Hypoglycemia

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Less than a year after the discovery of insulin, I had the good fortune to be one of a group of physicians invited to Toronto to arrange an extended clinical investigation of the use of insulin. Consequently I was one of those who received the early lots of insulin.

At that time my colleague, Dr. Walter Boothby, was studying the calorigenic action of epinephrine. He had found that the injection of epinephrine provoked not only a quick rise in the level of blood sugar but even more quickly a precipitate 30 or 40 per cent elevation of the metabolic rate. No one at that time had made any effort to find out if insulin had calorigenic activity like that of epinephrine or thyroxin. The fact, or at least we then thought it was a fact, that insulin hastened the burning of sugar, made the question very pertinent.

I had been working with Dr. Boothby on other metabolic phenomena in diabetes and it was natural for us, when we received that first insulin, to measure the oxygen consumption and carbon dioxide excretion of the patients to whom we gave it. We soon found that an insulin injection would provoke a transient increase in the metabolic rate, but this happened only if and when the level of the blood sugar had fallen below the normal fasting level.

We were puzzled at first by this effect of insulin on the metabolic rate and so we staged an experiment using the nondiabetic person, Russell Wilder, as a subject. Now it happened in those years that I was a victim of ragweed hay fever and had been in the habit, in the ragweed season, of injecting myself with epinephrine to relieve asthmatic symptoms. I thus had experienced personally the palpitation, sweating and feeling of anxiety provoked by epinephrine. The metabolic mask was bound over my face; insulin, in a dose of 30 units, was injected; and every 10 minutes the expired air and the blood were analyzed, the former for carbon dioxide and oxygen, the latter for glucose. Nothing unusual was experienced at first, but shortly after the fourth 10-minute period I was conscious that my arteries were pounding and my pulse and respiration were accelerated, and that I was sweating and experiencing a feeling of anxiety which I associated with injections of epinephrine. It occurred to me that these symptoms might be due to epinephrine secreted by my own adrenal glands and that this could be a purposeful phenomenon designed to release sugar from the liver and thus prevent extreme depression of the level of blood sugar.

In another room, in the meantime, Dr. Boothby had been receiving up-to-the-minute reports of the results of the analyses of the blood and the expired air. He was plotting these (Figure 1), and was struck by the similarity of the rapidly rising metabolic rate to that previously obtained when epinephrine was injected. He reached the same conclusion that I had, namely that the falling blood sugar had provoked release of epinephrine and that the epinephrine, not the insulin, was

Lecture delivered at meeting of New England Diabetes Association, Joslin Auditorium, New England Deaconess Hospital, Boston, Massachusetts, November 6, 1951.

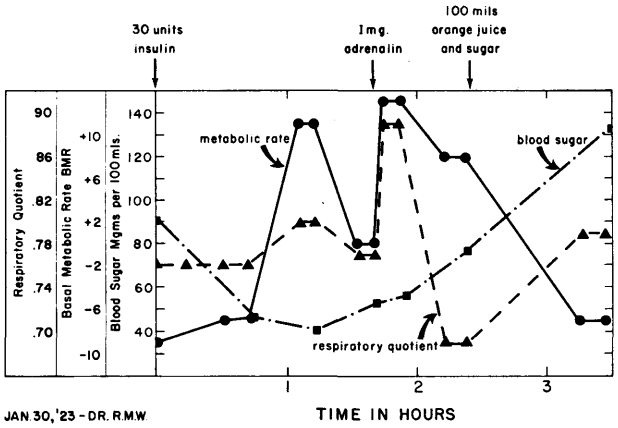

FIGURE 1 Metabolic rate, respiratory quotient and blood sugar levels before and following injection of insulin

responsible for the calorigenesis which was observed.

These observations were included with others in my report to the Insulin Committee in Toronto. Before they were published,[1,2] I gave a lecture in Boston, during which I reported on these studies. Dr. Walter Cannon, of blessed memory, was seated in the front row, and when I came to the account of the calorigenic effect of the hypoglycemia provoked by insulin I could clearly see that he was manifesting symptoms of epinephrinemia.

"The twin sisters, clinical observation and laboratory experiment, have walked in the field of diabetes very closely hand in hand." I am paraphrasing now from a friend and colleague in King's College, London, Dr. R. D. Lawrence.[3] Sometimes one has led, sometimes the other. But whichever led, the other soon proceeded to further progress to their mutual benefit and stimulation. We clinicians must gratefully acknowledge that the physiologist or biochemist usually has been out in front, but I take no little pleasure in the good fortune which was mine on that occasion to sow a seed in such a fertile soil as Professor Cannon's ear. He was working at the time with the denervated dog's heart and very soon thereafter could provide effective evidence of release of epinephrine by hypoglycemia. Thus another link was forged in the chain of balanced reactions whereby homeostasis is maintained in what Cannon later called the *Wisdom of the Body.*

It was shortly after announcing his and Dr. Best's discovery of insulin that Dr. Banting told me of their indebtedness to Mann and Magath, who only a year before had described the symptoms and fatal consequence of the hypoglycemia which they had induced in dogs by total removal of the liver. The symptoms could be arrested and the lives of the hepatectomized dogs could be prolonged by injecting glucose. Had it not been for this knowledge, Banting and Best would probably have attributed what they later called the insulin reaction, and which they saw when using their pancreatic extracts, to a toxic property of the extracts. Others who had investigated pancreatic extracts in earlier years may have made this mistake. Otherwise insulin might have been discovered ten or twenty years earlier! But of course we must remember that Banting and Best had available a micro-method for blood sugar analysis which their predecessors lacked.

Among the early visitors to the Toronto Laboratories when Drs. Banting, Best, Macleod and Collip, and their clinician associates Drs. Campbell and Fletcher, were pioneering with the early lots of insulin, was Dr. Seale Harris of Birmingham, Alabama.[4] He was quick to recognize that the symptom complex induced by insulin hypoglycemia was not unlike that which he had seen occurring spontaneously in certain of his patients. Soon thereafter he began reporting cases of unstable blood sugar. When the blood sugar levels fell, the patient became hungry, weak, tremulous and anxious, with hyperpnoea, tachycardia, sweating and occasional diplopia. Putting two and two together, Dr. Harris came to the conclusion that the episodes of hypoglycemia suffered by the patients in these cases were induced by an excess of insulin secreted by the pancreas. Consequently he came to diagnose this symptom complex as hyperinsulinism or dysinsulinism.

The conclusions reached by Dr. Harris were unacceptable to many because it was recognized by them that hypoglycemia and the symptoms which accompany it could result from several abnormalities in which the pancreas was not involved. Among such abnormalities were hypopituitarism, hypoadrenalism, some organic lesions of the central nervous system and some diseases of the liver, notably von Gierke's disease, so-called glycogenosis.

In 1927 a patient came to the Mayo Clinic presenting symptoms like those provoked by an excessive dose of insulin. However, he had had no insulin. I recently had read an article by Wagner and Parnas of Vienna that contained a report of glycogenosis in the case of a child. I was therefore on the lookout for such cases; and when this man was brought to my attention I thought at first that he might have this disease. However, our studies of the case did not bear out this supposition. Later, when the abdomen was explored at the patient's insistance and mine, a cancer of the pancreas was encountered. In the liver were a number of metastases. A bit of tissue was obtained from one of these and ex-

amined microscopically. It appeared to be composed of pancreatic island cells which looked like beta cells. The patient died some four weeks later. Necropsy was permitted, and extracts were obtained from the metastatic cancer, as well as from the tumor in the pancreas. Both extracts lowered the blood sugar when injected into rabbits; that from the metastases possessed activity representing an insulin content of not less than 40 units for each 100 grams of tissue. The case was reported jointly with Dr. Frank Allan, who was with us at that time, the chemist Dr. Marschelle Power, and the pathologist Dr. H. L. Robertson.[5]

This experience alerted us to look for cases of tumor of the pancreas with insulin activity, and before long more insulomas were discovered by ourselves and others. Some of them were malignant, others were benign. When these could be removed, the patients' episodes of hypoglycemia would completely disappear. However, there were other cases in which exploration would reveal no tumor. In some of them a second operation or necropsy would eventually reveal the presence of a tumor, but not in all. Especially confusing was a larger group of cases in which the patients' symptoms usually were less severe, cases resembling those described by Dr. Seale Harris. Operative search for insuloma in such cases was almost always fruitless.

Eventually we came to recognize that the patients in very many of these milder cases presented instability not only of the level of blood sugar but also of the vasomotor system—vasomotor instability not infrequently accompanied by emotional instability. A very few turned out to be malingerers, diabetic patients, nurses, or others acquainted with the use of insulin, who were purposely but surreptitiously injecting themselves with overdoses. Such malingering can be detected most conclusively by introducing a minute amount of radioactive iodine into the insulin container and later checking on the patient's urine with a Geiger counter. A fellowship assistant had that bright idea. Usually, however, the insulin reactions of malingerers are quite severe so that they resemble more those of patients with insular tumors.

It was also noted that the patients in these milder cases almost always developed their "reactions" in the daytime, three hours more or less after a meal, never at night, and never before breakfast. We had somtimes seen reactions which resembled theirs in diabetic suspects given a glucose tolerance test. The curve of the blood sugar level in such cases would rise more abruptly than is customary and later fall well below the base line. Furthermore, the patients in these milder cases would recover from their episodes of hypoglycemia spontaneously and rather promptly. This contrasted sharply with the behavior of the patients who had insulomas and who recovered from their episodes only after hours, if at all, unless they were given sugar.

So we introduced a diagnostic test—a fasting test which proved useful for separating the goats from the sheep. The patients were deprived of food from one evening's meal until the evening meal of the second day thereafter. Drinking water was permitted, but, because nicotine may stimulate the sympathetic nervous system, tobacco was prohibited. The level of blood sugar was examined every six hours and also whenever any symptoms developed. Exercise was restricted. The patient could be clothed and out of bed, but remained in his room under continuous surveillance.

The fasting test revealed that most of the patients in whom insulomas were detected later by the surgeon developed severe signs of hypoglycemia within from 6 to 36 hours. A few went longer without symptoms, but their blood sugar levels were down to 50 mg. per cent or lower by the second day or earlier. The other patients, those with milder symptoms and other instabilities, would behave quite differently. The level of their blood sugar would fall to 60 or 70, but it would not go any lower throughout the test period. Consequently these patients had no symptoms during fasting.

We called this "neurogenic hypoglycemia." Such cases can be detected also by a glucose tolerance test to which the patient usually, but not always, will respond with a more abrupt than normal rise in the level of blood sugar, followed in 3 hours or thereabouts by a fall to 60 mg. per cent or less. At that time they develop symptoms which, on occasion, are severe. However, the glucose tolerance test is less helpful for differential diagnosis than the fasting test, for sometimes patients with insuloma will respond with a similar sharp elevation and subsequent excessive fall of the level of blood sugar.

However, even though patients with hypoglycemia of the neurogenic type have no tumors or other hyperplasia of their islet tissue, we have not as yet excluded possible excessive function of their histologically normal beta cells. It is known that hyperglycemia provokes excretion of insulin by these cells. It has been supposed by certain scientists, although proof of this has not as yet appeared, that these cells also can be activated by the vagus nerve. In either case, Dr. Harris would be justified in his conclusion that the hypoglycemia in these cases was insulogenic. He, therefore, would be correct in diagnosing this as dysinsulinism.

However, it also is possible that either the stimulus of hyperglycemia or neurogenic stimuli are directed at the liver rather than the pancreas, and that in consequence this organ fails in its normal function of adding sugar to the blood from its glycogen reserves when the level of blood sugar falls. In that case excessive insulin would not be involved, and the designation insulogenic hypoglycemia would be incorrect.

This question, up to now, has not been answered for lack of a method to determine satisfactorily the amount of insulin in circulating blood. The technical difficulties involved in an assay of the blood for insulin can best be appreciated by recalling that the totally depancreatized man—and several patients are surviving now who for one reason or another have had the pancreas removed —requires only about 30 units a day. According to Waters and Best,[6] even if we assume that this insulin is equally diffused through the fluids of the extracellular compartment and that none of it is bound by cellular membranes, it would represent in a man weighing 60 kg. no more than a concentration in the order of one or two ten thousandths of a unit per cc. of blood, or 2×10^{-4}. How can such minute amounts be measured? It seems, however, that a method for doing this is right around the corner.

It will be recalled that insulin preparations formerly were assayed by injection into rabbits, and that a unit originally was defined as the amount of insulin necessary to provoke convulsions in a rabbit of a certain weight. As little as 0.01 units is convulsive for a mouse and less than this will lower the level of blood sugar to a detectable degree. In 1938, Hemmingsen and his associates in Sweden found that removing the adrenals of the mouse would increase its sensitivity to insulin about 5 times, so that 0.002 of a unit was detectable.[7] Gellhorn and others in 1941, at the University of Minnesota, found that hypophysectomy and adrenomedullectomy increased rat sensitivity to such a degree that 0.0002 units was detectable.[8] This was getting close to what might be required to assay the insulin in the circulating blood, but the question then arose as to whether insulin secreted by the rat's own pancreas was or was not affecting the results.

To settle this matter Dr. Evelyn Anderson and her associates alloxanized rats, and then removed the adrenal medullas, and subsequently the pituitaries.[9] Such animals proved so sensitive that only 0.125 milli-units (little more than 0.0001 units) of insulin produced detectable effects. The lowering of the blood sugar by larger doses was proportionately greater, as is shown by the chart from her report reproduced in Figure 2. A straight line relationship is observed between the logs of milli-units of insulin and the depression of blood sugar. Using this sensitive preparation, she and her associates obtained positive results from perfusion of the rat's pancreas in vitro, provided the pancreas of the rat was stimulated by perfusing sugar; but negative results (no evidence of insulin) when the sugar content of the perfusate was low. She also found that giving growth hormone would inhibit the stimulating effect of the perfusions of sugar.[10, 11]

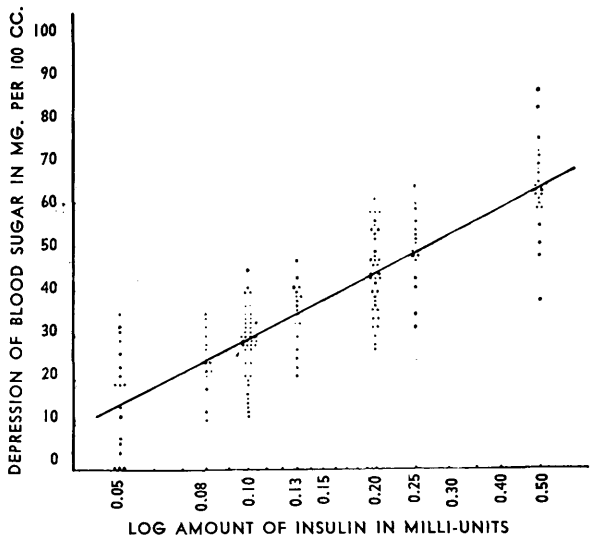

FIGURE 2 Relation of depression of blood sugar to log milli-units of insulin. Anderson, et al. [9, 10]

At this point I would like to refer to the recent work of Dr. Joseph Bornstein, a research fellow of the Baker Memorial Institute of Melbourne, Australia.[12] I have been rather out of touch with diabetes literature for the past year or so and did not know about his studies until I met him at Kings College, London, last June, through the kindness of Dr. R. D. Lawrence. Dr Bornstein is a jump or two ahead of everyone. Using rats which he has made diabetic with alloxan and has then hypophysectomized and finally adrenalectomized, he can detect as little as 0.05 milli-unit, or one twenty-thousandth of a unit, of insulin or even less. The depressions of the level of blood sugar obtained by him are proportional to the dose of insulin injected (Figure 3), a straight line relationship between the logs of insulin and the depression of the blood sugar. This result is exactly comparable to that of Dr. Anderson. However, he has gone much further. His controls are good and the results are quite impressive. The procedure is time consuming; nevertheless he has now made many determina-

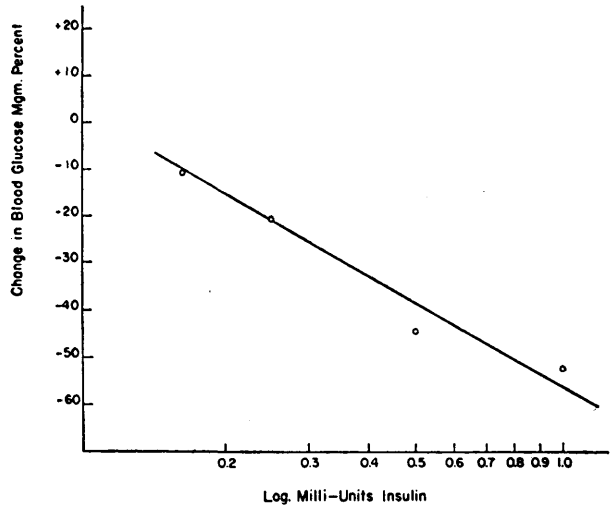

FIGURE 3 Relation of depression of blood sugar to log milli-units of insulin. Bornstein [11]

tions of the insulin content of circulating blood in normal persons before and after giving them sugar, in several diabetic patients, and in two patients with insulin-producing tumors.

Time does not permit a full review of Dr. Bornstein's observations. Briefly it appears that the amount of insulin in the circulating blood of 14 normal fasting subjects was detectable, but only barely so—from 0.025 to 0.05 of a milli-unit per cc. When sugar was injected the amount increased to peak levels, which ranged from 0.28 to 0.34 milli-units, or 0.0003 units per cc. The peak was attained at about 2½ hours after the glucose was injected, considerably later than the peak of the blood sugar curve. After that the fall was fairly rapid. In five cases of severe diabetes the values for insulin were zero, both before and after giving sugar to the patient. In milder diabetes, most of them being cases recently discovered in obese women, insulin was detectable after giving sugar. The amounts found approached but usually were smaller than those found in normal subjects. There were 9 such cases; in them the peak values per cc. of circulating blood were 0.10, 0.13, 0.17, 0.19, 0.19, 0.20, 0.24, 0.29 and 0.32. In the two cases of insuloma with symptoms of hyperinsulinism the fasting values were many times those found in the fasting normal subjects, higher even than any peak values of normals after sugar.

Dr. Bornstein has not yet studied patients with what we have called neurogenic hypoglycemia, but he has developed a method with which I think it will be possible to decide whether in this type of case we are dealing with excessive insulin secretion or not. He has confirmed Dr. Anderson's observation that growth hormone inhibited the secretion of insulin by the pancreas, but is uncertain about the interpretation of this. He suspects that the failure of the blood of persons who have been given growth hormone as well as sugar to lower the level of blood sugar in his sensitive test animals might mean that the growth hormone stimulates the alpha cells to a secretion of hyperglycemic factor, thus masking the effect of insulin.

The only drawback to early and more extensive clinical application of this procedure is the tediousness of the preparation of the test animals. Mortalities are high and control injections of insulin in known amounts are required before and after testing the blood for assay. It appears, however, that short cuts may be possible so that soon we will be able to use this as a tool of clinical significance, to tell us not only whether or not the hypoglycemia we encounter in a given case is insulogenic, but also whether our diagnoses of diabetes mellitus are sound.

REFERENCES

[1] Wilder, Russell M., Boothby, Walter M., Barborka, Clifford J., Kitchen, Hubert D., and Adams, Samuel F.: Clinical observations on insulin. J. Metab. Research 2:701-28, 1922.

[2] Boothby, Walter M., and Wilder, Russell M.: Preliminary report on the effect of insulin on the rate of heat production and its significance in regard to the calorigenic action of adrenalin. Med. Clin. North America 7:53-56, 1923.

[3] Bornstein, J., and Lawrence, R. D.: Two types of diabetes mellitus, with and without available plasma insulin. Brit. Med. J. 1:732, 1951.

[4] Harris, Seale: Hyperinsulinism and dysinsulinism. J.A.M.A. 83:729-33, 1924.

[5] Wilder, Russell M., Allan, Frank N., Power, M. H., and Robertson, H. E.: Carcinoma of the islands of the pancreas. J.A.M.A. 89:348-55, 1927.

[6] Waters, E. T., and Best, C. H.: The importance of developing an accurate method for the estimation of insulin in the blood. Proc. Am. Diabetes A. 7:171-83, 1947.

[7] Hemmingsen, A. M., Nielsen, A., and Nielsen, A. L.: Effect of insulin on adrenalectomized rats and mice. Acta Med. Scandinav. Supp. 90:105-10, 1938.

[8] Gellhorn, E., Feldman, J., and Allen, A.: Assay of insulin on hypophysectomized, adreno-demedullated, and hypophysectomized-adreno-demedullated rats. Endocrinology 29:137, 1941.

[9] Anderson, Evelyn, Lindner, Erna, and Sutton, Virginia: A sensitive method for the assay of insulin in blood. Am. J. Physiol. 149:350, 1947.

[10] Anderson, Evelyn, and Long, J. A.: The effect of hyperglycemia on insulin secretion as determined with the isolated rat pancreas in a perfusion apparatus. Endocrinology 40:92, 1947.

[11] —: Suppression of insulin secretion by the growth hormone of the anterior pituitary as determined with the isolated rat pancreas in a perfusion apparatus. Endocrinology 40:98, 1947.

[12] Bornstein, J.: A technique for the assay of small quantities of insulin using alloxan diabetic, hypophysectomized adrenalectomized rats. Australian J. Exper. Biol. & M. Sc. 28:87-91, 1950.