EDITORIALS

THE INSULIN CONTENT OF PANCREAS

At various times, starting soon after insulin was isolated, we have been interested in the amount of insulin in degenerated pancreas from the dog, in normal dog pancreas, fetal calf pancreas, normal beef pancreas, commercial pancreas from many species, in normal human pancreas and in pancreatic islet tumors. The variations in insulin content of beef pancreas with the age of the animal, the effect of starvation and of various diets on the insulin extractable from pancreas, and the effect of diabetogenic hormones from pituitary, adrenal or thyroid glands, of alloxan and related compounds, and of insulin itself, have all been investigated. In all these studies it has been fully realized that the amount of insulin extractable is the resultant of a number of factors and that we have little knowledge of most of them. The rate and amount of insulin formed in the islet cells, the rate of destruction in the islet cells (if this occurs), and the rate of liberation of insulin into the blood may be independent variables. But in spite of these reservations the data obtained have been stimulating and, when considered in relation to the metabolic state of the owner of the pancreas, highly informative. Of course we need to have accurate estimations of blood insulin routinely available, but then we would wish to know the rate of insulin secretion, the rate of its fixation, inactivation or destruction by blood or other tissues, and the rate of its excretion by the kidneys. We are progressing, and it is wise to consider the information we have available.

The extractable insulin of pancreas in animals is reduced by certain periods of fasting, by feeding a diet very rich in fat, and by giving a great excess of insulin. The fact that a diabetic type of glucose tolerance curve appears concomitantly with the reduction in insulin content suggests that one of the causes of the disturbed carbohydrate utilization is a decreased rate of liberation of insulin. We know that this is not the only cause. When pituitary extracts rich in growth hormone are given in large doses to susceptible dogs, the insulin content of the pancreas sinks almost to zero. The same is true after complete alloxanization. This state of affairs, considered in conjunction with the destruction of the beta cells and a severe diabetes which can be eliminated by the amount of insulin which we estimate is normally secreted, probably means that no insulin was being liberated. Tumors of the beta cells may yield 250 units of insulin per gram in contrast to 2 or 3 units from normal pancreas. This high value approximates the insulin content of pure islet tissue. The presence of insulin-rich tumors has been associated with

*The term "extractable insulin" is more exact and therefore preferable to "insulin content," but when the content has been estimated using the best available method of extraction, and the reader keeps this in mind, the two terms are interchangeable.

the clinical signs indicative of a high rate of insulin liberation, which may be restored to normal by removal of the offending cells. It is probably the absence of control of insulin liberation in the cells of the tumor rather than the increased number of islet cells which results in excess secretion of insulin.

It is entirely possible that a high rate of liberation of insulin might *reduce* the amount in normal pancreas.† There is some indirect but no direct evidence that this occurs. We do not know within what ranges the tremendous gradient between insulin content of beta cells and insulin content of blood, conservatively estimated as one million to one, is permitted to vary under normal or abnormal conditions. We know very little about the factors which control insulin formation. The molecule is presumably built up, in part at least, from dietary amino acids.

A great excess of sugar over a prolonged period may, in cooperation with normal or perhaps raised levels of diabetogenic substances, lead to the destruction of the insulin-producing mechanism in certain species of animals. A rise in sugar content of the blood perfusing the islands of Langerhans causes an outpouring of insulin. Diabetogenic pituitary extracts increase the insulin content of the pancreas in certain types of rats, but this has never been detected in the adult dog, whose islands are much more sensitive to the destructive effects of these substances. A rise in insulin content of pancreas might occur in the dog but escape detection by present methods. There are plenty of proliferative changes in islands, ducts, and acini in the early stages of pituitary administration. A temporary increase in the rate of liberation of insulin might be accomplished, without change in content, by an increase in the rate of production which corresponds precisely with the raised output. There might be an immediate fall in the insulin content of dog's pancreas when diabetogenic substances are given. A slight and transitory one would not be detected. We know that the decrease becomes very definite as the injections are continued but at this later stage there is no evidence of increased insulin output. This could be occurring and might easily be masked by the excess of the antagonistic substances. Blood insulin determinations will help to reveal the facts during this period when cessation of the injections of pituitary extract is followed by return of pancreatic insulin to normal levels.

If the level of blood insulin were the main factor controlling the insulin content of pancreas, one would expect that administration of an excess of insulin would lead to a fall in the level in pancreas. This effect is actually very well marked. The insulin content of pancreas may be reduced to a fraction of the normal level by giving large doses of insulin. One might expect also that hypo-insulinemia would lead to an increased rate of production and output of insulin. There are several great difficulties in the way of investigating this matter. The blood sugar rises when we deprive the animal of insulin unless the need for insulin is reduced by removal of opposing hormones. The increased sugar may be the stimulus rather than the decrease in insulin. Both blood sugar and blood insulin may prove to be factors regulating the output of insulin. We are just at the beginning of determinations of blood insulin (Bornstein and Lawrence).

The paper in this issue by Wrenshall, Bogoch and Ritchie records the results of by far the most thorough and comprehensive study of the insulin content of *human* pancreas as yet made. The actual figures for extractable insulin may change somewhat—there might even be a combined form of insulin which is not completely released by present methods. But this paper lays a firm groundwork for future developments. It answers some of the questions which have perhaps made other groups hesitate to enter the field. The actual findings speak for themselves and need little further comment. "Growth onset" diabetes and the form which waits for maturity, certainly lead to different levels of insulin storage in the pancreas. This does not prove, however, that the manner of production of the two types of diabetes is different. Something halts the decrease in insulin storage in the "maturity onset" group. Diabetic coma levels these differences and even the "maturity onsets" lose all their pancreatic insulin. Would storage of insulin have been restored to the pre-coma value if recovery from coma had occurred? How early in their diabetes do the "growth onset" types lose all their pancreatic insulin? There is some clinical evidence on this point which can perhaps be correlated with values for extractable pancreatic insulin.

In the future much more data on human pancreatic insulin will be secured. Insulin values in blood, at present of qualitative significance, will acquire greater reliability. It will be possible also to estimate in blood the amounts of each of the hormones which may oppose the anabolic effects of insulin. The physiological activities of liver and muscle cells obtained from patients by safe microbiopsies will be studied in the light of the

†The earlier work on Insulin Content of Pancreas was reviewed by Dr. R. E. Haist in Physiological Reviews, October 1944.

"spectrum" of their blood hormones. The pathologist using the refined histochemical methods of the day will report on the biopsy specimens and add his findings to the many which the clinician will evaluate.

—CHARLES H. BEST, M.D.

DIABETES DETECTION DRIVE—1951

Under the capable, enthusiastic and discriminating direction of Dr. John A. Reed of Washington, Secretary of the American Diabetes Association, the fourth annual campaign to discover unrecognized diabetes was launched in November 1951. A full week of national and local activities inaugurated a Drive which will continue on a modified scale throughout the year. Initiated by the American Diabetes Association in 1948, this campaign has broadened in scope and improved in effectiveness each year. The one this year is the largest and best yet.

Several important objectives are accomplished by the American Diabetes Association's detection activities. A substantial number of unknown cases is found. Many patients known to be diabetic are inspired to stop neglecting themselves. Perhaps of even greater importance, diabetics and the interested general public alike learn to understand diabetes better as a result of sound and authoritative information released through public channels during the Drive. Employment, insurance and other public attitudes are cultivated more intelligently thereby. Regional diabetes units are given an active and specific outlet for their energies in behalf of diabetics. Finally, the American Diabetes Association grows in prestige and in public confidence in direct proportion to the quality and amount of constructive accomplishment achieved in these and other areas by the campaign.

The medical profession must now be fully aware of the fact that the Association's basic philosophies in the conduct of this Drive are: help for all diabetic patients in all conceivable ways; active participation and direction by the profession; and avoidance of direct appeal for funds from the general public. The dignity and public trust resulting from these policies are assets which should be prized highly by everyone connected with the Association.

Many different patterns of performance in the execution of this work have evolved in various parts of the country. No standardized method has been accepted so far. Publicity efforts, urine testing procedures, follow-up diagnostic work, reporting of results and referral of patients for care are handled by a variety of different mechanisms, especially at local levels. This is as it should be, for the present at least. The best methods will emerge in time, with the Association acting as referee and clearing-house for the exchange of useful information. Probably a standardized method should never be adopted as long as active work is conducted independently by local diabetes units, each with its own problems and personnel. In the meantime the resourcefulness and imagination of many people working in a fertile field of common interest will perfect methods and mechanics more rapidly than a small national group could ever do.

The multitude of unselfish, crusading volunteers all over the country are to be congratulated for their interest, resourcefulness and devotion. Dr. Reed, and Dr. Howard F. Root who preceded him as commander of all detection activities, have won the admiration and confidence of the Association and the public for the energetic and wise manner in which the Drives have been conducted. The campaigns stand as imposing monuments of Association achievement.

—ARTHUR R. COLWELL, M.D.
President, American Diabetes Association

EMERGENCY MEDICAL CARE OF DIABETICS

Publication of the official Statement of the American Diabetes Association's Committee on Emergency Medical Care in *The Journal* of the American Medical Association in its December 1, 1951 issue[1] places the studies and plans of this Committee at the disposal of the medical profession, the Civilian Defense Administration and diabetics themselves. These plans were formulated as the result of over a year and a half of careful study intended to protect the interests of this large segment of population in event of war or any other major catastrophe. The emergency procedures recommended have been worked out in cooperation with the Federal Civilian Defense Administration and other responsible government agencies, the American Medical Association, and similar interested organizations. These recommendations should now be incorporated into all national and local programs designed to protect our civilian population in time of national emergency.

An abridgment of the original report appeared in the first issue of *Diabetes*,[2] together with a proposed handbill for general distribution, "The Diabetic and the Atomic Bomb." These simplified instructions to the patient should be reproduced by all responsible agencies