The Effect of Histamine upon the Flat Glucose Tolerance Curve as Encountered in Acute Tropical Sprue[1]

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THE ACTION of histamine on the secretory function of the stomach was proved in animal experimentation in 1920 by Popielski,[2] and by Keeton, Koch, and Luckhardt.[3] On the human stomach its effect was first observed by Carnot, Koskoulski, and Liebert,[4] and since that time it has been the subject of numerous investigations. Matheson and Ammon,[5] Gompertz and Vorhaus,[6] Andresen,[7] Bockus and Bank,[8] and Bloomfield and Polland[9] demonstrated that histamine, when injected either subcutaneously or intramuscularly, is a most reliable stimulant for gastric secretion, especially the secretion of free hydrochloric acid, and that the secretion of hydrochloric acid occurs within fifteen minutes after the injection of histamine, usually reaching a maximum in about thirty to sixty minutes.

Because of the increase in acidity, Katzenelbogen[10] reasoned that a corresponding general decrease of acidity should take place in all other body fluids. He observed that sixty minutes after the intra-

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2. L. Popielski, "B-imizolylathylamin und die Organextrakte: Einfluss der Saureu auf die Magensaftsekretion erregende Wirkung der Organextrakte," *Arch.f.d.ges.Physiol.*, CLXXVIII (1920), 214.

3. R. W. Keeton, F. C. Koch, and A. B. Luckhardt, "Gastrin Studies: III. The Response of the Stomach Mucosa of Various Animals to Gastrin Bodies," *Am.J.Physiol.*, LI (1920), 454.

4. P. Carnot, W. Koskoulski, and E. Leibert, "L'Influence de l'histamine sur la sécretion des sucs digestifs chez l'homme," *Compt.rend.Soc.de biol.* LXXXVI (1922), 575.

5. A. K. Matheson and S. E. Ammon, "Observations on the Effect of Histamine on the Human Gastric Secretion," *Lancet* I (1923), 482.

6. L. M. Gompertz and M. G. Vorhaus, "Studies on the Action of Histamine on Human Gastric Secretion," *J.Lab.& Clin.Med.*, XI (1925), 14.

7. A.F. R.Andresen, "Fractional Gastric Analysis with Histamine," *Tr.Am.Gastro-Enterol.A.* (1926), p. 53.

8. H. L. Bockus and J. Bank, "The Value of Histamine as a Test for Gastric Function," *Arch.Int.Med.*, XXXIX (1927), 508.

9. A. L. Bloomfield and W. S. Polland, "The Diagnostic Value of Studies of Gastric Secretion," *J.A.M.A.*, XCII (1929), 1508.

10. S. Katzenelbogen, "The Action of Histamine on the Alkali Reserve," *J.A.M.A.*, XCII (1929), 1240.

muscular injection of 1 cc. of 1:1000 histamine solution there was an increase of the alkali reserve from 22.2 percent to 105 percent, or an average of 50.55 percent. On the basis of these results and on the assumption that histamine increases the alkali reserve by draining acidity into the stomach, he suggested that it might be of value in the treatment of nondiabetic acidosis, especially if combined with the parallel elimination of the acidity, either by the removal of the gastric contents or by neutralization with alkali given by mouth. As to its use in diabetic acidosis, he concluded that histamine, as he and Abramson[11] and La Barre[12] showed, provokes hyperglycemia. Hiller,[13] on the other hand, found that the pH of the blood and the bicarbonate of the plasma were both decreased after the subcutaneous injections of histamine, using doses of from 0.1 to 3 mg. per kilogram of body weight in normal dogs. Corresponding with this, there was an increased excretion of alkali in the urine. Boyd, Tweedy, and Austin[14] injected 0.7 mg. of histamine subcutaneously into dogs weighing 9 to 12 kgm., and observed a rise in the blood pH, amounting to from 0.02 to 0.06, from one to two hours after the injection. With larger doses a decrease in pH was observed.

Because the response of the acid-base balance was found to vary with (*a*) the amount of histamine injected, (*b*) the manner in which it was administered, and (*c*) the species in which the observations were made, Hiestand and Hall[15] decided to investigate whether a change occurred in the alkali reserve in man when the dose corresponded to that employed clinically,[16] namely, 0.5 to 0.75 mg. Since Katzenelbogen and Abramson working with guinea pigs, Ni[17] working with dogs, and Fenyes[18] working with humans showed hyperglycemia to be produced by histamine injection, they decided to investigate the effects on the blood sugar in man. They reached the

11. S. Katzenelbogen and A. Abramson, "Les variations du taux de la glycémie consécutives aux injections intra-veineuse et intra-cardiague d'histamine," *Compt.rend.Soc.de biol.*, XCVII (1927), 240.
12. Jean La Barre, "A propos des variations de la glycémie consecutives á l'injection intra-veineuse d'histamine," *Compt.rend.Soc.de biol.*, XCIV (1926), 779.
13. A. Hiller, "The Effect of Histamine on the Acid-Base Balance," *J.Biol.Chem.*, LXVIII (1926), 833.
14. T. E. Boyd, W. R. Tweedy, and W. C. Austin, "Some Effects of Histamine on the Acid-Base Balance," *Proc.Soc.Exper.Biol.& Med.*, XXV (1928), 451.
15. R. F. Hiestand and J. L. Hall, "Effect of Histamine on Alkali Reserve and on Blood Sugar in Man," *Arch.Int.Med.*, XLIX (1932), 799.
16. S. Katzenelbogen and A. Abramson, *op. cit.*
17. R. G. Ni, "On the Inverse Change between the Concentration of Glucose and Chloride in the Blood," *Am.J.Physiol.*, LXXVIII (1926), 158.
18. Georg Fényes, "Ueber die Wirkungen des Histamins," *Wien.Arch.f.inn.Med.*, XX (1930), 287.

following conclusions: that intramuscular injections of 0.5 and 0.75 mg. of histamine do not produce a significant increase in the blood sugar of man, and that the same doses usually produce a small increase in the alkali reserve in man.

Chambers and Thompson[19] found that, during the first fifteen minutes of canine histamine shock, there is a decrease of nearly 80 percent in the glycogen content of the liver, and a 60 percent decrease in the glycogen content of the heart and skeletal muscles. During the first thirty minutes, blood sugar increases 200 percent, blood lactic acid about 133 percent, and plasma inorganic phosphates about 50 percent. According to La Barre,[20] hyperglycemia following histamine shock is due to the excitation of the parasympathetic, which causes rapid transformation of the muscle and liver glycogen into free sugar.

We have been unable to find any reference in the medical literature in relation to the effect of histamine upon a flat glucose tolerance curve. The idea of testing the response of patients having a flattened curve struck us when fasting blood sugar was taken from a sprue patient with a known low fasting blood sugar, into whom histamine was injected for a gastric analysis. The patient showed a concentration of over 140 mg. percent in his blood.

We decided to perform a glucose tolerance test in all sprue patients upon admission to the hospital. A test was performed without histamine, and the next day another test was done after histamine injection. The dose of the drug was 0.01 mg. per kilo of body weight, and was injected subcutaneously. Seventeen consecutive patients were submitted to the test. All were native Puerto Rican indigents. Ten were females and seven were males; their ages were between fifteen and fifty years. One of the male patients had hookworm disease. A female had hyperthyroidism with a thyroid adenoma complicating the state of sprue. All were of the white race except one female who was a mulatto. The blood samples were taken as follows: an initial amount of blood was taken before injection of histamine, glucose 1.75 grams per kilo was given *per os*, the drug was injected, and then four different samples were obtained half an hour, one hour, two hours, and three hours after the administration of the drug. The patients had been fasting at least ten to twelve

19. E. K. Chambers and K. W. Thompson, "Quantitative Changes in Tissue Glycogen, Blood Sugar, Plasma, Inorganic Phosphates and in Blood Lactic Acid in Canine Histamine Shock," *J.Infect.Dis.* XXXVII (1925), 229.
20. Jean La Barre, *op. cit.*

hours previous to the tests, and the blood sugar levels were calculated by the method of Folin-Wu.

Ten of the patients had severe diarrhea, and in seven the symptoms appeared to be moderate. In none of the patients was a state of anachlorhydria encountered, while all had a hypochlorhydria. Twelve of the patients were markedly undernourished, and five had lost weight moderately.

The duration of the condition was between two months and eight years, averaging two years and seven months. All patients were in an acute state when admitted to the hospital. The condition of the intestinal and gastric mucosa revealed atrophy in the majority of the cases and in 30 percent of them, the prothrombin time was prolonged, due either to faulty absorption or to deficient function of the liver; but it, as well as the flatness of glucose tolerance curve, has been attributed to deficient intestinal absorption.

In seven of the patients the curve remained unchanged or very slightly altered after the use of histamine. In ten of the cases the blood sugar presented a definite rise in the first half hour of an average of 29 mg. percent. In the first hour the rise from normal was around 31 mg. percent. After that, with the exception of only a few cases, the blood sugar approached the initial values.

The average maximum variation from initial sample among the tests performed without histamine was 12.2 mg. percent, while the curves with the use of the drug presented an average of 26.3 mg. percent. The average variation from initial blood sugar level in curves without the drug was as follows: +1, +6, +7, and —1, corresponding to one half, one, two, and three hours after ingestion of glucose. The average variations in the ones treated with histamine were as follows: +11, +20, +10, and +2, following the same procedure in collecting samples.

In only five (30 percent) of the cases was there an increase in the blood sugar level amounting to over 40 mg. percent within the first hour. The highest increase was of 50 mg. percent, and the lowest in this group was 42 mg. percent.

SUMMARY

According to Todd and Sanford,[21] when 100 grams of glucose are ingested by normal individuals in performing a glucose tolerance test, a sharp rise in the blood sugar to 150 mg. percent occurs within

21. J. C. Todd and A. H. Sanford, *Clinical Diagnosis by Laboratory Methods* (8th ed.; 1936), p. 366.

half an hour to one hour. The normal rise should be from 40 to 50 mg. percent during the first hour. Taking into consideration that most of the patients studied were markedly undernourished, we administered 1.75 grams of glucose per kilo of body weight. All the patients received less than 100 grams of glucose. Yet, in five (30 percent) of the cases there was an increase in the blood sugar to above 40 mg. percent within the first hour after the ingestion of glucose and the administration of histamine.

The average variation in the blood sugar in our cases after the administration of histamine was moderate, but significant, if it is compared with the average variation in the blood sugar levels without the use of the drug (See chart).

We tentatively suggest that the failure to produce a true hyperglycemic reaction in our cases may have been due to the probable depletion of glucose in the liver and other tissues in the body as a result of long-continued deprivation of carbohydrates due to faulty absorption through the intestinal mucosa.

	Without Histamine						With Histamine					
U. H. No.	Initial	½ Hr.	1 Hr.	2 Hrs.	3 Hrs.	Highest Variation	Initial	½ Hr.	1 Hr.	2 Hrs.	3 Hrs.	Highest Variation
A–825	89.3 mg.	95.2 mg.	105.3 mg.	94.6 mg.	84.7 mg.	16.0 mg.	93.0 mg.	111.1 mg.	100.0 mg.	83.3 mg.	90.0 mg.	18.0 mg.
A–930	86.9	93.0	102.6	97.6	87.3	16.0	79.7	106.4	105.3	101.0	90.9	27.0
A–1185	95.2	105.3	111.1	111.1	94.6	16.0	80.0	111.0	83.3	83.7	80.0	31.0
A–1297	83.3	86.9	86.9	83.3	83.7	4.0	90.9	111.1	111.1	100.0	111.1	21.0
A–278	83.3	90.9	105.0	100.0	90.9	22.0	90.9	125.0	144.0	100.0	90.9	50.0
A–432	76.0	80.0	83.0	79.0	71.0	7.0	76.0	125.0	125.0	125.0	125.0	49.0
A–141	83.3	90.9	111.0	111.0	83.3	28.0	90.9	111.0	133.0	125.0	90.9	44.0
A–191	90.9	100.0	111.1	111.1	90.9	20.0	100.0	116.0	120.0	106.0	100.0	20.0
A–38[a]	83.3	111.0	117.0	100.0	83.3	34.0	100.0	100.0	142.0	117.0	100.0	42.0
A–305	83.3	90.9	90.9	83.3	83.3	7.0	83.3	125.0	111.0	90.9	83.3	42.0
A–271	83.3	83.3	90.9	83.3	83.3	7.0	100.0	125.0	111.1	111.1	100.0	25.0
A–685	93.0	93.0	92.0	90.9	92.6	.0	80.0	117.0	102.0	76.9	74.1	22.0
A–816	82.6	84.7	86.2	84.4	83.0	4.0	84.7	88.5	90.1	88.9	80.2	6.0
A–817	74.3	80.0	81.3	80.2	77.7	7.0	88.5	90.9	92.6	95.2	76.6	7.0
A–37	90.9	100.0	100.0	90.9	90.9	9.0	83.3	100.0	90.9	90.9	83.3	17.0
A–285[b]	111.1	111.1	100.0	100.0	100.0	.0	100.0	111.0	100.0	100.0	100.0	11.0
A–858	73.3	83.3	99.0	88.9	75.5	16.0	87.0	95.0	90.9	86.0	85.0	8.0
Average	86.0	87.0	92.0	93.0	85.0	12.2	89.0	100.0	103.0	99.0	91.0	26.3
Average Variation		1	6	7	—1			11	20	10	2	

[a]Patient suffering from hyperthyroidism.
[b]Patient suffering from hookworm disease.