid	
		7 a.m.	9 a.m.	11 a.m.	7 a.m.	9 a.m.	11 a.m.	Increase	Decrease
		mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	per cent	per cent
1937									
Mar. 25	1	105.3	106.4	95.2	2.5	2.4	2.9	16	
Mar. 25	2	100.5	95.2	94.6	3.8	3.6	3.2		15.8
Mar. 25	3	102.6	98.5	97.6	2.6	2.7	2.3		11.5

candy each 15 to 30 minutes after the study was begun (Table IV). Clinical evidence of hypoglycemia did not appear in any of these patients during the studies; nevertheless, the value for the uric acid in the blood fell markedly. It seems,

therefore, that one can administer a large dose of insulin, prevent the development of hypoglycemia by the administration of carbohydrate, and yet produce a considerable drop in the concentration of uric acid in the blood.

## COMMENT

The literature includes the following reports of studies on the interrelationship of carbohydrate and purine metabolism: In 1923, Rémond and Rouzaud (1) observed a relationship between the concentration of dextrose and uric acid in the blood. They stated that the concentration of uric acid is decreased by administration of carbohydrate. In 1924 Lennox (2) noted that the concentration of uric acid in the blood is increased by starvation and diminished again when the feeding of carbohydrate and protein is resumed. Lockie and Hubbard (3) found that diets high in fat and low in carbohydrate induce an increase in the concentration of uric acid in the blood of patients who have gout and that diets high in carbohydrate lower the concentration in these cases. Quick (4) has shown that ketosis or a lack of antiketogenic substances can cause a retention of uric acid in the body.

Tashiro (5) induced a decrease in concentration of uric acid in the blood of geese by the injection of insulin whereas Liotta (6) reported an increase in the dog. Kürti and Györgyi (7) observed that the time necessary to excrete a given amount of uric acid is prolonged by administration of insulin but Chrometzka (8) stated that he had been unable to influence purine metabolism with insulin. Taubmann (9) described an increase in

TABLE IV

*Concentration of uric acid and sugar in the blood in cases in which sugar was given at intervals of 15 to 30 minutes after the administration of insulin*

Date of analysis	Case	Units of insulin administered	Sugar			Uric acid			Maximal decrease in concentration of uric acid
			7 a.m.	9 a.m.	11 a.m.	7 a.m.	9 a.m.	11 a.m.	
			mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	mgm. per 100 cc. of blood	per cent
1937									
May 2 . . . . .	4	95	125.0	81.6	74.1	2.3	2.0	1.1	52.0
May 3 . . . . .	4	95	105.3	67.1	71.4	3.5	2.7	1.7	51.5
May 4 . . . . .	5	100	111.1	62.5	69.0	2.2	1.5	1.8	18.2
May 4 . . . . .	6	65	90.9	83.3	66.6	1.3	1.3	1.1	15.3
May 4 . . . . .	7	70	76.9	63.9	60.6	2.4	1.5	1.2	49.0
May 4 . . . . .	8	100	125.0	76.9	71.2	2.5	2.2	1.7	32.0
May 4 . . . . .	9	90	86.9	60.6	64.5	2.9	1.9	1.5	48.2

excretion of allantoin in dogs following injection of insulin whereas Ogawa (10) reported a decrease. Buadze (11) stated that in dogs he had induced an increased excretion of uric acid accompanied by a decreased output of allantoin by injection of insulin.

A series of studies (12, 13, 14, 15) which have appeared from Chaikoff's laboratories bear on the subject of the relation of purine and carbohydrate metabolism in dogs. These workers have shown that either injection of insulin or epinephrine increases excretion of allantoin by ordinary breeds of dogs and increases excretion of uric acid in Dalmatian dogs. They found that insulin could not induce these changes in the absence of the adrenal glands, or if the effect of the insulin was counteracted by carbohydrate feeding.

A method of bringing about a marked fall in the concentration of uric acid in the blood, such as has been observed following the administration of insulin, in the present investigation, may have some therapeutic usefulness in cases of gout. Experiments to determine this are under consideration.

#### CONCLUSIONS

1. Subcutaneous injection of approximately one to two units of insulin per kilogram of body weight causes a marked fall in the concentration of uric acid in the blood of man.

2. The drop in concentration of uric acid is independent of the appearance of hypoglycemia. It occurs when hypoglycemia is permitted to develop and also when the lowering effect of insulin on the concentration of blood sugar is counteracted by administration of carbohydrate.

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