Glucagon as a Regulator of Insulin Function

George E. Anderson

Medical literature has given the impression, apparently an erroneous one, that glucagon is antagonistic to insulin (*1–3*). This view has been fostered by the fact that hyperglycemia can be produced by the hormone. Our group at the State University of New York College of Medicine has brought forth evidence in man and in the dog by a series of acute experiments to suggest that in normal individuals insulin and glucagon are mutually synergistic. The following observations have been made.

1) Glucagon in man and in the dog acts as a potentiator of insulin function, it being capable on intravenous administration of adding immediately and materially to the momentum of a fall in blood glucose induced by a small dose of glucagon-free insulin given by vein. Extrinsic glucagon, on the other hand, seems to be able to weight a momentum in either direction, implementing a rise or a fall, depending on which of these two phases it happens to meet (Fig. 1).

2) Glucagon seems to serve as a trigger mechanism to insulin function throughout the *postabsorptive* period, much as glucose acts as the incitor of insulin function during the *absorptive* state. Postabsorptive blood glucose is in no sense a fixed value (*4*). It is constantly oscillating throughout the entire postabsorptive period, changes taking place from moment to moment. When these are recorded at 1-minute intervals, the curves produced (Fig. 2, before "insulin I.V.") follow a characteristic pattern. We have found that the level of blood glucose is variable, and markedly so, even down to the 15-second interval (Fig. 3). The sugar has been identified as being true glucose by parallel quantitative fermentation procedure. The Somogyi-Nelson macro true-glucose method was employed in all determinations, many of which were in duplicate. Chi-square tests on aliquots of multiple single blood samples, as well as on the variations found in the curves, have shown that the findings are statistically significant and far beyond the range of error incidental to the methodology employed.

Figure 3 also shows curves drawn at 1-minute intervals, which exhibit undulations characteristic of those found in all of the 100 men and 20 dogs studied. These undulations are consistently present throughout the entire postabsorptive period. They are irregular or aperiodic in timing rather than rhythmic at any time. It might well be speculated that some of the variation, especially in the 15-second oscillations, may be related to periodic changes in blood circulation at the capillary and venous levels incidental to pulsatory phenomena. This could conceivably change the glucose content of venous blood returning from the capillary regions. Such change arising from transient capillary pooling might be expected in venous blood but not in arterial. With carefully controlled constancy of blood flow and simultaneity in blood sampling, there is consistently a lowering of the venous level precisely at the time of the rise in the arterial blood glucose. This finding would strongly suggest that these waves are more related to the supply and utilization of glucose (the gradient of entrance into cells) than to mechanics of circulation.

The descents in the postabsorptive wavelets in all probability represent changes in the gradient of entrance of glucose into peripheral cells, a well-accepted function of insulin. The glucose rises in the undulations are less easily explained. They probably represent the release of glucose from liver glycogen through activation of liver phosphorylase. Such action could take place via adrenal medullary or glucagon function, or through both, or by some mechanism as yet unexplored or unidentified. It is our opinion that the transient rises in blood glucose result from glucagon effect. This has been suggested by our studies in animals, and especially in man. It is postulated that the waves represent an interplay of the two hormones, insulin and glucagon, one activating but limiting the function of the other.

Acute dog experiments in which adrenal medullary effect was abolished by heavy ergotaminization and subsequent surgical resection of the adrenals failed materially to change the normal postabsorptive undulations, suggesting that in normal animals glucagon is capable, apart from any activity of the adrenal medulla, of producing transient releases of glucose into the blood. On the other hand, in a dog subjected to abdominal evisceration, and thus deprived of all known possible sources of glucagon and capable of only short survival, the arterial undulations disappear and are replaced by a relatively flat arterial glucose level (Fig. 4, "post-op."). The

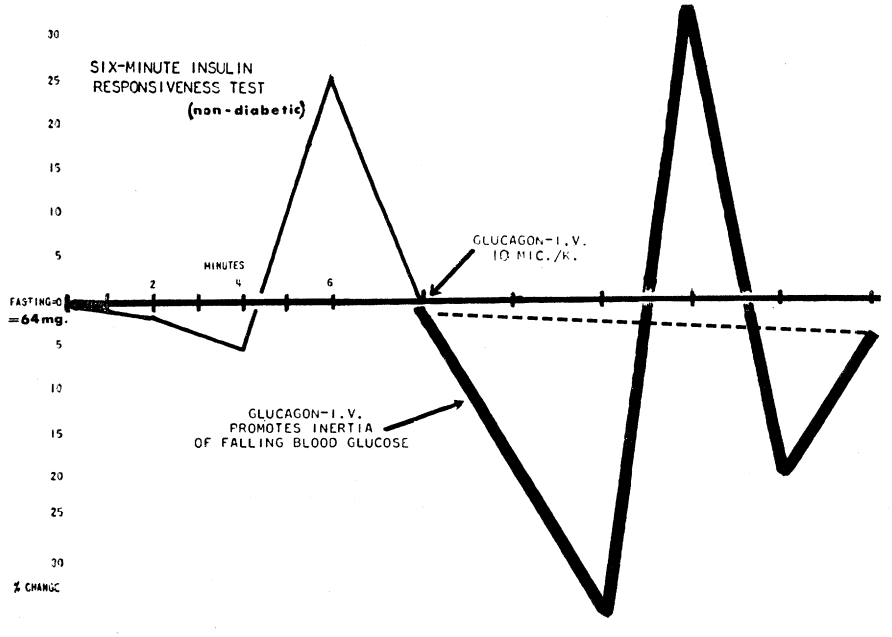

Fig. 1. Venous glucose curves in man (postabsorptive). At zero time, subject received 3 units of glucagon-free insulin—I.V. Note reinforcing of the hypoglycemic effect of insulin, a "pumping up" or crescendo of the glucose flings, which is initiated by intrinsic glucagon (the upward fling at 4 minutes) but furthered by glucagon I.V.

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wavelets are, however, immediately reactivated by the intravenous injection of glucagon (10 microgram per kilogram). Since the liver has been ablated, the source of the glucose for even these small increases after glucagon by vein comes up for question: Could the glucose be from peripheral sources?

Experimental work in man suggests that the transient facile spurts in blood glucose are presumably incidental to intrinsic glucagon effect, each rise seeming to "trigger" into action a short phase of insulin function. With each brief spurt of arterial glucose, there is, both in the dog and in man, a fall in venous glucose and an accompanying phase of increased arteriovenous difference (probably increased peripheral utilization) (see Fig. 2) (*3, 5*). Accordingly, glucagon would seem to be capable of promoting the peripheral utilization of glucose. Admittedly, the presence of an increased arteriovenous difference does not necessarily mean an increase of cellular utilization. Proof of such utilization must await tagged carbon studies; but, with carefully controlled circulatory constancy in animals, the simultaneous fall in venous glucose attending each arterial rise would strongly suggest tissue utilization of the glucose as the cause of the phenomenon.

3) Insulin, on the other hand, during the postabsorptive period would seem to trigger intrinsic glucagon into action. In 60 individuals with low mean fasting blood glucose levels, a small dose (1 to 3 units) of glucagon-free insulin given by vein primarily caused a prompt rise (*6–8*), rather than fall (Fig. 1) in blood glucose anticipated with insulin. In the absence of symptomatic evidence of adrenal medullary activity or of changes in the titers of lactic acid in the blood, it is likely that these rises in blood glucose were due to glucagon. In these same people, after the initial effects of the insulin had been registered, an intravenous injection of glucagon promptly caused a marked sharpening and precipitous accentuation of both the rises and the falls in blood glucose—a "pumping up" (Fig. 1) or priming effect of parenteral glucagon on the insulin effect already induced by the glucagon-free insulin. This intensification of insulin effect does not necessarily mean further production of insulin by the organism, since it occurs also in the abdominally eviscerated dog, in which the only possible available insulin is that which may still remain in the tissues after surgery. Evidently, glucagon activates and potentiates the function of insulin in tissues.

4) In the eviscerated ergotaminized dog under the influence of glucagon administered by vein, there is occasionally exhibited a venous return from an isolated extremity which is higher in its

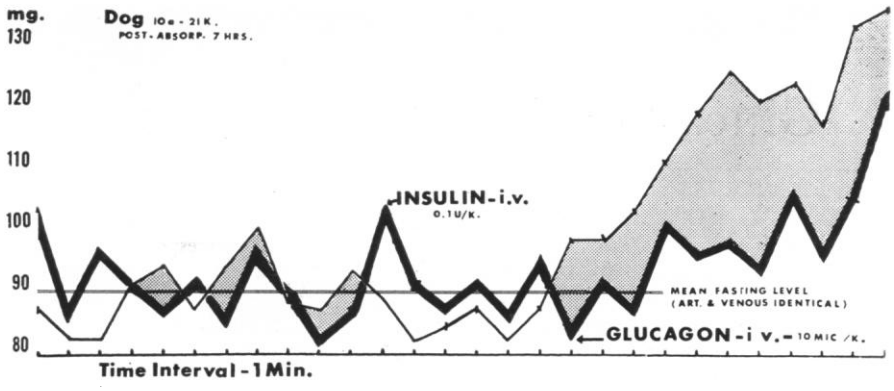

Fig. 2. One-minute macro arterial and venous blood-sugar curves in dog. Heavy line, venous; fine, arterial; shaded, a-v difference. Note the negative a-v difference immediately after glucagon-free insulin I.V. and the subsequent markedly accentuated differences after glucagon I.V.

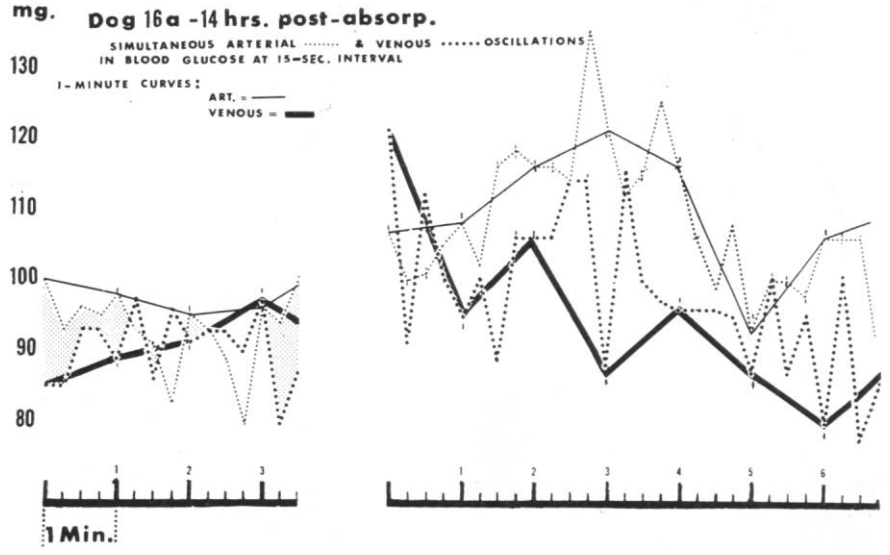

Fig. 3. In an intact normal dog, note intense excursion from reading to reading. The break in the curves represents an interval of 1 hour. A resumption of readings shows even more pronounced oscillations. The explanation for this accentuation we do not have.

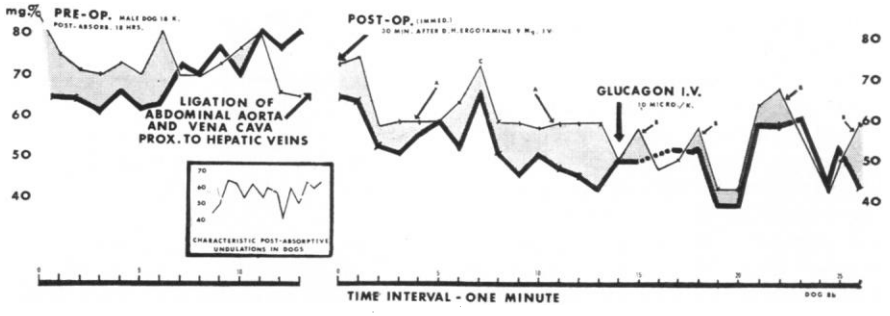

Fig. 4. Glucose curves after abdominal vascular ligations. Arterial and venous lines as in Fig. 2. Note flat level (A) over 10 readings, interrupted only once by an upward fling (probably a final effect of glucagon still residual in the peripheral circulation). Between 13 and 14 minutes, there is another drop in arterial glucose which is halted, presumably by glucagon I.V. Note prompt return of the glucagon-effected undulations. The probable source of this new glucose is peripheral tissue, since the animal has no functioning liver. This glucose rise is small, the result of depletion by extensive surgery and a long interval (18 hour) since food ingestion.

glucose content than is the arterial supply to the extremity. This finding is quite challenging since it suggests that under certain circumstances glucagon may be capable of functioning through enzyme systems other than liver phosphorylase in the release of glucose from glycogen. The phenomenon is presently being explored by studies in completely isolated extremities, the venous blood being collected in reservoirs. In addition, metabolic incubator studies are also in progress.

The seeming paradox of glucagon action, now raising and now lowering blood glucose, evidently depends precisely on which phase of the glucose wave is being exposed to the hormone. Whether the direction of the blood-glucose trend is upward or downward, the momentum of an uncompleted phase is increased or potentiated by glucagon.

The implications of the afore-described findings in clinical diabetes are legion. Is the clinical diabetic or the prediabetic individual one who has a perverted insulin-glucagon functional relationship? In these people, does insulin, intrinsic or extrinsic, in small "catalytic" dosage have the functional effect of touching off an overresponsive intrinsic glucagon mechanism at a high level of blood glucose? In similar manner, in *nondiabetic* individuals glucagon activity with its hyperglycemic effect is thrown into function by small doses of insulin only when this is administered at low mean fasting glucose levels. This finding was made in 100 nondiabetic individuals. If a perverted functional relationship exists in the diabetic suffering from a relative deficiency of insulin, the afore-mentioned concepts open up wide vistas for improving the underlying functional defect. Fortunately, in many individuals with the obese-adult type of diabetes, such apparent perversion of function is reversible by adequate therapy (*8*). This improvement is readily measurable by the so-called "six-minute responsiveness test to glucagon-free insulin," a measure of the body's ability to *respond* to insulin rather than to make it (*9, 10*).

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J. P. Marble, Research Geochemist

John Putnam Marble was born in Worcester, Massachusetts, 30 May 1897, and died suddenly in Washington, D.C., 6 June 1955. Since the drysaltery business was the pursuit of the family, his interest in chemistry developed at an early age. He graduated *cum laude* from Williams College in 1918 after election to Phi Beta Kappa in his junior year. He was corecipient of the John Sabin Adriance Prize in Chemistry. He entered the Chemical Warfare Service of the Army in 1918; after his discharge in early 1919, he attended Clark University as a part-time student. At the end of the school year he entered the family drysaltery business, where he continued until 1926. He then began his work at Harvard University, taking his master's degree in chemistry in 1928 and his doctorate in analytical chemistry in 1932 under G. P. Baxter.

He began, then, to find his broad interests, applying his knowledge of chemistry to the research analysis of radioactive minerals in the laboratories of the U.S. Geological Survey (1931–35) and the Smithsonian Institution (1935–55) under the auspices of the Committee for the Measurement of Geologic Time of the National Research Council. This work still occupied much of his time up to his death. During the summers through the 1930's and into the 1940's, he worked at Harvard on chemical atomic weights and devoted some time at Yale in 1939 to the preliminary preparation of thorium standards. During World War II he served as technical aide and special assistant of the National Defense Research Committee of the Office of Scientific Research and Development. His work on radioactivity and isotopes took him into close association with Alfred C. Lane, with whom he worked on the Committee on the Measurement of Geologic Time, first as a member, then as vice chairman (1936–46), and, from shortly before Lane's death, as chairman (1946–55). His work in preparing reports of the committee, with extensive critical international bibliographies, was increasingly large as the field became more and more active. The reports are a valuable addition to the literature, and the demand for them is increasing. In addition to his annual reports of the Committee on the Measurement of Geologic Time, he was the author of some 20 papers on age determinations and related subjects published in various journals, chiefly the *American Mineralogist.*

His was a work of love, and his diligence in pursuing it so actively bespeaks the character of the man and his true qualities as a scientist. There was something of a Newton and a Darwin in his perseverance and his integrity.

The work on isotopes and geologic time took Putnam more and more afield from chemistry into the realms of geochemistry and geophysics, and his boundless energy to pursue the tasks that he undertook placed many calls on him. He claimed not to like people, and yet he was always doing for people—as trustee of Sidwell Friends School, as chairman of the Committee on Meetings of the American Geophysical Union, and, for the last 2 years, as its general secretary, and in various other activities. He liked people and liked doing for them, but his Quaker background caused him to dislike the controversy and tensions that often arise from disagreements and differences of opinion. The problems involved weighed on him heavily, whether as general secretary of the American Geophysical Union, a member of the Council of the American Association for the Advancement of Science, or secretary-treasurer of the American Geological Institute. His life was truly that of a scholar who rather resented the intrusions of modern-day life caused by the rapid development of science.

He was never happier than when he was at work in his laboratory, unless it was with hammer and lens on scientific field trips, or exploring the wilds of the Adirondack Mountains, where he spent many summers.

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