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Methodology and Clinical Application of Continuous *in vivo* Glucose Analyses

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By *Chr. Trendelenburg*

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Participants:

- Dr. A. M. Albisser, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada
 Prof. Dr. Dr. h. c. G. Berg, Forschungsabteilung für Ernährung und Stoffwechselkrankheiten, Medizinische Klinik mit Poliklinik der Universität Erlangen-Nürnberg, Postfach 3560, D-8520 Erlangen, Germany
 Mr. M. Bonnafé, Technicon International Division S. A., 12-14 Chemin Rieu, CH-1208 Geneva, Switzerland
 Dr. D. A. Gough, Elliott P. Joslin Research Laboratory, Harvard Medical School, 170 Pilgrim Road, Boston, Mass. 02215, USA
 Prof. Dr. U. Gottstein, Medizinische Klinik des Bürgerhospitals, Nibelungenallee 37-41, D-6000 Frankfurt/Main, Germany.
 Prof. Dr. K. D. Hepp, Institut für Diabetesforschung, Kölner Platz 1, D-8000 München 40, Germany
 PD Dr. H. J. Hinckers, Universitäts-Frauenklinik, Venusberg, D-5300 Bonn-Venusberg, Germany
 Prof. Dr. Dr. V. Klingmüller, Leibnizstraße 21, D-6800 Mannheim, Germany
 Prof. Dr. J. D. Kruse-Jarres, Klinisch-chemische und Experimentelle Laboratorien, Zentrum für Chirurgie, Universität Freiburg, Hugstetterstraße 55, D-7800 Freiburg/Brsg., Germany
 Prof. J. Mirouze, Clinique des Maladies Metaboliques et Endocriniennes, Hôpital Saint-Eloi, F-34059 Montpellier, France
 Prof. Dr. G. D. Molnar, Department of Medicine, Clinical Sciences Building, The University of Alberta, Edmonton, Alberta T6G 2G3, Canada
 Prof. Dr. E. F. Pfeiffer, Abteilung Endokrinologie und Stoffwechsel, Zentrum für Innere Medizin und Kinderheilkunde, Universität Ulm, Postfach 554, D-7900 Ulm/Donau, Germany
 Dr. R. Renner, Institut für Diabetesforschung, Kölner Platz 1, D-8000 München 40, Germany
 Dr. D. Sailer, Forschungsabteilung für Ernährung und Stoffwechselkrankheiten, Medizinische Klinik mit Poliklinik der Universität Erlangen-Nürnberg, Postfach 3560, D-8520 Erlangen, Germany
 Dr. G. S. Spathis, St. Helier Hospital, Wrythe Lane, Carlshalton, Surrey SM5 1AA, England
 Dr. Chr. Trendelenburg, Klinisch-Chemische und Experimentelle Laboratorien, Zentrum für Chirurgie, Universität Freiburg, Hugstetterstraße 55, D-7800 Freiburg/Brsg., Germany

Organization: J. D. Kruse-Jarres, Freiburg

Summary: Our insight into blood glucose regulation has been improved by continuous *in vivo* analyses. The basis for an artificial endocrine pancreas is provided by an automatic monitor connected to a computer which calculates the actual blood glucose concentrations, supervises alterations and controls infusion therapy. Glucose monitoring has a wide variety of potential clinical applications, such as diagnosis and therapy of carbohydrate disorders, supervisory measures during surgical operations, in intensive care and pregnancy, and observation and mathematical calculation of rhythms and diurnal variations.

The methodology of continuous blood glucose monitoring is still subject to difficulties as far as the sensor technique is concerned. Some progress in this field may be made by measuring the tissue glucose over a long period. For blood glucose monitoring, however, wet chemistry methods still surpass the sensor technique, even though an inconvenient time delay is a major disadvantage. Preliminary studies of continuous radioimmunological insulin monitoring *in vivo* provide better conditions to observe the main glucose regulating hormone.

Methodik und klinische Anwendung der kontinuierlichen Glucosebestimmung in vivo

Zusammenfassung: Der Einblick in die Regulierung der Blutglucose ist durch kontinuierliche *in-vivo*-Messungen wesentlich größer geworden. Durch Koppelung der vollautomatisch arbeitenden Meßmethode mit einem Rechner zur Berechnung der Blutglucosekonzentration, zur Überwachung von Konzentrationsveränderungen und zur programmierten Steuerung einer Infusionstherapie ist die Grundlage für ein künstliches endokrines Pankreas geschaffen. Die wesentlichen Anwendungsgebiete sind die Diagnose und Therapie von Kohlenhydrat-Stoffwechselstörungen,

die Überwachung während Operationen, in der Intensivpflege und während der Schwangerschaft, und die Beobachtung und mathematische Berechnung von Rhythmen und Tagesschwankungen.

Methodische Schwierigkeiten bereitet noch die Vollblut-Analyse der Glucose mit Hilfe eines Sensors. Verschiedene Vorgehen haben dagegen im Gewebe bereits gute Ergebnisse bei längerer Verweildauer gezeigt. Vorerst ist noch den naß-chemischen Verfahren bei der kontinuierlichen Blutglucosebestimmung der Vorzug zu geben, wenn hierbei auch hinderliche Zeitverzögerungen in Kauf genommen werden müssen. Erste Versuche einer kontinuierlichen Aufzeichnung radioimmunologisch bestimmten Insulins lassen auf eine baldige bessere Beobachtung des wesentlichen Glucose-regulierenden Hormons hoffen.

Introduction

Continuous blood glucose monitoring is still carried out only in a few specialized laboratories around the world, but the number of investigators is going to rise. The motives for adopting this methodology are varied. Approximately 20 years have passed since the beginning of continuous analysis by *Ferrari et al.* A great deal of hard work has been done to simulate blood glucose regulation by natural functions.

This workshop conference was convened to bring together workers in the field of continuous in vivo glucose analysis. It was made possible by the generous sponsorship of the German Society of Clinical Chemistry, which recognized the value to many medical disciplines of a meeting of experts in the field of blood glucose regulation for intensive discussions. There was a pleasant series of opportunities for formal and informal exchanges of views on accomplishments to date and prospects for future developments.

Methodology

General review of automated in vivo applications

M. Bonnafé, Geneva

Applications were described of analysis in vivo in the fields of pathology, physiology, pharmacology and cybernetics. The following problems were covered:

1. Heparinization in toto or the use of a double lumen cannula.
2. Separation of blood cells and interfering macromolecules by:
 - a) Dialysis
 - b) Agglutination and continuous filtration
 - c) Gravity by the technique of *Albisser*
3. Use of the technique for monitoring patients in acute care therapy.
4. Application to automatic maintenance of blood parameters at constant levels by feed-back systems.
5. Special applications to cell or bacteria culture and parasitology.

Discussion

The advantages of cuprophane over nitro-cellulose membranes are that cuprophane membranes are more

sensitive, and noncoated. The porosity is the same (4–6 nm), so the rate of transit through the cuprophane pores is faster (*Albisser*). The amount of blood drawn for the enzymatic methods of glucose determination is about 1 ml/h. Micro-electrodes do not consume as much, but they are very quickly coated with a protein film (*Pfeiffer, Bonnafé*). However, since they are very sensitive, high dilutions can be used. That leads to the advantage that there is less protein film on the electrode if used extracorporally (*Kruse-Jarres*).

The status of electrochemical sensors for in vivo glucose monitoring

D. A. Gough, Boston

The principles and state of development of two versions of the glucose sensor were discussed:

The first is the so-called enzyme electrode. In this sensor, a membrane of immobilized glucose oxidase is placed over a catalytic metal electrode that can detect concentration changes of coreactants or products. Glucose and oxygen diffuse into the reactive layer and are catalyzed to gluconic acid and H_2O_2 . The detection by the electrode of either a decrease in oxygen or production of peroxide is taken, after certain corrections, as the glucose measurement. Some success has been demonstrated with this type of sensor for in vitro monitoring and for short-term in vivo monitoring in animals. However, major problems of biocompatibility, lifetime, and stability remain to be addressed before the sensor can be used in humans.

Another type of sensor is the catalytic metal electrode on which glucose reacts directly. This sensor contains: a metal anode for glucose oxidation coated with a permselective membrane; a counter electrode separated from the anode by an ion-exchange membrane; and a reference electrode. The device can work if the metal remains active for glucose oxidation or can be easily regenerated and operating conditions can be found so that selectivity to glucose is obtained. The same requirements of biocompatibility, lifetime, and stability apply.

Discussion

The transport of the substrate across the electrode depends on major differences in sensor construction. The sensor can readily be designed so that when operating in a continuous, steady-state-mode, the response to in-

stantaneous concentration changes is less than a minute — provided that glucose transport in external media or tissue to the sensor is not limiting (*Spathis, Gough*). The device will have to be calibrated *in vivo*. This has been done by relating the sensor signal to blood glucose measured in the conventional way during an intravenous glucose tolerance test. — Blood glucose is simply the most convenient measurement with present technology. The β -cell, however, sees glucose in tissue fluid. *Gough* therefore plans to develop a dynamic transport model to relate blood and tissue glucose so that the sensor signal can be precisely related to blood glucose. There is an important difference between the work that SIEMENS is doing and what *Gough* is doing. In the first case a fuel cell requires relatively high transport of substrate so that reasonable power demands can be met. *Gough* does not care about power and he can work with small currents. His only constraint is that the current — however small — is related to glucose concentration.

Simultaneous *in vivo* glucose and insulin analysis *Chr. Trendelenburg, Freiburg*

No method has yet been described in the literature by which insulin has been analysed using continuously monitoring techniques. Now a running curve of actual insulin concentrations *in vivo*, measured radioimmunologically, has been realized by means of

1. continuous withdrawal of venous blood with a rolling pump during an extracorporeal hirudinization,
2. separation of plasma and the blood corpuscles by continual polybrene agglutination and subsequent decantation,
3. radioimmunological assay with antibodies bound to Sephadex particles using a 2-hour incubation at 37 °C,
4. separation of free and bound antigen by a current decantation and,
5. final computerized analysis employing a flow-through gamma counter and plotting method.

These mechanized techniques lead to simultaneously recorded concentration curves of glucose and insulin, which, however, are dephased in time on account of the indispensable long incubation period in inert tygon coils.

Discussion

A significant leakage of insulin antibodies from the Sephadex solid phase has not been observed during incubation. The sedimentation of Sephadex depends on the proportion between Sephadex and antibodies;

however, it depends mainly on the flow rate (*Kruse-Jarres*). The method runs with 6 ml/h whole blood. There is no experience yet with magnetic stirring or antibodies bound to magnetic solid phase (*Bonnafé, Spathis*). It has still to be proved whether insulin concentrations in whole blood differ from plasma values as glucose concentrations do (*Albisser*).

Experience in glucose metabolism monitoring *D. Sailer, Erlangen*

For the continuous recording of metabolic parameters a Technicon AutoAnalyzer II for the determination of glucose (neocuproin method) together with a flowmeter (Eschweiler Company) for pCO₂ and pH was used. Data processing is performed with a measuring system of Hewlett Packard and a calculator HP 9830. The data obtained appear on the display and are, at the same time, represented graphically by means of a plotter.

Within the last 4 years, approximately 500 measurements were carried out using this method. It performed long-term glucograms, determined insulin simultaneously, investigated the influence of meal frequencies on the glucogram, measured the effect of oral antidiabetics, and stabilized and monitored decompensated diabetics.

One main point of the investigations was to establish an infusion program for an automatic stabilization of diabetics with metabolic imbalances, supplying water, electrolytes, glucose, buffer substances and insulin according to the requirements. This program is based on empirically obtained data on the requirements for these substances during an optimum diabeto-therapy. The infusions are controlled by a computer and corrected to the actual data obtained.

Discussion

The formula for insulin requirements in the treatment of diabetics was found empirically. On the basis of the insulin needs in a number of pre-tested diabetic patients, an approximate equation was made. The computer calculation includes a formula for the periods between the 1st and the 3rd and between the 3rd and the 24th hour after insulin treatment. It is very difficult to include the information concerning insulin antibody-binding and relative or absolute insulin resistance (*Molnar*). Additionally, a lot of so-called resistant diabetics showed little relationship between antibodies and insulin requirement. It was the treatment that had gone wrong; they were on big doses (*Spathis*). In diabetes coma with ketoacidosis a number of cases have been observed which require more insulin, at least on the empirical grounds of relation between the glucose values and insulin which is administered by a pump system (*Pfeiffer*).

Lessons from continuous arterial and venous sampling

G. S. Spathis, Carlshalton

Some of the technical hazards were discussed, and criteria drawn up by which the adequacy of recording might be assessed. Attention has been drawn to some of the artefacts which may be produced using a double lumen catheter, as well as to the advantages of continuous monitoring. Insight was gained into physiological processes:

1. i. v. insulin tolerance testing showed that insulin has a transient central (? hepatic) effect and a more prolonged peripheral one.
2. Arterial blood glucose is more constant than venous, and the latter may be misleading in studies of arterio-venous difference. Arterialized blood should be used whenever possible.
3. Prolonged venous sampling confirms the constancy of the blood sugar in normals. In diabetics it seemed likely that gluconeogenesis was responsible for fasting hypoglycaemia; and despite rapidly rising blood sugar, insulin sensitivity is maintained at this time. Frequent small doses of insulin are preferable to fewer larger ones.

Discussion

It is most important to insist, when people are talking about minor fluctuations in the monitored curves, that they also define just how responsive their system is in toto (*Bonnafé*) and what are their criteria of accuracy (*Gottstein, Spathis*). The glucose monitors should not be standardized against simple aqueous standards or even serum standards. They have to be standardized against an independent laboratory glucose analyzer. Furthermore, it is important to demonstrate that, when whole blood glucose is interpreted in terms of plasma glucose, there is a straight-line relationship between these. Otherwise there is no point in trying to analyze small differences, particularly in the normoglycemic range or to compare results from one laboratory with those of another (*Albisser*). There is a fairly constant feature of rapid blood glucose rises during the early hours of the morning (4–5 o'clock) (*Hepp*) that was better explained by excess gluconeogenesis than by growth hormone (*Spathis*).

Clinical and Research Application

Glucose homeostasis under continuous intravenous insulin therapy in diabetics

K. D. Hepp, München

Diabetic complications are believed to result from the lack of continuous control of blood glucose under con-

ventional insulin therapy. The results of an investigation of the potential of continuous intravenous insulin delivered by an insulin pump, which is controlled by a profile based on physiological secretion patterns, were presented. A commercial infusion pump was connected to a special controlling device which allows for programming an infusion profile over 24 h with delivery rates from 0.3–6 units/h. Glucose was measured in 1–2 hour intervals throughout the 2–4 day infusion period; in some patients glucose was continuously monitored with an AutoAnalyzer for shorter periods. In two groups of stable and labile diabetics, respectively a better control was achieved than with conventional therapy with one or more injections of insulin. Although the final goal is a sensor-controlled device, the described system appears to be a promising new approach to diabetes therapy.

Discussion

Amazingly, it does not make a difference whether insulin is administered by portal or by peripheral vein (*Molnar*), so peripheral intravenous insulin administration would be satisfactory. Many of the insulin-treated cases still have a number of molecules of endogenous insulin left, which are sometimes regenerated during the night, and their endogenous insulin is released in the early morning and compensating for breakfast. To evaluate this question we need to have a quicker technique with clear-cut results. We cannot get around the sensor, we will have to have it some day (*Pfeiffer*).

Continuous blood glucose monitoring in insulin-treated diabetes

J. Mirouze, Montpellier

The response of diabetics receiving insulin either in single or multiple daily injections or by automatic intravenous administration as a function of the glycemia has been studied.

Continuous blood sugar recording in conventionally insulin-treated diabetes

Continuous blood sugar recording gives very important information for the control of difficult cases. It helps to detect the very frequent latent hypoglycemic episodes and permit their prevention. The duration of insulin efficiency may be measured quite precisely; thus, the choice of insulin and the number of injections per day can be accurately monitored in each patient. A spontaneous nightly rise in blood glucose without food intake indicates a severe form of diabetes which must be carefully controlled.

Rapid rises in blood sugar, with or without insulin, and abrupt falls in blood sugar after insulin are the best

indicators of the severity and the lability of diabetes. Continuous monitoring of such diabetes shows that there is no phase of blood sugar stability.

In addition, continuous blood sugar monitoring permits the calculation of various parameters: the M value of *Schlichtkrull* evaluates diabetic control; mean amplitude of glycemic excursions (MAGE) and rate of blood glucose rise (RBGR) indicate the brittle character of diabetes; the rate of blood glucose fall (RBGF) indicates the sensitivity to antidiabetic therapy; nightly RBGR will give a warning against ketosis.

Continuous blood glucose monitoring connected with insulin infusions under appropriate control

An insulin infusion has been connected to continuous blood recording by means of various appropriate controls: "on-off" system, proportional control with saturation, programmable multiconnections system. The "on-off" system gives an unsatisfactory control, due essentially to insulin overshoot in relation to high insulin flow during glycemic fall. The proportional control with saturation gives highly variable results between 0.90 and 1.85 g/l. In all but one case glycemia is not very well controlled during glycemic fall and rise. The programmable multiconnections system gives the best control. Insulin infusion is quickly increased when glycemia rises and quickly decreased when glycemia falls. Maximum amplitudes of glycemic excursion vary from 0.95 to 1.35 g/l.

This work also permits the study of the effects of insulin on carbohydrate homeostasis. There is a period of latency of 18 ± 12 min for injected insulin in spontaneous nightly rises. The hypoglycemic action is prolonged for 28 ± 2 min after stopping the insulin administration. It varies during the day: 21 ± 3 min in the morning, 32 ± 3 in the afternoon, 25 ± 3 min during the night. The differences between morning and afternoon values are significant ($p < 0.01$). It would appear that there is a circadian rhythm for the action of insulin. The slopes of prandial fluctuations are much sharper than the slopes of spontaneous fluctuations, regardless of the time of the day considered.

Discussion

These results are similar to those of *Kadish* in 1962, characterized by marked swings in blood glucose resulting from automatic infusion of insulin and glucose when critical blood glucose values are reached. Complete normalization of the blood glucose homeostasis is not achieved, only a significant improvement (*Pfeiffer*). We would recommend altering the program and the algorithms from limiting absolute levels to the start and angle of glucose rise or fall (*Spathis, Albisser*). For the analytical procedure, it

seems worth knowing that using only plastic material and a dextran solution (because of the adherence problem) a loss of less than 10% has been observed in immunoassay. But even polyvinyl chloride absorbs insulin. The interesting thing is that even labelled insulin can be displaced from glass or plastic with large amounts of cold insulin (*Hepp*)⁻

The development of an artificial endocrine pancreas and its application in research and clinical investigation

A. M. Albisser, Toronto

In operation it is a closed-loop control system which attaches to the diabetic subject by two indwelling intravenous cannulae. Through one blood is drawn for glucose analysis. Through the other the two glucoregulatory hormones (insulin and glucagon) can be delivered. Their delivery is under the minute by minute control of a small computer which interprets the glucose reading and sets a rate of insulin and glucagon delivery according to a set of mathematical relationships, the parameters of which are established by the experimenter. This instrument is capable of restoring normal glucose tolerance and maintaining euglycemia in both diabetic humans and surgically diabetic dogs. Experiments have been conducted to verify these capabilities. The instrument has been applied to demonstrate the restoration of normal glucose tolerance in diabetic subjects given a 50 gram oral glucose tolerance test on three consecutive days and to compare the metabolic state and the glycemic response before, during and after exercise in patients given either maintenance level subcutaneous insulin doses or basal insulin infusions. It has also been used in animal subjects to demonstrate the absence of a significant difference between the portal and peripheral intravenous routes of insulin delivery in terms of the amount of insulin required and the glycemic levels achieved before, during and after uniform glucose loading tests.

Discussion

Albisser, in contrast to *Pfeiffer* and *Renner*, did not find exercise to be necessary to maintain euglycemia in insulin-infused diabetics. The tracer studies *Albisser* has done in those patients who are on subcutaneous insulin have shown that they do not mobilize glucose from hepatic sources. Probably more insulin is given than the liver is programmed to deal with (*Spathis*). When insulin is injected portally one needs 20% more than when putting it in peripherally. A poorer glucoregulation results. The implication is that there is increased destruction over the period of the infusion but not in the basal state before and after the challenge. The rule of thumb for programmed insulin application, regard-

less of body weight, is as follows: those people who require less than 40 U total of insulin per day in their management and who are under acceptable control can be treated by the artificial pancreas with parameters set to allow a maximum insulin delivery rate of 400 mU/min with a slope such that the hyperbolic tangent function used permits a basal delivery rate of 12 mU/min at a blood sugar of about 80 mg/dl. Patients requiring more than 80 U automatically get 800 mU/min as a maximum rate (Hepp, Albisser).

Artificial endocrine pancreas in experimental research

E. F. Pfeiffer, Ulm

An artificial endocrine pancreas has been used successfully for treatment of coma and precoma diabeticum and in diabetes-related surgery and delivery. After these clinical experiences, a number of clinical research projects have been attached, e. g., insulin-deficient diabetics have been maintained up to 3 days within normal glucose range without restrictions in food intake. The rate-dependent infusion of insulin during the rise of blood glucose following glucose load (regulated by various types of algorithms) has been found to be of particular importance for complete normalization of metabolism. Further experience has been gained in pancreatectomized as well as in hypophysectomized patients. The system has also been used to profile the actual insulin and glucose requirements in response to oral antidiabetic agents, after administration of somatostatin and in cases of chronic hypoglycemia due to insulinoma.

The metered amounts of exogenous insulin were compared to

- a) the immunomeasurable insulin (IMI) of the peripheral vascular system,
- b) the proinsulin, and
- c) the C-peptide.

Some information has been accumulated on the behaviour of endogenous and exogenous insulin despite antibody formation, and in the role of "rest" production of endogenous insulin in control metabolism in long-lasting diabetic conditions.

Discussion

Much of the confusion which exists in the diabetic clinical literature is due to failure to describe patients as to age, juvenile or maturity type of onset or adequate treatment of their diabetes. The information on his insulin-making ability as well as details of blood glucose fluctuations under standardized conditions must be known to characterize a diabetic patient adequately (Molnar). The C-peptide rises at midnight and the

early morning. Obviously an explanation is that everyone (the healthy as well as the diabetic subject) has a tendency to raise his blood sugar (*Spathis*). The normal person, however, produces insulin and holds it down, but the diabetic can't produce insulin. Otherwise there is the opposite opinion that insulin is not under feedback control of insulin. That seems to be against nature (Pfeiffer).

Pathobiochemical Rhythms and Variations

The sex-specific interrelations between the fetoplacental unit and the maternal glucose tolerance

H. J. Hinckers, Bonn

On the basis of values of glucose tolerance obtained in the normal pregnancy via a continuous i. v. glucose tolerance test, the results obtained in 2000 tests permit the following conclusions as far as the interrelations between the fetoplacental unit and the maternal glucose tolerance are concerned:

1. The fetus seems to modify the maternal glucose tolerance in late pregnancy. In pregnancies with female fetuses, the group of pregnancies with suspect or pathological glucose tolerance tests are clearly distinguished from the group with normal values. This is documented by a two-peak distribution of the values of the glucose assimilation coefficient (k_G). In contrast, in pregnancies with male fetuses there is a normal distribution of k_G values.
2. The generally observed negative influence of pregnancy on glucose tolerance is mainly due to the behaviour of the gravidae bearing male fetuses. It seems as if the maternal glucose tolerance during pregnancy is more influenced in case of a male fetus. This is more expressed — even in a significant depression of glucose tolerance — when negative conditions like multiparity, age, relative and absolute overweight, as well as a combination of hereditary and anamnestic factors, are present.
3. The glucose tolerance in pregnancies bearing female fetuses is not significantly altered under these conditions. However, from the sex specifically different intrauterine growth of male and female fetuses, it can be derived that female fetuses respond more sensitively to an altered maternal glucose tolerance, in that they react with an overshooting growth. Consequently, the meaning of the symptom "overweight baby" depends on its sex. While the overweight of a female baby might be due to a disturbed glucose tolerance of the mother, the overweight of a body could be due to genetic factors other than glucose tolerance.
4. The observation of a fetal sex-dependent modification of the maternal glucose tolerance, on the one hand, and a different response of male and female fetuses to an enlarged nutritive offer by the maternal organism on the

other should be seen in context with the observation of higher choriogonadotropin values in the third trimester of pregnancies with female fetuses. The absence of this second choriogonadotropin peak, and therefore the absence of the insulinotropic effect of choriogonadotropin on the maternal and fetal pancreas in male pregnancies, and the protective effect of testosterone could account for the lack of overweight in male babies in the presence of a disturbed glucose tolerance.

Discussion

In so-called *Cohen*-diabetic rats (3rd to 5th generation of constantly sucrose-fed rats) the repetition of the *Cohen*-experiment is not possible after removing the gonads, i. e. removal of the male gonads protects against the diabetogenic action of sucrose (*Pfeiffer*). — Oscillations in the glucograms are obviously more marked in the early than in the advanced pregnancy (*Kruse-Jarres*, *Hinckers*).

Continuous monitoring of arterial and cerebral-venous glucose concentrations in man. The effect of intravenous applications of glucose and insulin, of drugs or of hyperventilation and inhalation of 5% CO₂ on the cerebral metabolism

U. Gottstein, Frankfurt

The glucose concentrations have been analysed continuously in the blood of the femoral artery and the superior bulb of the internal jugular vein over a period of 2–4 hours. Small polyethylene catheters of 1 mm diameter were placed via injection needles into the vessels. After the needles were removed the patients felt comfortable and were usually asleep during the examinations of longer duration.

1. After intravenous glucose infusions the arterio-venous (a-v) differences do not increase significantly.
2. After simultaneous infusions of glucose and insulin there is a significant elevation of the a-v differences, demonstrating an increased glucose uptake in the brain.
3. During slowly insulin-induced hypoglycemia the glucose a-v differences do not change down to a blood sugar of about 45–50 mg/dl. Under this critical threshold the a-v differences begin to decrease, demonstrating a decreased glucose uptake in the brain.
4. Intravenous infusions of Actihaemyl (extr. sanguin. depot. sicc., Hormonchemie, München) have no influence on a-v differences, demonstrating a missing effect on the cerebral glucose consumption.
5. During hyperventilation or inhalation of 5% CO₂ the glucose arterial-cerebral venous differences change as fast as the oxygen a-v differences. Thera-

peutical hyperventilation in treatment of stroke or pathological hyperventilation in cerebral diseases is of no benefit for the brain. Due to the decreased cerebral blood flow and the blood-alkalosis, the oxidative glucose metabolism decreases and the production of lactic acid in the brain increases, which is harmful for it.

6. The continuous measurement and registration of arterio-cerebral venous glucose concentrations has great advantages in pathophysiological studies. We have tested the degree of sensitivity of the autoanalyzers with different blood and glucose samples and with different aspiration periods.

Discussion

There is some similarity between the cerebral metabolic values of diabetics with complications and of patients with senile dementia or severe arteriosclerosis as far as the reduced glucose metabolism and the deficiency of glucose uptake by the brain is concerned (*Pfeiffer*, *Gottstein*). Because of the important effect of insulin on brain metabolism (*Molnar*), it seems to be helpful to infuse glucose together with insulin in senile patients (*Gottstein*).

Cybernetic evaluation of bio-dynamic properties of the blood glucose control circuit

J. D. Kruse-Jarres, Freiburg

Observations made in men and animals during continuous monitoring of glucose up to 36 hours at a time were reported. To demonstrate different input-output patterns, several feasible calculation models were chosen:

1. System theoretical approaches
2. Control theory
3. Compartment theory
4. Network theory
5. Matrices calculation

The glucograms were evaluated according to the characteristics of cybernetics processes (terrace function = continual interference, impulse function, ascent function, definition of frequency modulation, stochastic phenomena —whistling processes). In this way regularities can be conceived, the knowledge of which permits an unbiased interpretation of irregular metabolic disorders and the computerized supervision of dynamic properties of blood glucose.

Discussion

Because we do not understand all operations of regulation in terms of their components, pattern recognition seems to be a most feasible way of computer calculation of

glucose alterations (*Berg*). The oscillations during an intravenous glucose tolerance test defy all calculation, though there are obvious regularities concerning the initial glucose peak and the following oscillations, especially in pregnancy and potentially diabetic subjects (*Hinckers, Kruse-Jarres*). Continuously measured insulin will bring more information in these cases (*Albisser*), though there is some doubt that a relationship exists between the circulating insulin and the actual blood glucose level (*Pfeiffer*).

Diurnal glucose variability and hormonal regulation

G. D. Molnar, Edmonton

Matched groups of normal, stable diabetic and unstable diabetic volunteers were studied under prolonged ambulatory-fed as well as under resting-fasting conditions. The diabetics had prolonged preparation in a metabolic ward to attain clinically optimal diabetes regulation. Timing and composition of meals, as well as the timing and intensity of (walking) exercise, were consistent throughout for all subjects.

During ambulatory-fed studies, blood glucose was continuously monitored for 48-hour periods. These 48-hour blood glucose monitorings were done at the mid-point of 6-day metabolic balance studies. The shorter, more intensive periods of study were found to be representative of the longer periods during which less frequent sampling of blood constituents was undertaken.

To obtain some well-characterized subjects under less complex conditions than these, standard tests were also done. Under the resting — fasting conditions (after suitable preparation) oral glucose, and intravenous saline,

insulin, arginine, epinephrine or tolbutamide were given and the previously listed blood variables were measured.

Unstable diabetics were found to have the widest and most variable blood glucose fluctuations when fed and exercised. They also had the greatest growth hormone increases diurnally. They had the least ability to respond with insulin secretion to a variety of stimuli. Unstable diabetics also differed from stable diabetics and normals in their plasma glucagon response to hypoglycemia. They were also most prone to prompt and large plasma ketone body increases when withdrawn from exogenous insulin therapy.

Attempts have been made to abbreviate and simplify these arduous experimental methods for characterizing diabetic patients during ambulatory-fed conditions. Fewer, but critically timed plasma glucose measurements, during prolonged studies of urine glucose monitoring, yielded clinically useful but scientifically much less adequate data than during continuous blood glucose monitoring.

Discussion

Hyperglycemia suppresses the glucagon level neither in stable nor in unstable diabetics. There is a difference, however, in that in unstable diabetics hypoglycemia does not increase the glucagon level (*Molnar*). It would be most interesting to see whether, after prolonged normalization, perhaps the glucagon responsiveness to hypoglycemia might also recover. Perhaps in the unstable diabetic the lack is more exaggerated and glucagon more dominant by way of insulin deficiency (*Albisser*). The growth hormone levels did not correlate with blood glucose levels or changes in stable or in unstable diabetics (*Molnar*).

Dr. Chr. Trendelenburg
Hugstetterstraße 55
D-7800 Freiburg