Conferences on Insulin-Glucose, Padova, Vienna, Sept 14, 1979

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CONFERENCES ON INSULIN-GLUCOSE

PADOVA-VIENNA SEPTEMBER 1-14,1979

PER HAGANDER

INSTITUTIONEN FÖR REGLERTEKNIK
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Abstract

This report describes a visit I did to Padova and Vienna Sept 1 to Sept 14, 1979. One conference was held in Padova on measurements and modeling of the carbohydrate system. The conference was in the form of a closed workshop with about 30 participants. The 10th International Diabetes Federation Meeting was held in Vienna the following week with about 3000 participants. The latter conference had several sessions on insulin delivery systems and the artificial endocrine pancreas. There was also an exhibition where Miles presented there latest version of the Biostator. After the conference in Padova I visited C Cobelli and G Ricci at LADSEB-CNR. Some comments are also included on a satellite symposium in Heviz, Hungary, which i did not attend.

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Introduction

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Padova

The symposium was held in Padova Sept 4-6, 1979 and organized by Claudio Cobelli, LADSEB-CNR, together with Richard Bergman, Evanstone (currently at USC). The program is reproduced in Appendix 1. C.C. is an electrical engineer with special interest in biological systems, while R.B. is a physiologist with special interests in modeling. He is the editor of one of the sections of the American Journal of Physiology.

The workshop was closed with invited speakers and participants, and the atmosphere was very open and friendly, maybe apart from some of the scientific discussions. The social program was excellent. The proceedings will be published by Wiley hopefully during 1980.

The participants had mainly two types of background: modelbuilding or quantitative physiology (partly with clinical emphasis). The aim of the conference was to provide the modelers with data and the data-collectors with modern modeling tools. Some collaboration might also be the result of the conference. The research front in glucose-metabolism was well represented. Karl-Goran Tranberg and I had a paper that K-G T presented.

Among the talks I will comment on the following:

Albisser, Toronto, and Tiran Israel, presented two joint talks on liver and peripheral uptake of insulin. They describe experiments in dogs without pancreas. My impression is that they did bad modeling. The model was organ-oriented like the work by Bischoff et al in pharmacokinetics. They assumed suitable flows and distribution volumes in accordance with the literature, while they fitted the insulin uptake coefficients to the measured data. They also tested some simple nonlinearities. Their result is a 40% uptake in the liver and kidney blood-flows together with a

squared term in the periphery. They did all their experiments during a constant glucose infusion. The insulin infusions were closed loop (Bootz' algorithm) or open loop and peripferal or intraportal but with the same nominal pulse form (20 mU/min during 60 min). The data was obtained during 1972-6, and the modeling was done in 1978-9. The model contained 13 state variables for the insulin part and 15 for the glucose part. The programming was done in CSMP using about 200 cards. Their main message from the modeling is that the peripheral infusion implies high peripheral insulin concentrations also during control, and that this might be responsible for some of the metabolic abnormalities that are often reported also during closed loop control of the blood glucose.

Similar experience of metabolic abnormalities during artificial pancreas control were reported in a solid paper by Noy and Nosadini. Noy is working with a Biostator in Alberti's group. He has also a method of his own for continuous measurement of lactate, puryvate and glycerol (maybe some more). He is dialysating, and uses immobilized enzymes and fluorecense techniques. His glucagon assays in particular gave astonishing results. The main criticism was that his patients started with quite high glucose values and that the experiments only lasted about 12 h. In the discussion it was suggested that the metabolic normalization takes a number of weeks. Bob Sherwin suggested that part of the problem was caused by a too simple regulator algorithm, which injected too much insulin. During his 7-14 days experiments with a subcutaneous pump in humans (performing some exercise) he had almost perfect normalization. Albisser privately and also later in Vienna expressed a similar opinion, based on a system where the patient presses a button before meals. Noy suggested that the continuous metabolic measurements should be used for control, and they will try.

Cherrington (Vanderbuilt), Sherwin (Yale) and Vranic (Toronto) presented experiments concerning the glucogen formation and degradation in the liver and how that is influenced by the glucagon concentration. Epinephrine and cortisole were also discussed. There results were to some extent contradictory. The elements of modeling were minor. The dynamical aspects and the control mechanisms of the liver as a storage for glucose and hormones is still an open question. New experiments will be needed, but modeling using current data would certainly enhance the understanding of these complex relations.

Kolterman (Colorado) addressed the question why the insulin concentration of obese people is elevated both in the fasting state and at elevated glucose concentrations. He ruled out bad insulin and antibodies, and tried to distinguish between receptor defects and postreceptor defects by looking at a dose response curve. He used glucose

clamp (80 mg/100 ml) and constant insulin infusion rate. The dose response curve starts off approximately linearly and then saturates. A lowere sensitivity would be called a receptor defect, while a lower saturation level was called a postreceptor defect. In most he found a slightly lowered sensitivity and considerably lower plateau. He also checked hepatic glucose production using tritiated glucose, the insulin MCR, and the binding of labeled insulin. Porte (Seattle) questioned the stationarity, and Bob Sherwin (Yale) reported conflicting results.

Zeleznik (Pittsburg) discussed insuling binding, its reversibility and degradation. Different labels and insulin from different species were used in combination with each other. The assumptions necessary for the interpretation were considerable.

Goodner (Seattle) had his interest in the baboons and also the rhesus monkey. In the latter species he could find significant 10 min oscillations in glucose, insulin and glucagon. Glucose and insulin were in phase, while insulin and glucagone were in opposite phase. C-peptide followed insulin. The variations were glucose: 8.8±1.2, insulin:102±23, glucagon: 40±12. Note the very high insulin concentrations as compared to humans. The wave form of insulin was like a first order response to a square wave. Three different explanations were suggested: a) error in a feedback system liver-pancreas b) CNS c) intrinsic in the pancreas release. Questions were raised on how the islets could communicate with each other to achieve synchrony. The effect on liver glucose by the insulin and glucagon in opposite phase would be doubled. G suggested that the oscillations were induced to prohibit down regulation which seems reasonable from an adaptive control point of view. No modeling was introduced but the experiments seemed to be performed very competently. This research would have been much easier using a CGM-system.

Radziuk (London, Ontario) used his method with timevarying transfer rates on very nice experiments to estimate the storage and degradation of an oral glucose load, while Filo (Pisa) showed how easily the method is misused.

Cerasi (Jerusalem) discussed his old model (Cerasi Fick Rudemo) in the light of new experiments. Different nonlinearities were needed for early and late insulin secretion. Patients with high potentiation coefficient were verified to have a high potentiation in a two pulse experiment, while a high inhibition coefficient did not give any higher inhibition. Calcium, cAMP, and different kinds of sugars were also discussed.

Licko (UCSF) presented his work that resultad in the Grodsky model. Cerasi privately reported that a two pulse experiment would give potentiation also of the late phase, which

contradicts the Grodsky model.

Carson and Cramp (London) made a nice presentation of their latest model version containing most of the short term effects. The model has a biochemical fundament and contains several saturated enzyme steps.

The main model building was done by the organizers Cobelli and Bergman, who modeled both insulin and glucose in dogs after 300 mg/kg glucose injections. They tested a lot of different models and started to investigate their a priori identifiability. One main assumption was discussed: insulin measurements were regarded as the input to the glucose part of the model giving glucose output and vice versa for the insulin part. Thus it has to be assumed that the signals are sufficiently exciting the system, and that there is no other coupling between the two parts than via the plasma concentrations (i.e. not via tissue or liver concentrations).

Atkins (Edinburgh) gave a new model survey and Norwich (Toronto) pledge for worldwide coorporation for communication and review of models and data.

Some general comments should be made. First of all it was astonishing how bad data the modelers in general were working with, and how little modeling that was used in the work that presented original experiments. So far it must be questioned if modeling has contributed anything to the understanding of the glucose system. By its air of science it has most certainly hidden many serious mistakes. However when models begin to be used more easily and their limitations are properly stated, they can be a topic of scientific discussion and thus useful. Modeling and simulation will then prove necessary for the understanding and possibility to communicate conclusions.
Secondly there was an intense discussion both in session and during the evenings on the relative merits of iv and sc infusions and of closed loop systems versus preprogrammed pumps. A significant point seemed to be to what extent a patient could be trusted with a button to press before meals. Such a button would be almost necessary for a preprogrammed pump while it would considerably help a closed loop system. No design of closed loop systems seemed to be based on any reasonable modeling. The quality of the Biostator control algorithm was questioned by some groups. Cobelli would probably join a project in Padova to develop an AEP. He suggested some collaboration to share our experience. I had fruitful privite discussions with most of the participants, especially with Noy, Albisser, Cerasi, Carson and Yates.

Visit to LADSEB-CNR

After the conference in Padova I visited LADSEB, which is a separate research institute sponsored by the Italian research council CNR and devoted to dynamical systems and bioengineering. Part of their annual report (1978) is reproduced as Appendix 2. Their library and computer facilities were extensive.

C Cobelli was heading a biological systems group of 3-4 people with collaborators at different medical clinics. In the carbohydrate field he was working with R Bergman on data-oriented modeling (a NSF-CNR contract) as described at the Padova conference, an AJP paper, a Fed Proc paper, and a Darmstadt paper. Together with Clinical Medicine, Padova, he was continuing the Leipzig conference work on complex phenomenological modeling (to be presented in Italian at the IMACS-conference). A project on closed loop insulin control of glucose was about to start. C C was also continuing the bilrubin tests. Their main theoretical work was still identifiability of compartment models. A number of recent papers have surveyed the field. Together with Carson C C gave an identification survey at Darmstadt. C C showed great interest in our simulation and identification programs (SIMNON LISPID etc).

G Picci in the stochastic systems group was collaborating with A Lindquist on realization of stochastic processes. We had a long discusion on my thesis work.

10th Congress of the IDF

The Vienna conference was monstrous with many parallel sessions and a wide scope of interest. The program and the most interesting sessions are listed in the Appendix 3. As a whole most sessions contained very much biochemistry and very little of a whole organ or whole body approach. Not even in conclusions or speculations there was used any "systems analysis". A few exceptions were presented by Art Campfield (See also AJP paper) and Bergman-Cobelli. Almost without relation to those sessions there was a clinical orientation with experience of current diabetes therapy. This report contains my personal viewpoint. The impression of a clinician or diabetes researcher would probably be different (see eg. A.W. private communication 1979). The congress probably didn't change its pattern from previous IDF-congresses.

I visited some of the panels and free communications on both insulin secretion and on insulin binding - action. All effects seem to be nonspecific and parallel, the different channels being of different importance at various doses and in different "metabolic states".

Insulin release is complicated. Among others Ashcroft, Matschinsky, Malaisse, Grodsky and Hellman gave interesting surveys. Several chemical steps, electrical activity and even membrane changes are postulated, and to some extent made plausible. Some time aspects were discussed. The influence of somatostatin, nervous signals and gastric hormones was also emphasized, while L Hedding questioned the validity of Immunoreactive insulin (IRI) by showing that the proinsulin following a stimulation of insulin secretion first decreased from 30 to 15% then increased considerably to 60%. The difficulty to model the effect of oral insulin secretagoues is quite understandable in this light. The Biostator was used for glucose clamps in several of the studies.

Concerning insulin action Olefsky gave an overview of insulin sensitivity (refered to the complicated G Reaven test) and discussed insulin downregulation of receptors and its reversibility. The effect at the receptor level of starvation, diet, and training was indicated in several studies (Beck-Nielsen, a Gothenburg group etc), as well as post receptor effects. Diurnal variations of insulin sensitivity were reported by Golia et al (193).

The clinical sessions ranged from epidemiology, pseudoetiology to diabetic care and patient education. I did not participate at all in these sessions.

Almost as a separate conference there were one panel on infusion systems, two free free communication sessions and one poster session on the artificial endocrine pancreas (AEP). In the exhibition rooms Ames had a prominent place with their Biostator. The stand was constantly manned with both chemical and electronics expertise. I naturally concentrated on these sessions and the exhibition by Biostator. There was no exhibition of any other machine and it was striking also in the talks what a monopoly on the market that Ames have achieved. About 50 machines are spread out over the world. The clinical experience is accumulating in a very irradic fashion.

No one seems to have had a patient on a machine for more than a couple of days. There was no discussion in session on the the design of control algorithms and the quality of control. However some standard measures have been used to assess the behavior during meals etc.

The vast majority of these papers discussed a comparison of open loop and closed loop systems, the use of closed loop systems to program open loop systems, or the construction of different i.v. or s.c. infusion systems. The pump by Klein et al (185g plus insulin) and the Mill Hill seemed very nice. Other pumps were presented by Albisser, Deckert, Mirouze and Hepp.

The results by Kraegen (Sydney) that much better control was achieved by an open loop system with a meal-pushbutton than with the Biostator was striking. The (approx 15 min) delay in detecting a meal was shown to be responsible for this. Nobody suggested that a closed loop system should be combined with a meal-pushbutton!

W. Kerner demonstrated that the Biostator insulin profiles were clearly unsuitable for open loop control, although his conclusions were stronger.

Pfeiffer, Ulm, the big man in these sessions, presented results from the Biostator including some portal infusions. In the controversy between AEG and preprogrammed pumps he considered AEG to be superior even for a normal diabetic, while a diabetic with the flue was the real evidence. He mentioned pancreatectomy and adenoma as some applications for the AEG.

Albisser (11) reported open loop peripheral and portal iv infusions in pancreatectomized dogs (2 years) using a new peristaltic pump: Weight 550 g including a full insulin reservoir. The concentration used was 1-2 U/ml. Comparison was made in glucose normalization but also in lactate and alanine. A. emphasized a filter used when refilling the insulin reservoir. Ref Diabets June.

Deckert's s.c. pump had 10 rates programmable at 30 min intervals and a pushbutton for meals. The next version would have an additional button for snacks . He warned against long term iv because of sepsis, and tried currently peritoneal without good results. Albisser warned here for fat deposites like around implanted betacells. Kalle T: meaningless.

Hepp from Munich representing the Siemens pump, had used venous catheters for up to 4 weeks but no longer. S.c. required 40 % more insulin. H thought sensors were not realistic but also not necessary and suggested implanted preprogrammed pumps, may be to some extent patient controlled. Many comments were made by Irsigler Vienna (Diabetes March 79).

Clemens (Ames) presented the standard slidee on the new Ames regulator (submitted for patent) and tried to explain why it is so much better than the one by Bootz.

In the poster session and later as comments to several talks the Karlsburg group (Jutzi and Fischer) discussed their PD-regulator based on model building.

Renner from the Munich-Siemens group discussed how they manually used glucose readings and a PD-algorithm graph to control iv and so insulin in order to program the Siemens pump individually. It was found that 6 min sampling interval

was too long, 2 min was better. Comments from the Rochester group emphasized the basal rate and the concentration of the infused insulin especially in the sc case.

Sacca and Sherwin showed diffences between normals and diabetics in how insulin modify glucose uptake and liver output. An interesting poster on 15-min oscillations in insulin, glucose and glucagone was presented by Lang, Oxford (344), while Caygill, London (94) hypothesized a serum factor to activate insulin action.

Discussion with the Miles lab people.

I had long discussions with Wasser, Grant and Clemens. They were quite open, but some questions were always transfered to Clemens, who was busy. The machine is not yet approved by FDA and therefore shipped to Europe in parts. The first bid was that it contained a special purpose computer; Later admitted to be a Intel 8088 or Motorola 6800. Some of the programming was done in Cobol?? The price of the system is approximately $ 50 000. See Appendix 4.

The algorithm used and the standard parameters are as follows: (reference also Application for German patent 1979-05-31)

```
IRS = RI * ( (GY-BI)/QI + 1) ** 2

m   = (2*G0 + G1 - G3 - 2*G4) / 10

GY  = 2*m + (G0+G1+G2+G3+G4)/5

K   = if m>0 then KR else KF

IRD = if GY-BI < 0  then 0 else 0.1*K*m*(GY-BI)

IR  = IRS + IRD
```

G0 is the most recent glucose value

```
RI = 14 mU/min     (ie 0.2 mU/min/kg)
BI = 80 mg/dl
QI = 30 mg/dl
KR = 30
KF =  8

max IR = 500 mU/min
```

The sampling interval is 60s, while the delay in the machine is 90s. The length of the tubings are absolutely fixed just like the flow. Current values are a compromise. The algorithm had been applied to sc infusion as well. Clemens could not remember exactly what happened but thought that the standard algorithm was no good, but that basal level plus IRD with high KR gain worked allright, ie saturation plus basal rate. No data filtering was applied. Clemens talked in Heviz about the effect of the timedelay. Changes in control algorithms might be delivered by Miles, if the suggested algorithm is sent to Miles for testing and incorporation into the memory of the machine.

Workshop on artificial beta cell in diabetes research and management

After Vienna a special workshop on AEG was held in Hungary. B Schersten presented a contribution on the Gambro CGM-system. I did not participate. All major groups were represented there, and several interesting projects were sketched. The program and some the abstracts are reproduced in Appendix 5. Some slide copies are also included there.

Acknowledgements.

The financial support from Knut och Alice Wallenbergs stiftelse, Gambro AB, and Lund University is gratefully acknowledged.

Appendices

1 Program from Padova conference
2 Excerpts from the annual report LADSEB-CNR
3 Program etc from 10th IDF congress
4 The Biostator
5 Program etc from the Heviz workshop

Schedule for

Symposium on: CARBOHYDRATE METABOLISM: QUANTITATIVE PHYSIOLOGY AND MATHEMATICAL MODELING

to be held in Padova, September 4-6, 1979 at the Accademia Patavina di Scienze, Lettere ed Arti.

C. Cobelli and R. Bergman
Chairmen

	TUESDAY 4		WEDNESDAY 5		THURSDAY 6	
8:15 - 8:30	INTRODUCTION					
8:30 - 9:15	O. KOLTERMAN "Mechanisms of altered glucose homeostasis in obesity"		A. CHERRINGTON "Regulation of glucose production by insulin and glucagon in the dog"		C. GOODNER "Oscillations in the secretion of pancreatic islet hormones"	
		DISCUSSANT:		DISCUSSANT:		DISCUSSANT:
9:15 - 10:00	T. ZELEZNIK "In vivo demonstration of the insulin receptor"	R. SHERWIN	M. VRANIC "Interaction of epinephrine, glucagon and insulin in the control of turnover in normal and diabetic dogs"	G. HETENYI	E. YATES "Temporal organization of metabolic processes: a biospectroscopic approach"	J. BOGUMIL
	COFFEE		COFFEE		COFFEE	
10:30 - 11:15	~~M. BERMAN "Quantification of receptors for in vivo insulin kinetics"~~		R. SHERWIN "Influence of counterregulatory hormones and blood glucose concentration on hepatic glucose production"		M. ALBISSER "Blood glucose regulation in clinical and experimental diabetes mellitus using closed - and open-loop insulin delivery mechanisms"	DISCUSSANT:
11:15 - 12:00	K. TRANBERG "Insulin kinetics after brief intraportal and peripherical infusions of unlabeled insulin"		R. BERGMAN "Further integration of the control of hepatic glucose handling in vitro and in vivo"		G. NOY "Metabolic effects of glucose clamping at normal and hyperglycemic levels"	J. MIROUZE
12:00 - 12:30	DISCUSSION		DISCUSSION			
	LUNCH		LUNCH		LUNCH	
14:30 - 15:15	E. CERASI "Differential actions of glucose on insulin release"		G. HETENYI "Calculation of the rate of gluconeogenesis in vivo"		E. CARSON "Dynamics of short term blood glucose regulation"	
		DISCUSSANT:		DISCUSSANT:		DISCUSSANT:
15:15 - 16:00	V. LICKO "Modeling insulin-secretion: analysis of glucose tolerance tests"	D. PORTE	J. RADZIUK "Glucose and glucagon metabolism following glucose ingestion: a turnover approach"	R. BERGMAN	K. NORWICH "On the methods of modeling: the need for worldwide cooperation"	C. COBELLI
16:00 - 16:45	C. COBELLI "Minimal modeling and partition analysis for estimating insulin-glucose interactions in the intact organism"		A. PILO "Analysis of the glucose production and disappearance rate following an oral glucose load: a tracer study in the normal subject"		G. ATKINS "A biologist view of modeling glucose homeostasis"	
16:45 - 17:15	DISCUSSION		DISCUSSION		DISCUSSION	

RELAZIONE SULL'ATTIVITA' SVOLTA NELL'ANNO 1978 e RENDICONTO ANALITICO DEI FONDI AVUTI A DISPOSIZIONE PER LO STESSO ANNO

LABORATORIO PER RICERCHE DI DINAMICA DEI SISTEMI E DI BIOINGEGNERIA (LADSEB)
Corso Stati Uniti, 35100 PADOVA, Tel.049-760933

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COBELLI CLAUDIO	Coll.T.P.	CNR	Ricercatore	4 ,8
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RUNGGALDIER WOLFGANG	Prof. Stab.	Univ. PD	Ricercatore	1 ,8
TOFFOLO GIANNA	Borsista	CNR	Ricercatore	4 ,8

Coll.T.P.=Collaboratore Tecnico Professionale
Ass.T.P.==Assistente Tecnico Professionale
Op.T.P. =Operatore Tecnico Professionale

PARTE I

RELAZIONE SULL'ATTIVIA' SVOLTA NELL'ANNO 1978

INDICAZIONE DELLE RICERCHE

1) Teoria della stima e problemi di rappresentazione interna, identificazione e approssimazione di sistemi stocastici (LADSEB 1.3)
2) Gestione interattiva di un esperimento di grandi dimensioni (LADSEB 2.8)
3) Applicazione della teoria dei sistemi dinamici a sistemi economici (LADSEB.3.5)
4) Modelli di sistemi biologici (LADSEB 4.2)
5) Informatica clinica (LADSEB 5.2)
6) Strumentazione per applicazioni biomediche
7) Intelligenza artificiale
8) Altre ricerche.

N.B. Le sigle sono articolate in conformità ai criteri previsti per i programmi del G.N.A.S. e cioè la prima parte indica la sede presso la quale si svolgono le ricerche, la seconda il numero d'ordine della ricerca, la terza il numero del sottogruppo del G.N.A.S. nella cui attività la ricerca va inquadrata.

Monday, September 10, 1979

	A	B	C	D	E	F	G	PE
8:30 h								
9:00 h	Minkowski Lecture S. Ashcroft	Audiovisual Transmission from Hall A			Audiovisual Transmission from Hall A			
9:30 h								
10:00 h	What is Diabetes? Definition, Aetiology, Natural History, Diagnosis Chairman: R. Levine	Viruses in Diabetes Chairman: J. E. Craighead	Epidemiology of Diabetes Mellitus: Changing Prevalence and Incidence Chairman: P. H. Bennett	Lipid Disorders and Diabetes Chairman: S. Sailer	Neuropathy I	Gastroentero-Insular Axis I	Islet Metabolism I	
10:30 h								
11:00 h								
11:30 h					Neuropathy II Biochemistry of Complications	Gastroentero-Insular Axis II Growth Hormone	Islet Metabolism II	
12:00 h								
12:30 h								Poster Session I
13:00 h								
13:30 h								
14:00 h	Treatment (With What? When? How?) Chairman: K. Seige	Insulin Infusion Systems Chairman: E. F. Pfeiffer	Somatomedins and NSILA Chairman: K. Hall	Autoimmunity and Genetics in Diabetes Mellitus Chairman: W. J. Irvine				
14:30 h					Somatostatin I	Endocrine Interactions	Insulin Secretion In Vitro I	
15:00 h								
15:30 h								
16:00 h								
16:30 h					Somatostatin II	Nephropathy	Insulin Secretion In Vitro II	
17:00 h		Complications	Patient Care I	Nutrition/ Rodenticides				
17:30 h								
18:00 h								
18:30 h								

Tuesday, September 11, 1979

	A	B	C	D	E	F	G	PE
8:30 h ▶								
9:00 h ▶	H. Eppinger Lecture W. Waldhäusl	Audiovisual Transmission from Hall A			Audiovisual Transmission from Hall A			
9:30 h ▶								
10:00 h ▶	Acute (Early) Complications Chairman: A. Bloom	Glucagon and Glucagon-Like Substances in Diabetes Chairman: R. H. Unger	Diabetes in the Tropics Chairman: M. M. S. Ahuja	Islet Hormone Chemistry, Biosynthesis and Gene Studies Chairman: D. F. Steiner	Immunology I	Patient Care II	Insulin Receptors I	
10:30 h ▶								
11:00 h ▶								
11:30 h ▶					Immunology II	Exercise	Insulin Receptors II	
12:00 h ▶								
12:30 h ▶								Poster Session II
13:00 h ▶								
13:30 h ▶								
14:00 h ▶	Chronic (Late) Complications Chairman: C. Binder	Gastrointestinal Hormones Chairman: W. Creutzfeldt	Biochemistry of Diabetic Complications Chairman: R. G. Spiro	Exercise and Diabetes Chairman: J. Wahren	Ketoacidosis I	Insulin Action I	Insulin Receptors III	
14:30 h ▶								
15:00 h ▶								
15:30 h ▶								
16:00 h ▶					Ketoacidosis II	Insulin Action II	Diabetes in the Young Chairman: W. Mayes Jr.	
16:30 h ▶		Diabetes in Animals		Obesity				
17:00 h ▶								
17:30 h ▶								
18:00 h ▶								
18:30 h ▶								

Wednesday, September 12, 1979

	A	B	C	D	E	F	G	PE
8:30 h ▶								
9:00 h ▶	B. A. Houssay Lecture L. Leloir	Audiovisual Transmission from Hall A			Audiovisual Transmission from Hall A			
9:30 h ▶								
10:00 h ▶	Education: An Important Part of Treatment Chairman: S. S. Ajgaonkar	Oral Anti-diabetic Agents Chairman: H. Keen	The Central Nervous System and the Endocrine Pancreas Chairman: R. Luft	Insulin Secretion and Insulin Resistance in Insulin-Independent Diabetes Chairman: S. S. Fajans	Artifical Pancreas I	Insulin Biochemistry and Metabolism	Genetics	
10:30 h ▶								
11:00 h ▶								
11:30 h ▶					Artifical Pancreas II	Insulin Secretion in vivo	Somatomedin-NSILA	
12:00 h ▶								
12:30 h ▶								
13:00 h ▶	EASD General Assembly							
13:30 h ▶								
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15:00 h ▶								
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16:00 h ▶								
16:30 h ▶							IDF General Council	
17:00 h ▶								
17:30 h ▶								
18:00 h ▶								
18:30 h ▶								

Thursday, September 13, 1979

	A	B	C	D	E	F	G	PE
8:30 h								
9:00 h	Claude Bernard Lecture D. A. Pyke	Audiovisual Transmission from Hall A			Audiovisual Transmission from Hall A			
9:30 h								
10:00 h	Diabetes Today and Tomorrow Chairman: A. E. Renold	Local Treatment of Diabetic Retinopathy Chairman: H. W. Larsen	Insulin Receptors: Relation to Disease and to Insulin Action Chairman: C. R. Kahn	Somatostatin (SRIF) Chairman: P. Brazeau	Oral Antidiabetic Agents I	Glucagon and Diabetes	Haemoglobin A_{1c}	
10:30 h								
11:00 h								
11:30 h					Oral Antidiabetic Agents II	Glucagon Secretion	Lipids	
12:00 h								
12:30 h								Poster Session III
13:00 h								
13:30 h								
14:00 h	The Young Diabetic II Chairman: D. D. Etzwiler	Treatment of Metabolic Derangements in Diabetic Coma Chairman: K. G. M. M. Alberti	Insulin Release Chairman: W. J. Malaisse	Metabolic Fuels Chairman: D. M. Kipnis				
14:30 h					Insulin Treatment	Hepatic Metabolism	The Pregnant Diabetic Chairman: J. J. Hoet	
15:00 h								
15:30 h								
16:00 h					Islet Trans-plantation	Metabolic Fuels and Muscle Metabolism		
16:30 h			Patient Care III	Hormone Receptor Interaction				
17:00 h		Pregnancy in Diabetic Animals						
17:30 h								
18:00 h								
18:30 h								

Friday, September 14, 1979

	A	B	C	D	E	F	G	PE
8:30 h								
9:00 h	Jacobaeus Lecture H. Goodman	Audiovisual Transmission from Hall A			Audiovisual Transmission from Hall A			
9:30 h								
10:00 h	Organising the World for the Fight Against Diabetes Chairman: R. Luft	Diabetic Pregnancy: Maternal Fuels and Fetal Developments Chairman: N. Freinkel	Insulin Action Chairman: J. Larner	Islet Cell Transplantation and Islet Cell Culture Chairman: P. E. Lacy	Classification and Epidemiology	Coagulation	Microangiopathy I	
10:30 h								
11:00 h								
11:30 h					Epidemiology (continued)	Neural Regulation of Glucose Homeostasis	Microangiopathy II	
12:00 h								
12:30 h	Closing Session	Audiovisual Transmission from Hall A			Audiovisual Transmission from Hall A			
13:00 h								
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9:00–9:45 h Audiovisual transmission of plenary lecture from hall A.

Panels

10:00–12:30 h **Viruses in Diabetes**
J. E. Craighead (USA), chairman
Possible role of viruses in human diabetes and of viruses in experimental diabetes.

A. Notkins (USA)
Genetically-determined susceptibility to viral insulitis.

D. R. Gamble (UK)
Epidemiology of virus-induced diabetes in man.

A. A. Like (USA)
Viruses and experimental insulitis.

H. Müntefering (FRG)
Effect of viruses on morphology and function of islets in culture.

W. Gepts (Belgium)
Viruses and insulitis in human diabetes.

14:00–16:30 h **Insulin Infusion Systems**
E. F. Pfeiffer (FRG), chairman
Introduction.

A. M. Albisser (Canada)
The artificial endocrine pancreas.

A. A. Seid-Gusejnov (USSR)
Insulin infusion systems. A surgeon's view.

T. Deckert (Denmark)
Preprogrammed insulin delivery.

J. Mirouze (France)
Insulin delivery systems.

K. D. Hepp (FRG)
Open loop systems for i.v. insulin therapy.

A. H. Clemens (USA)
Blood glucose sensors and control dynamics for insulin infusion systems.

Poster Session I

Artificial pancreas

Position

40 P Bojsen J., Deckert T., Kohlendorf K., Lorup B. (Copenhagen/Denmark)
Patient-controlled portable insulin infusion pump in diabetes *(Abstract No. 67*

41 P Hulst S. G. Th., Smit J. W. (Enschede/The Netherlands)
Management of insulin-dependent diabetics using a simple adjustab continuous subcutaneous insulin infuser (CSII) *(Abstract No. 253).*

42 P Jutzi E., Fischer U. (Karlburg/GDR)
The mathematical models of the glucose-insulin-relation as the basis closed-loop and open-loop systems *(Abstract No. 280).*

43 P Kawamori R., Morishima T., Yamasaki Y., Oji N. (Osaka/Japan)
The normalization of circadian profiles of plasma glucose, immunoreactiv glucagon, immunoreactive C-peptide in diabetics: long-term treatment wi pre-programmable insulin infusion pump. *(Abstract No. 293).*

44 P Noy G. A., Kurtz A. B. (Newcastle upon Tyne, London/UK)
Differential response of insulin-dependent diabetics to infusions of bovine an highly purified porcine insulins using the "artificial pancreas" (Biostator) as glucose clamp *(Abstract No. 454).*

45 P Rodger N. W., Shepherd G., Champion M., Dupre J. (London/Canad
Feasibility of self-administered continuous subcutaneous infusion of insulin the treatment of diabetes mellitus *(Abstract No. 508).*

46 P Sherwin R. S., Tamborlane W., Genel M., Felig P. (New Haven/USA)
Prolonged normalization of plasma glucose in juvenile onset diabetics b subcutaneous insulin administered with a portable infusion pump *(Abstract No. 554).*

47 P Shichiri M., Kawamori R., Okada A., Abe H. (Osaka/Japan)
Secretion of anti-insulin hormones and metabolic changes in response to th normalization of oral glucose tolerance in diabetics controlled with our artifici beta cell system *(Abstract No. 556).*

48 P Slama G., Klein J. C., Delage A., Ardila E., Lemaignen H., Papoz L Tchobroutsky G. (Paris/France)
Physiological control of meal intake by the artificial pancreas *(Abstract No. 568*

49 P Tamas Gy. Jr., Banyai Zs., Bojta J. (Budapest/Hungary)
Basal and "modulating" insulin demand in pregnant, non-pregnant and insulir resistant diabetics assessed by an artificial pancreas *(Abstract No. 593*

50 P Vague Ph., Altomare E., Moulin J. P., Vialettes B., Lopez N., Vague (Marseille/France)
Efficacy of insulin regimen preplanned with the use of artificial pancreas (A.P in brittle diabetics. A long term study *(Abstract No. 628).*

51 P Beyer J., Jäger H., Cordes U. (Mainz/FRG)
Demonstration of improved carbohydrate tolerance of insulin depender diabetics to the administration of a saccharase inhibitor using the artificia pancreas *(Abstract No. 56).*

Poster Session II

Position

92 P Lang D. A., Matthews D. R., Harris E., Peto J. (Oxford/UK)
Cyclical oscillations of basal plasma insulin, glucagon, pancreatic polypeptide and glucose in normal and diabetic man *(Abstract No. 344).*

Hormones 2: Insulin Action

93 P Oka Y., Akanuma Y., Kasuga M. (Tokyo/Japan)
The effect of high fat diet and high glucose diet on insulin binding and glucose metabolism in rat adipocytes *(Abstract No. 459).*

94 P Plas C., Menuelle P., Moncany M. L. J. (Bicetre/France)
Insulin glycogenic effect antagonized by glucagon and epinephrine in cultured fetal rat hepatocytes *(Abstract No. 485).*

95 P Loten E. G., Sneyd J. G. T., Boyes S. P. (Dunedin/New Zealand)
Energy dependent activation and Mg^{2+}dependent inactivation of cyclic nucleotide phosphodiesterase *(Abstract No. 372).*

96 P Nath R., Sidhu H., Kumar V. (Chandigarh/India)
Preparation properties and in vitro insulin potentiating activity of glutathione-nicotinic acid-chromium complex *(Abstract No. 440).*

97 P Laurent F., Mialhe P. (Strasbourg/France)
Effect of insulin on the glucose metabolism of the alpha cell *(Abstract No. 351).*

98 P Caygill C., Ayling C., Dandona P. (London/UK)
Activation of exogenous insulin in plasma *(Abstract No. 94).*

99 P Brown P. M., Juul S., Preswich S., Sönksen P. H. (London/UK)
The metabolic effects of infusions of a semisynthetic insulin, A_1-B_{29} dodecoyl insulin, and native insulin in diabetic patients *(Abstract No. 81).*

100 P Craig J. W., Larner J. (Charlottesville/USA)
Insulin stimulation of glycogen synthase activity in cultured human fibroblasts from diabetic and control subjects *(Abstract No. 118).*

101 P Bergman R. N., Ider Y. Z., Cobelli C. (Evanston/USA; Padua/Italy)
Quantitative estimation of insulin sensitivity *(Abstract No. 51).*

102 P Shigeta Y., Harano Y., Kobayashi M., Hidaka H., Yasuda H., Kosugi K., Nakano Y., Ohgaku S., Sakakibara S. (Ohtsu, Mino/Japan)
Decreased insulin sensitivity in vivo and its mechanism in diabetes mellitus *Abstract No. 557).*

103 P Navalesi R., Ferrannini E., Pilo A., Giampietro O., Maneschi F., Benzi L., Tallarigo L., Lenzi S. (Pisa/Italy)
Insulin kinetics in various conditions of insulin resistance: Diabetes, acromegaly, and uraemia *(Abstract No. 441).*

NOTES

Panels

10:00–12:30 h **Insulin Secretion and Insulin Resistance in Insulin-Independent Diabetes**

S. S. Fajans (USA), chairman
Heterogeneity of insulin responses in MODY and MOD.

E. Cerasi (Israel)
Basic Factor in MOD: Insulin deficiency.

R. C. Turner (UK)
Control of basal insulin secretion.

J. B. Halter (USA)
Hyperglycaemia: Compensation for impaired insulin secretion.

C. N. Hales (UK)
Pharmacologic modification of insulin secretion.

G. Reaven (USA)
Insulin resistance in diabetes.

9:00–9:45 h Audiovisual transmission of plenary lecture from hall A.

Free Communications

10:00–11:30 h **Artificial Pancreas I**
Chairmen: G. Slama (France), A. E. Lambert (Belgium)

10:00 h Albisser A. M., Goriya Y., Bahorio A., Jackman W. S., Ferguson T., Zinman B. (Toronto/Canada)
The control of experimental diabetes using preprogrammed portal insulin infusions *(Abstract No. 11).*

10:15 h Klein J. C., Slama G. (Fontainebleau/France)
A sophisticated programmable miniaturised pump for insulin delivery *(Abstract No. 312).*

10:30 h Sacca L., Sherwin R. S. (New Haven/USA; Naples/Italy)
Glucose regulation during continuous insulin infusion: Implications for pre-programmed insulin delivery systems in the treatment of diabetes *(Abstract No. 519).*

10:45 h Renner R., Piwernetz K., Hepp K. D., Mehnert H. (Munich/FRG)
Optimizing open-loop systems for continuous intravenous insulin therapy *(Abstract No. 503).*

11:00 h Seid-Gusejnov A., Shumakov V., Livshits A., Levitskij E., Ignatenko S., Gor N., Adasko A., Galitskij A., Voloshin A. (Moscow/USSR)
Artificial endocrine pancreas *(Abstract No. 544).*

11:15 h Nosadini R., Alberti K. G. M. M., Nattrass M., Orskov H. (Newcastle upon Tyne/UK; Chicago/USA; Aarhus/Denmark)
Metabolic normalisation of insulin-dependent diabetics using a glucose-controlled insulin infusion system *(Abstract No. 451).*

11:45–13:15 h **Artificial Pancreas II**
Chairmen: K. G. M. M. Alberti (UK), G. Tamas (Hungary)

11:45 h Granic M., Topic E., Mesic R., Stavljenic A., Skrabalo Z. (Zagreb/Yugoslavia)
Further results of the application of Biostator and continuous subcutaneous insulin infusion in the treatment of insulin dependent diabetics *(Abstract No. 200).*

contd.

Free Communications

12:00 h Kerner W., Beischer W., Pfeiffer E. F. (Ulm/FRG)
Comparison of diurnal blood glucose control in juvenile diabetics under feedback controlled and preprogrammed insulin infusion *(Abstract No. 304).*

12:15 h Kraegen E. W., Chipps D., Chisholm D. J., Bell D., Zelenka G., Lazarus L. (Sydney/Australia)
Insulin delivery during meals to diabetics using computer-assisted insulin delivery systems *(Abstract No. 329).*

12:30 h Hansen Aa. P., Hansen H. E., Orskov H., Nosadini R., Noy G. (Aarhus/Denmark; Newcastle upon Tyne/UK)
The growth hormone hypersecretion and the hypersecretion of glucagon in diabetes and uraemia. Studies with artificial kidney and artificial pancreas *(Abstract No. 216).*

12:45 h Eaton R. P., Schade D. S., Davis T. (Albuquerque/USA)
The kinetics of peritoneal insulin absorption
(Abstract No. 147).

13:00 h Tze W. J. (Vancouver/Canada)
Implantable artificial endocrine pancreas for islet xenograft in dogs *(Abstract No. 621).*

Free Communications

10:00–11:15 h **Insulin Biochemistry and Metabolism**
Chairmen: L. G. Heding (Denmark), A. Rubenstein (USA)

10:00 h Permutt M. A., Chyn R., Goldford M. (St. Louis/USA)
Purification of proinsulin messenger RNA and synthesis of its complementary DNA *(Abstract No. 478).*

10:15 h Zühlke H., Jahr H., Ziegler M., Ziegler B. (Karlsburg/GDR)
Influence of newly synthesized insulin-specific mRNA of isolated pancreatic islets on proinsulin biosynthesis
(Abstract No. 688).

10:30 h Bone A. J., Swenne I., Hellerström C. (Uppsala/Sweden)
Regulation of fetal islet growth and insulin biosynthesis
(Abstract No. 70).

10:45 h Bachmann W., Böttger I., Haslbeck M. (Munich/FRG)
On the mechanism of insulin resistance in liver disease: Studies in D-galactosamine-hepatitis and in partial hepatectomy in rats
(Abstract No. 30).

11:00 h Yokono K., Imamura Y., Sakai H. (Kobe/ Japan)
Purification, characterization, immunological properties and biological significance of insulin degrading enzyme from pig and rat skeletal muscle *(Abstract No. 677).*

11:30–13:15 h **Insulin Secretion in vivo**
Chairmen: P. Vague (France), R. C. Turner (UK)

11:30 h Strubbe J. H., Van Wachem P. (Haren/The Netherlands)
Insulin secretion of transplanted neonatal pancreases during intracardiac glucose injection and spontaneous ingestion of food *(Abstract No. 580).*

11:45 h Michaelis D., Rjasanowski I. (Karlsburg/GDR)
Relationship between b-cell function and the development of chemical and insulin-dependent diabetes in youth
(Abstract No. 408).

12:00 h Taborsky G. J. Jr. (Seattle/USA)
Infusion of an insulin-selective analogue of somatostatin as a model of maturity-onset diabetes *(Abstract No. 588).*

12:15 h Heding L. G., Kasperska-Czyzykowa T.
(Copenhagen/Denmark; Warsaw/Poland)
Proinsulin in fasting and post-glucose non-diabetics
(Abstract No. 224).

contd.

67 P. Patient-controlled portable insulin infusion pump in diabetes

J. BOJSEN, T. DECKERT, K. KØLENDORF and B. LØRUP, Copenhagen, Denmark

Ten brittle diabetics, mean duration 10,2 years, all treated with highly purified porcine NPH insulin twice daily, were placed on highly purified porcine regular insulin 4 times daily for 2 days. Thereafter preplanned intravenous insulin infusion was started. Insulin in an amount corresponding to the daily insulin requirement was infused by a portable infusion pump. Immediately before the main meals the postprandial infusion programme was initiated by the patients by pushing a button. Capillary blood glucose was taken every 30 min after meals and every 2 hours during the night. C-peptide response after 1 mg of glucagon intravenously and also insulin antibodies were evaluated in every case. After an equilibration period of 7 hours, blood glucose fluctuations were in the physiological range in nearly all patients during the infusion period. Mean blood glucose (MBG) was 5.4±0.7 mmol/l (mean±SD), and the standard deviation of MBG was 1.7±0.5 mmol/l. Glucose homeostasis was significantly better during the infusion days. It is concluded that near-normal blood glucose fluctuations can be achieved in brittle diabetics by a preplanned insulin infusion programme initiated by the diabetics.

280 P. Mathematical models of the glucose-insulin relation as the basis of closed-loop and open-loop systems

E. JUTZI and U. FISCHER, Karlsburg, G.D.R.

The purpose of our study was to explore the quantitative aspect of the blood glucose concentration on the rate of insulin secretion in man. In order to evaluate the relation between insulin response, glucose load and glucose disappearance rate, 15 normal subjects were given a glucose dose of 12 mg/kg.min for 60 min by a continuous intravenous infusion. A mathematical model for the calculation of the insulin secretion rate was developed:

$$CISR = F.IS\ (IRI_{t+\Delta t} - IRI_{t}.e^{0.693.\Delta t/HLI})$$

where CISR=calculated insulin secretion rate, F=proportional factor, IS=insulin space and HLI=half-life of insulin. The coefficients of multiple regression analysis of the blood glucose and the insulin secretion rate patterns were prepared for use in insulin infusions by a closed-loop system in diabetes:

$$ID = a_0 + a_1\ (PG-90) + a_2\Delta PG$$

where ID=insulin dose and PG=plasma glucose. In a further study, 12 normal subjects were observed for 24 hours. The multiple regression model allows estimation of the 'basal' (glucose-independent) insulin secretion rate (a_0) over the whole time. There is a circadian rhythm of the basal insulin secretion rate with an increase in the morning and a decrease in the afternoon. These data suggest a rhythmic insulin treatment by open-loop infusion systems.

293 P. The normalization of circadian profiles of plasma glucose, immunoreactive glucagon and immunoreactive C-peptide in diabetics: long-term treatment with pre-programmable insulin infusion pump

R. KAWAMORI, T. MORISHIMA, Y. YAMASAKI and N. OJI, Osaka, Japan

In view of the difficulties in the development of a portable glucose sensor, a small and light pre-programmable insulin infusion pump (pre-pro pump) was applied to diabetics. In this system, the time pattern of the insulin infusion rate over 24 hours obtained from our bedside-type artificial beta-cell was pre-programmed in a microcomputer, which controlled the pump. The results show that small amounts of intravenous insulin produced adequate glucose homeostasis, far superior to that produced by much larger doses of subcutaneous insulin. The quality of control was consistent in all cases studied. Immunoreactive glucagon (IRG) and C-peptide (CPR) responses to intravenous insulin by the pre-pro pump were compared in each subject with subcutaneous regular insulin 3 times a day, or with subcutaneous intermediate-acting insulin injection once a day. IRG levels were significantly lower when blood glucose response and plasma immunoreactive insulin levels were normalized by the pre-pro pump, than when postprandial hyperglycemias were pronounced in spite of subcutaneous intermediate-acting insulin injection. In many insulin-dependent diabetics, CPR was elevated when plasma glucose concentrations were high, despite subcutaneous insulin injections, but CPR was kept in the lowest concentrations during insulin infusion, showing that beta-cell function was kept in resting state. This seemed to be effective in lowering remarkably the insulin requirements thereafter.

of insulin in the treatment of diabetes mellitus

N.W. RODGER, G. SHEPHERD, M. CHAMPION and J. DUPRE, London, Canada

We have examined the feasibility of subcutaneous infusion of insulin in insulin-dependent diabetics using doses designed to normalize overnight-fasting blood glucose and prevent glycosuria. Portable pumps delivered insulin solution at 50 µl/hr between meals and at 400 µl/hr (high rate) for selected intervals before or during meals. Infusion was initiated with 80% of the daily dose established with conventional injections using high rate (initiated by subject) for 15 min before meals, with subsequent adjustment of insulin concentration and/or duration of high rate infusions. 9 insulin-dependent diabetic volunteers were studied in hospital for 2-4 days. Mean (±SEM) blood glucose concentrations before breakfast, 90 min after breakfast, before lunch, before supper, before bedtime, on 2 consecutive days were 67±6.6, 175±16, 129±14, 135±13, 120±10 mg/dl respectively. Mean 24-hr urine glucose output was 1.90±0.7 g/day. In 7 subjects, exercise (450-600 k.p.m./min, 30 min) with continued infusion of insulin and omission of breakfast did not result in hypoglycemia. In 6 diabetics, infusions were maintained without difficulty for 2-8 weeks. Two subjects monitored blood glucose by reflectance meter and administered their infusions during normal activity outside hospital and reported overnight fasting blood glucose levels of 71±4,72±6 mg/dl, 12 observations each. It is concluded that self-administered subcutaneous insulin infusion is a practical means of attaining excellent control of blood glucose during normal activity in insulin-dependent diabetics.

554 P. Prolonged normalization of plasma glucose in juvenile-onset diabetics (JOD) by subcutaneous insulin (I) administered with a portable infusion pump

R. S. SHERWIN, W. TAMBORLANE, M. GENEL and P. FELIG, New Haven, CT, U.S.A.

Preprogrammed I delivery systems using the i.v. route are often hampered by problems of infection or thrombosis. Recently we reported normalization of plasma glucose (PG) for periods of 48-96 hr with a miniaturized (6x18x7 cm), portable (400 g) infusion pump which is worn by the patient and delivers I via the subcutaneous route at preprogrammed basal rates with pulse dose increments 30 min prior to each meal. In the present study, long-term efficacy of this system was examined in 4 brittle JOD (age 16-26) treated with the pump for 2 wk while fully ambulatory. PG (198±32 mg/dl on conventional therapy) fell to 89±5 on day 7 (P<0.01) and 85±2 on day 14 (P<0.01). Maximal excursions in PG also fell from 230±24 mg/dl (conventional therapy) to 85±5 mg/dl (day 7, P<0.01) and 82±6 mg/dl (day 14, P<0.01). Glycosuria (49±12 g/24 hr pre-pump) was completely eliminated during pump therapy. No patient experienced symptoms of hypoglycemia. The total daily I dose delivered by the pump (48±7 U) was less than or equal to the patient's usual I dose. Conclusion: Long-term (2 wk) normalization of PG can be achieved in ambulatory JOD with a portable I infusion system which requires neither a glucose sensor nor the i.v. route.

568 P. Physiological control of meal intake by the artificial pancreas

G. SLAMA, J. C. KLEIN, A. DELAGE, E. ARDILA, H. LEMAIGNEN, L. PAPOZ and G. TCHOBROUTSKY, Paris, France

We have studied the effects of mixed meals and dextrose intake on blood glucose (BG) and insulin delivery by the artificial pancreas in 24 insulin-dependent diabetics. Twelve patients had three meals containing at random 20, 40 and 60 g of complex carbohydrates (CHO); 12 other diabetics, comparable in weight, age and duration of diabetes, received at random 20, 40 and 60 g of dextrose. Physiological BG variations were observed in these diabetic patients with a good reproducibility of glycemic control and amount of insulin delivered from one subject to another. Dextrose ingestion led to higher initial BG increase than mixed meals, but the duration of BG increase lasted significantly (P 0.001) longer after mixed meals than after dextrose. The areas under the curves of hyperglycemia were not significantly different; time delay between the starting of food intake and BG increase were between 11±1 and 25±5 min and were usually not shorter after dextrose than after a mixed meal. The total amount of insulin delivered in order to restore the initial BG values was highly (but not linearly) correlated to the amount of CHO administrated. On the other hand, it was not correlated to the age, body weight, duration of diabetes, initial BG values (in the range of 3.7 to 6.5 mmol/l) nor to the nature and order of administration of the CHO load. 5.10±1.58 to 13.66±2.09 units were needed for a period of 94±11 to 132±11 min. Because of the overall physiological pattern obtained

593 P Basal and 'modulating' insulin demand in pregnant, non-pregnant and insulin-resistant diabetics assessed by an artificial pancreas

Gy. TAMÁS Jr, Zs. BÁNYÁI and J. BOJTÁ, Budapest, Hungary

Different components of insulin requirement were investigated in 8 non-pregnant, 10 pregnant (6 cases, 2-3 times during pregnancy, n=20) and 2 insulin-resistant diabetics by means of an artificial endocrine pancreas (Biostator® GC11S, Miles). Basal insulin necessary for maintaining normoglycemia in the resting fasting state (1-7 a.m.) calculated from the amount of insulin given by Biostator was 1276±656 mU/hr (X±SD) in non-pregnant (n=11 nights), 1277±745 (n=8) in early pregnant diabetics having maximum at onset of sleep (rise in HGH) and a minimum between 3-4 a.m. coinciding with minimum of cortisol secretion. A moderate increase during pregnancy was found (1806±972; n=8, 1522±755; n=10; 2nd and 3rd trimester respectively). 'Modulating' demand, calculated by subtracting mean basal from total insulin given over 2.5 hours after a meal expressed as mU per g carbohydrate, was practically the same in pregnant and non-pregnant diabetics (100-300 mU) showing a diurnal rhythm in 8 cases. A slight rise in the evening demand compared to non-pregnants was observed during pregnancy. In resistant cases, basal insulins were 4400 to 45600 mU/hr, 'modulating' demand 490-1360 mU. These results might be helpful in optimization of conventional insulin therapy and pre-programming of portable insulin infusion systems.

628 P Efficacy of insulin regimen preplanned with the use of artificial pancreas (AP) in brittle diabetics: a long-term study

Ph. VAGUE, E. ALTOMARE, J.P. MOULIN, B. VIALETTES, N. LOPEZ and J. VAGUE, Marseilles, France

Is it possible to establish a preplanned programme of insulin regimen with long-term effectiveness in brittle diabetics? 15 insulin-dependent diabetics (diabetes duration >10 years, CPR <0.1 nmol/l) previously on multiple daily insulin injections and careful medical control were connected for 30 hours to AP (Biostator). The insulin dose infused over 24 hours was 1.03±0.3 U/kg (M±SD) divided into 20.9±7, 13.3±7, 12.6±3.7% (M±SD) for the 90 min following breakfast, lunch and supper respectively and 7.8±3, 13.1±5, 31.7±6% during the intervals. The personal infused insulin profile was used to establish for each patient the subsequent subcutaneous insulin regimen consisting of 2 daily injections of a mixture of short and intermediate acting insulins. On out-patient follow-up the control was judged on the mean of 6 glycemias per day which were 309±17 mg/100 ml before, 196±19 8 days, 209±16 3 months and 204±12 6 months later and M values (82.8±11, 44.3±6, 39.5±8 and 61±13 respectively). Hb Alc decreased only slightly. Averaging the doses infused by AP to the patients and establishing a standard insulin regimen on these basis did not help to control 8 other brittle diabetics. It seems that every brittle diabetic has peculiar fractional insulin needs. These needs are relatively stable over several months and therefore a personalized preplanned programme may be used.

56 P. Demonstration of improved carbohydrate tolerance of insulin-dependent diabetics to the administration of a saccharase inhibitor using the artificial pancreas

J. BEYER, H. JÄGER and U. CORDES, Mainz, F.R.G.

The effect of a saccharase inhibitor was studied on 10 insulin-dependent diabetics on an artificial pancreas over a period of twice 48 hours. The patients were examined at random after a therapy of at least 3 weeks with a saccharase inhibitor or a placebo respectively for control on an individual standardized diet. In the first 24 of the 48 hour period a continuous blood sugar profile was made with the usual insulin therapy. Then over a period of 24 hours the glucose-controlled insulin infusion was administered by the artificial pancreas. In this period the effect of the enzyme inhibitor regarding the insulin consumption for 24 hours and the respective postprandial and basal insulin consumption of the food-free time was measured. The saccharase inhibitor reduced the insulin consumption significantly over 24 hours, in the mean from 95 to 61 U and the evening postprandial consumption in the mean from 4.9 to 3.1 U. The nightly and the basal insulin consumption remained unchanged. The postprandial blood sugar peaks showed a lesser increase with an unchanged time of resorption. The fasting blood sugar values were decreased significantly in the mean from 228 to 131 mg%. The lower blood sugar peaks after the meals as well as the lesser postprandial insulin consumption demonstrate that less glucose is taken from the food. In connection with the lower fasting

11 F The control of experimental diabetes using preprogrammed portal insulin infusions

A.M. ALBISSER, Y. GORIYA, A. BAHORIO, W.S. JACKMAN, T. FERGUSON and B. ZINMAN, Toronto, Canada

We developed a portable insulin delivery device and showed that glycemia (G) in the postprandial (PP) and the postabsorptive (PA) periods could be normalized in unrestrained pancreatectomized dogs given their usual diet. Insulinemia (I) was higher than healthy controls in the PA (15±1 vs 10±1 μU/ml, P = 0.001) and in the PP (85±7 vs 25±4 μU/ml, P < 0.001) periods, perhaps due to the peripheral intravascular route of insulin infusion. The present study used the same experimental model except that insulin was infused directly into the portal vein via an externalized indwelling silastic catheter. PA insulin delivery rates were less with the portal (0.36±0.01 mU/kg/min) than with the peripheral (0.44±0.03 mU/kg/min) routes, P < 0.05, and resulted in normal PAI. During the PP period, the basal rate was accelerated 7-fold for 7½ h, as before. With this simple waveform of insulin delivery, PPG was normalized but PPI was about twice normal, P < 0.05. It is concluded that insulin can be delivered into the physiological (portal) route in diabetic dogs, that a constant basal rate alone will normalize the fasting glycemia and insulinemia, that the glycemic response to meals can also be normalized and that the PP insulin levels can be significantly reduced compared to those observed with the peripheral route of infusion. Complete normalization appears feasible by further refinements of the meal insulin waveform.

312 F A sophisticated programmable miniaturized pump for insulin delivery

J.C. KLEIN and G. SLAMA, Fontainebleau, France

An insulin infusion system has been developed with an original computing unit built into a small syringe pump. The unfilled system weighs 184 g. The mechanical part of this device and its body are from a commercial Pye Dynamics Limited ^{R} module. The patient has access, by 2 multichannel knobs, to the determination of an adequate insulin infusion program and to the time delay between the beginning of the food intake and actual insulin infusion. 8 profiles of insulin infusion are stored in a programmable integrated memory. Each of these occupies 63 steps, each step determining the insulin injection rate for the next 2 min. By the last step the rate has returned to the basal insulin infusion where it remains until further order. These 8 programs correspond to 8 possible meals containing 10-80 g complex carbohydrates or sucrose. Time delay, profiles and the total amount of insulin infused are inferred from previous observations on each patient during control by the closed-loop artificial pancreas, then modified, if necessary, after continious blood glucose monitoring. 11 young diabetic patients have been controlled by this method with a near-physiological blood glucose response pattern. The originality of this system lies in the possibility for the patient to choose the time, the nature and the amount of his food intake. Programmed chips can be easily interchanged to adapt the appliance to particular cases.

519 F. Glucose regulation during continuous insulin infusion: implications for preprogrammed insulin delivery systems (PPIDS) in the treatment of diabetes

L. SACCÀ and R. S. SHERWIN, New Haven, CT, U.S.A. and Naples, Italy

Lack of an implantable glucose sensor precludes diabetic treatment with an artificial pancreas. PPIDS may provide an alternative for improving diabetic control. However, it remains unestablished whether such systems which provide continuous between-meal insulin are likely to produce hypoglycemia. We therefore measured glucose kinetics (3-^{3}H-glucose) in normals and juvenile-onset diabetics during continuous insulin infusion (0.4 mU/kg/min). In normals and diabetics, plasma glucose (PG) fell at comparable rates and later stabilized at identical levels (55-60 mg/dl), despite 5-fold elevations in plasma insulin. In normals, the PG decline resulted from a 30% fall in glucose output (Ra) and a 30% rise in glucose disappearance (Rd). Subsequent stabilization occurred as Ra and Rd returned to baseline. Rebound increases in Ra preceeded (by 30-45 min) elevations in counterregulatory hormones. In diabetes, the PG decline was entirely due to suppression of Ra; however, later PG stabilization resulted from a 50% fall in Rd (P<0.01) as Ra remained suppressed. Conclusions: (1) Insulin infusions twice basal secretory rates do not cause symptomatic hypoglycemia. (2) In normals a rebound rise in Ra is a principal mechanism preventing hypoglycemia, while in diabetes hypoglycemia is prevented by an exaggerated fall in Rd. (3) Homeostatic

503 F. Optimizing open-loop systems for continuous intravenous insu therapy

R. RENNER, K. PIWERNETZ, K. D. HEPP and H. MEHNERT, Munich, F.R.G.

Insulin-dependent diabetics can be better controlled with continuou: sulin infusions than with conventional injections. In order to estal optimal infusion profiles for portable open-loop systems, 7 insulin-dependent diabetics were studied during a standard breakfast and lu: (36 g carbohydrates). Control algorithms were developed for a close loop system consisting of a manually-controlled infusion pump (5-20(mU/min) in combination with a glucose analyzer (YEllow Springs) for intermittent glucose determinations at 6 min intervals. With this s: system, postprandial blood glucose excursions never exceeded 70 mg/c additional glucose infusions were not necessary. The infusion rate i creased from a basal rate (10 mU/min) ca. 20 min after the beginnin each meal. At half-maximal rates the mean width of the insulin peak were for breakfast 44 and for lunch 31 min. Basal rates were reache again 90 min (breakfast) and 65 min (lunch) later. The mean insulin at lunch was 74% of the breakfast dose. These values were used for p programming miniaturized open-loop systems with fixed profiles or patient-operated control.

544 F. Artificial endocrine pancreas

A. SEID-GUSEJNOV, V. SHUMAKOV, A. LIVSHITS, E. LEVITSKIJ, S. IGNATENKO, N. GOR, A. ADASKO, A. GALITSKIJ and A. VOLOSHIN, Moscow, U.S.S.R.

The paper discusses surgical treatment of severe forms of diabetes mellitus complications and glucose metabolism disturbances in patients with surgical pathology with the help of 3 main types of artificial endocrine pancreas (AEP): stationary (SAEP), paracorporal (PAEP) and implantable (IAEP). At the terminal stage of diabetes nephropathy, AEP is applicable in transplantation of a kidney and a donor pancreas in various operations and hemodialysis. The application of SAEP, PAEP and IAEP is discussed in patients with severe lesions of the pancreatoduodenal zone (pancreonecrosis, chronic pancreatitis, tumors) who underwent various surgical operations and who in acute and chronic states demonstrated diabetes-like disturbances of glucose metabolism. AEP application is discussed in diabetics with complications due to various surgical operations. Special attention is given to the application of AEP in patients with steroid diabetes after the transplantation of a kidney as a result of intensive hormone immunosuppression and in patients with surgical interventions caused by diabetes angiopathy. Topics discussed include methods of long-term insertions of PAEP, use of external signals registering glucose in blood for controlling IAEP use of fuel and enzyme glucose sensors in PAEP and control programmes in various new types of AEP.

451 F. Metabolic normalization of insulin-dependent diabetics using a glucose-controlled insulin infusion system (GCIIS)

R. NOSADINI, K.G.M.M. ALBERTI, M. NATTRASS and H. ØRSKOV, Newcastle upon Tyne, U.K., Chicago, U.S.A. and Aarhus, Denmark

Normoglycaemia can be achieved using a GCIIS, but it is unclear whether overall metabolic normalization results, as insulin must be infused peripherally rather than intraportally. We have therefore studied metabolic profiles in 6 diabetics on usual therapy (SC) or with glucose clamped at 4-6 mmol/l (GC) and in 20 normal subjects. Metabolites and hormones were measured half-hourly for 12 hours from 0830 hours and usual meals given. Glucose turnover was assessed by bolus i.v. 3-H3/1-C14 glucose injections 4 hours after lunch in 5 diabetics and 4 normals. Normoglycaemia was achieved within 3 hours with CG with values higher on SC. Gluconeogenic precursors, glucagon and GH were normal on GC. Alanine (0.352±0.007 vs. 0.309±0.006; P<0.01) and pyruvate (0.105±0.004 vs. 0.098±0.004; P<0.05) were signifi[illegible] higher on SC than GC, while glycerol was lower (0.074±0.005 vs. [illegible]05; P<0.05). The predinner ketone body peak was significantly [illegible]er than normal with SC (0.35±0.07 vs. 0.16±0.03 mmol/l; P<0.01) wh[illegible] were decreased (0.73±0.07 vs. 0.92±0.09 mmol/l; P<0.01). Glucose [illegible] was similar in normals (1.51±0.20 mg/kg/min) and GC (1.47±0.1[illegible] suppressed in SC diabetics (1.13±0.11; P<0.05). Thus, with peripheral insulin infusion there is normalization of carbohydrate metaboli[illegible]

200 F. Further results of the application of the Biostator and continuous subcutaneous insulin infusion (CSII) in the treatment of insulin-dependent diabetics

M. GRANIĆ, E. TOPIĆ, R. MESIĆ, A. STAVLJENIĆ and Z. ŠKRABALO, Zagreb, Yugoslavia

Twenty insulin-dependent diabetics were treated with continuous subcutaneous insulin infusion for 7-14 days. The optimal dose of insulin during 24 hours was determined by means of the Biostator. Our indications for the application of CSII were: (1) states after diabetic ketoacidosis and coma, (2) during and after surgery in diabetics, (3) during pregnancy in diabetic pregnant women, and (4) acute phases of non-regulated diabetes. The value of CSII application was determined by means of glucose profile of intermediary metabolites and hormones. A statistically significant difference was found between the mean 24-hour glucose value (MBG 265.39±79.46 m%) before CSII application and Biostator, as well as during the application of Biostator (MBG 155.67±59.65 mg%). There was no statistically significant difference between the mean lactate value (10.27±2.45 mmol/l) and pyruvates (0.65±0.25 mmol/l) during the Biostator application, and the mean lactate value (10.55±2.34 mmol/l) and pyruvates (0.97±0.38 mmol/l) during the application of CSII. No technical problems appeared during CSII application. The combination of Biostator and CSII contributes to the treatment of certain states in insulin-dependent diabetics.

304 F. Comparison of diurnal blood glucose control in juvenile diabetics under feedback controlled and preprogrammed insulin infusion

W. KERNER, W. BEISCHER and E.F. PFEIFFER, Ulm, F.R.G.

Attempts at improvement of insulin therapy in diabetic patients have given rise to the development of the artificial endocrine pancreas (AEP) and pumps for preprogrammed insulin infusion (PII). In the present study, diurnal blood glucose (BG) profiles during treatment with AEP and PII, using insulin infusion rates derived from AEP, were compared. Eight juvenile diabetics without residual insulin secretion were connected to the AEP (Biostator ®). After an overnight BG equilibration, the patients were given 6 standardized meals for 24 hours. BG concentrations and insulin infusion rates for each minute were stored on a tape (Teleprint 390). Some days later, the same patients were attached again to the AEP for overnight BG equilibration. During the following 24 hours, while the patients were given the standardized meals, insulin was infused on a minute to minute basis in the same amount as on the first day. This was accomplished by a specially designed electronic device, which was loaded with the data from the tape and which controlled the action of the insulin infusion pumps of the AEP. BG was continuously monitored during the second day. Mean blood glucose (MBG) concentrations and mean amplitudes of glycemic excursions (MAGE) during application of PII were higher as compared to treatment with AEP (MBG:AEP 92-105, PII 94-114 mg/100 ml; MAGE:AEP 37-43, PII 55-110 mg/100 ml). We conclude that BG control with PII - despite application of insulin infusion rates derived from AEP - is inferior to feedback-controlled treatment with AEP.

329 F. Insulin delivery during meals to diabetics using computer-assisted insulin delivery systems

E.W. KRAEGEN, D. CHIPPS, D.J. CHISHOLM, D. BELL, G. ZELENKA and L. LAZARUS, Sydney, Australia

The aim of this study was to design and test a computer algorithm for preplanned (open-loop) delivery of insulin to diabetics during meals and to compare this with a closed-loop artificial pancreas. Total insulin delivered for meal regulation was based on previous data using a closed-loop system and the shape of the meal infusion profile was derived from data of insulin clearance. The algorithm delivered 1 unit of insulin over the first 20 min of the meal with a total of 7 units in the 3-hour postprandial period and was implemented on a bedside computer-assisted infusion system developed by us. Clinical studies were performed on 9 insulin-requiring diabetics with and without C-peptide reserve. Blood glucose was normalized using a variable infusion rate of insulin (0.5-2.5 U/hr) and the meal program activated on commencement of a mixed meal of 500 kCal containing 50 g carbohydrate. Increments in plasma free insulin (mean 65 mU/l at 60 min) closely approximated insulin increments in normal subjects given identical meals. Plasma FFA and alanine remained in the normal range during the meal. Blood glucose varied from a pre-meal level of 5.2±0.5 mmol/l to a peak of 7.0±0.6 mmol/l, approximately 1 mmol/l lower than peaks typically produced using the closed-loop artificial pancreas ($P<0.05$). Prompt delivery of insulin coincident with food intake using a pre-planned insulin program provides excellent regulation of meal peaks compared with a closed-loop system in which changes in insulin delivery follow blood glucose changes.

in diabetes and uraemia. Studies with artificial kidney and artificial pancreas

Aa. P. HANSEN, H. E. HANSEN, H. ØRSKOV, R. NOSADINI and G. NOY, Aarhus, Denmark and Newcastle, U.K.

Five uraemic long-term diabetic patients on long-term treatment with haemodialysis were studied during a 24-hour period involving a 5-hour haemodialysis. 17 experiments included morning as well as evening dialysis against glucose free dialysant with and without blood sugar control at 150 mg% using the artificial pancreas. The dialysis tubing was not permeable to molecules greater than 2000 Daltons. Half-hourly blood samples were taken. The growth hormone hypersecretion was completely suppressed immediately after the start of dialysis in cases with artificial pancreas controlled normoglycaemia as well as in cases with hypoglycaemia. In only 1 of 17 cases was a single growth hormone peak observed during dialysis. Elevated growth hormone levels did not recur within the first 3 hours after a session of dialysis except in 2 cases. While the behaviour of both hormones was similar, the described pattern was less clear-cut for glucagon. These findings may point to a dialysable substance being responsible for the hormonal hypersecretion in diabetes and uraemia. The preliminary results seem to exclude FFA, beta-hydroxybuturate, alanine, lactate and glycerol. Currently, other candidates and non-diabetic uraemics are being studied. The difficult problems in controlling electrolyte and metabolic aberrations during and after dialysis so often encountered in uraemic diabetics were in practice abolished when the artificial pancreas was utilized.

147 F. The kinetics of peritoneal insulin absorption

R. P. EATON, D. S. SCHADE and T. DAVIS, Albuquerque, NM, U.S.A.

The technical feasibility of peritoneal insulin delivery by an artificial pancreas has been previously demonstrated, but the rapidity of the insulin absorption and the importance of volume and concentration are unknown. Therefore, we defined the kinetics of peritoneal insulin absorption in 36 somatostatin-diabetic dogs. Non-anesthetized mongrel dogs were given a fixed quantity of regular insulin (2 units) intraperitoneally at 3 different concentrations for 30 min (3.2 U/ml, 0.64 U/ml, or 0.13 U/ml respectively). Endogenous insulin secretion was blocked by somatostatin. Both the rate and magnitude of peritoneal insulin absorption into the peripheral circulation were compared with a control saline study and an intravenous insulin infusion study. The transport of insulin across the peritoneal surface demonstrated a time-dependent dose-response, with a 10 min lag period prior to plasma detection.Maximal peripheral plasma insulin levels of 32 + 8 µU/ml were achieved at a peritoneally infused insulin concentration of 0.64 U/ml which was not enhanced by infusing the equivalent amount of insulin at a concentration of 3.2 U/ml. The decline in plasma glucose was directly related to the magnitude of the absorbed peritoneal insulin. We conclude that both delivery volume and insulin concentration are important determinants of peritoneal insulin absorption. The absorption of peritoneally infused insulin is rapid and results in a reduction in plasma glucose concentration. Thus, the peritoneal delivery of insulin by an artificial pancreas is biologically feasible.

621 F. Implantable artificial endocrine pancreas (IAEP) for islet xenograft in dogs

W.J. TZE, Vancouver, Canada

An implantable artificial endocrine pancreas (IAEP) unit with a coiled single artificial capillary containing xenogeneic rat islets (100/kg body weight) was implanted in streptozotocin-alloxan induced diabetic dogs. Following implantation a decrease in plasma glucose level from an initial value of 370 mg% to normoglycemic level and a corresponding increase in circulating immunoreactive insulin up to 120 µU/ml were observed in the recipient animals. In addition, normal plasma glucose and appropriate insulin responses to intravenous glucose were also demonstrated. These findings suggest that xenogeneic rat islets implanted as an IAEP can maintain a normal glucose homeostasis in a diabetic dog recipient. This IAEP system would appear to have the potential for future clinical application in man.

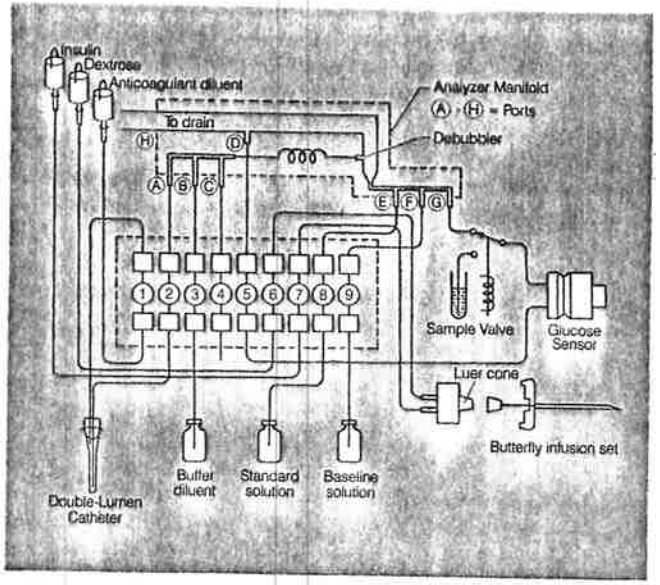
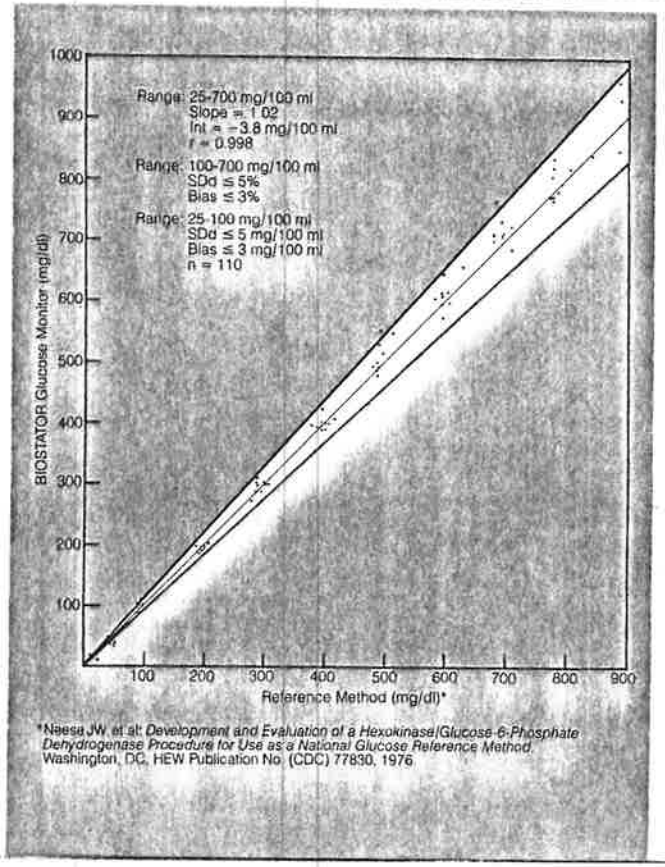


Fig. 1. Flow diagram of the BIOSTATOR Glucose Controller Pump Module. Note that the scheme permits a rapid two-point calibration of the sensor and the overall calibration of the on-line analyzer without removing the Double-Lumen Catheter from the patient's vein.[3]

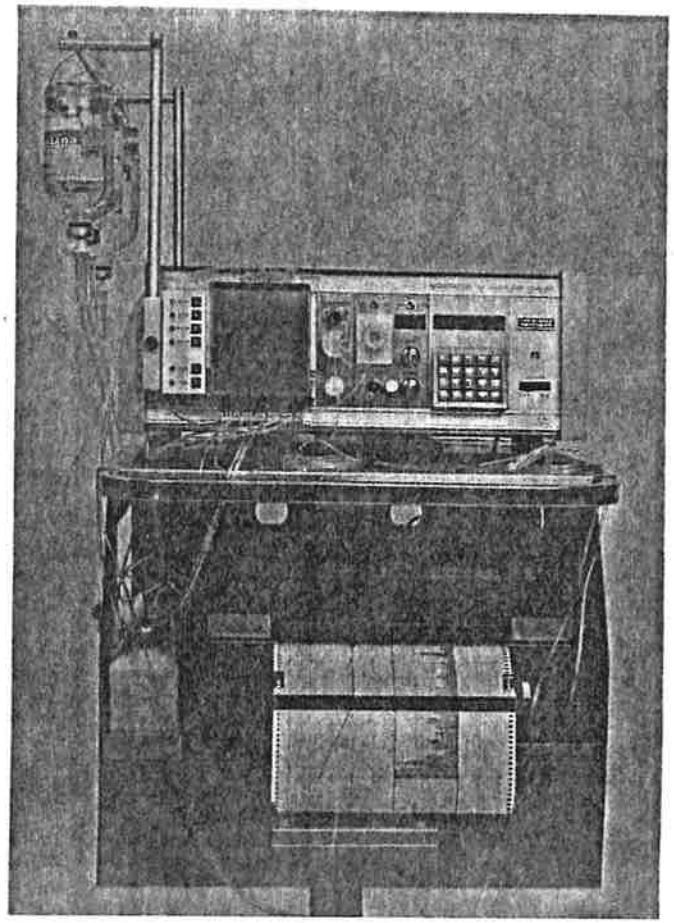


*Naese JW, et al: *Development and Evaluation of a Hexokinase/Glucose-6-Phosphate Dehydrogenase Procedure for Use as a National Glucose Reference Method.* Washington, DC, HEW Publication No. (CDC) 77830, 1976.

Fig. 2. Correlation curve compares the performance of the BIOSTATOR Glucose Analyzer Module with the proposed glucose reference method (hexokinase/glucose-6-phosphate dehydrogenase).[2]

BIOSTATOR® GLUCOSE CONTROLLER

for achievement and maintenance of normoglycemia



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4. *BIOSTATOR® Glucose Controller Operating Manual.* Elkhart, Ind, Lile Science Instruments, Miles Laboratories, Inc., 1978.

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10th CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

SATELLITE SYMPOSIUM:

Advanced Postgraduate Course in Hungary

WORKSHOP ON ARTIFICIAL BETA CELL IN DIABETES RESEARCH AND MANAGEMENT

ABSTRACTS

HÉVIZ, HUNGARY, September 19-20, 1979

SEPTEMBER 19, 1979

08:15 - 08:25 Welcome
A. H. Clemens, Chairman

08:25 - 11:00 Recent Developments for Closed-Loop Systems
Moderator: A. H. Clemens

A. Sensors

08:25 - 08:40 P-1
On-Line Monitoring of Blood Glucose, Potassium and Calcium by Electrochemical Sensors
A. H. Clemens, E. J. Fogt, A. R. Eddy

08:40 - 08:50 P-2 A/B
Development and Evaluation of Blood Glucose Measuring Unit without Blood Loss
A. Quarnstrom, B. Schersten, U. Nylen, P. Hagander, T. Lindholm, H. Thysell, D. Heinegard, L-G. Ohlsson, H. Hakansson, C-A. Gullberg

08:50 - 09:00 P-3
The State of Development of an Electrocatalytic Sensor
G. J. Richter, G. Luft, U. Gebhardt

Discussion

09:00 - 09:05 D-4
Glucose Measurements by the Biostator® System
P. Aaby Svendsen, J. Sandahl Christiansen, U. Soegard, M. Frandsen

09:05 - 09:10 D-5
Investigations in a System for the Extracorporal Continuous Registration of Blood Glucose
P. Abel, P. Wulfert, W. Wilke

B. Control Algorithms for Closed-Loop Systems

09:10 - 09:20 P-6
Evolution of Control Algorithms for Biostator® Systems
A. H. Clemens

09:20 - 09:35 P-7 A/B/C
Physiological Algorithms for Glucose Controlled Insulin Infusion (GCI); Use of GCI to Investigate Insulin Half-Life versus Insulin Requirements and Circadian Rhythms of Glucose and Insulin
U. Fischer, E. Jutzi, E. Salzsieder, E.-J. Freyse, G. Albrecht, W. Wilke, P. Abel, W. Unger, M. Heil

09:35 - 09:45 P-8
The Artificial Endocrine Pancreas with the Computer Algorithm for Self-Adaptive Control of Blood Glucose Concentration
M. Shichiri, R. Kawamori, Y. Yamasaki, T. Morishima, H. Abe

Discussion

09:45 - 09:50 D-9
Linear Systems Theory Approach for Modeling the Human Blood Glucose Regulation in Normal and Pathological States
R. Menier, J. L. Beneytout, T. Deutsch

[illegible] Insulin Control on Glucose Metabolism
T. Deutsch, M. Schulz, Gy. Tamas

[illegible] - 10:00 D-11
Studies in Order to Optimize Constants Used in the Algorithms of the Biostator® GCIIS
J. Sandahl Christiansen, P. Aaby Svendsen, E. Mathiesen, P. Rubin, B. Ronn

[illegible] - 10:15 General Discussion

10:15 - 10:30 Coffee

C. Insulin

10:30 - 10:40 P-12
Immunology, Structure and Function of Insulin
E. R. Arquilla

10:40 - 10:50 P-13
The Stability of Highly Concentrated Neutral Insulin Solutions
H. Thurow

[illegible] - 11:00 General Discussion

11:00 - 12:30 Closed-Loop Systems in Metabolic Research

11:00 - 11:10 Moderator: E. F. Pfeiffer

11:10 - 11:20 P-14
Insulin Selfinhibition in Vivo in Healthy and Overweight Subjects
W. Beischer, M. Schmid, K. Kerner, L. Keller, M. Maas, E. F. Pfeiffer

11:20 - 11:30 P-15
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B. Schulz, K. P. Ratzmann, P. Abel, H. Goraczka

11:30 - 11:40 P-16
Hba_1 (a+b+c) and Motor Sensory Conduction Velocity (MCV,SCV) Before and After 72 Hours of AEP Application
P. Brunetti, M. Massi-Benedetti, F. Santeusanio, G. Calabrese, L. Scionti, M. de Angelis, G. Bolli, V. Gallai

11:40 - 11:50 P-17
Glucose-Alanine Turnover Rates During Closed-Loop Control (Biostator® GCIIS) of Blood Glucose Concentrations and the Response to Acute Insulin Withdrawal
W. Clarke, E. Ben-Galin, M. Haymond, J. Santiago

11:50 - 12:00 P-18
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K.G.M.M. Alberti, G. Noy, R. Nosadini, Aa. P. Hansen, M. Nattrass, A. L. J. Buckle, H. Orskov

Discussion

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S. Raptis, K. Karaiskos, Ch. Zoupas, G. Boufas, G. Dimitriadis, S. Moulopoulos

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The Influence of Physical Exercise on Blood Glucose and Need of Insulin in Juvenile Diabetics
J. Beyer, H. Schoell, U. Cordes, U. Krause

12:10 - 12:15 D-21 Daily Insulin Requirement in Insulin-Treated Diabetics in Dependence on B-Cell Function
H. Bombor, D. Michaellis, I. Rjasanowski H. Keilacker, M. Ziegler, W. Bruns

12:15 - 12:20 D-22 The Metabolic and Hormonal Consequences of Glycemic Normalization by the Artificial Pancreas in Diabetic Man
B. Zinman, E. B. Marliss

12:20 - 12:30 General Discussion

12:30 - 14:15 Lunch

14:15 - 15:45 **Closed-Loop Systems in Clinical Research**

14:15 - 14:25 Moderator: A. M. Albisser

14:25 - 14:35 P-23 The Glucose Clamp, a Technique for the Study of Carbohydrate Metabolism in Man
R. Andres

14:35 - 14:45 P-24 Determination of the "Courses" of Insulin-Effects Using the Artificial Beta Cell (Biostator® GCIIS)
P. Bottermann, P. Huegler, U. Schweigart, Th. Zilker, K. Giebler, F. Enzmann

14:45 - 14:55 P-25 The Influence of Normoglycemia on Serum Concentrations of Growth Hormone, Glucagon and Free Fatty Acids in Juvenile Diabetics
W. Kerner, D. Schock, M. Schultz, V. Maier, E. F. Pfeiffer

14:55 - 15:05 P-26 Use of Artificial Beta Cell (Biostator® GCIIS) to Compare Insulin Requirements after Standard Meals Containing Sucrose or Fructose in Insulin-Dependent Diabetes
N. V. Bohannon, J. H. Karam, C. W. Young, A. Burns, P. H. Forsham

15:05 - 15:15 P-27 Use of Artificial Pancreas in Measuring Insulin Requirements after Diabetes Diet, Xylitol or Sucrose in Insulin Dependent Diabetics
W. Hassinger, G. Sauer, U. Krause, U. Cordes, R. Buehler, J. Beyer, K. H. Bessler

Discussion

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P. Brunetti, M. Massi-Benedetti, G. Calabrese, F. Santeusanio, A. Puxeddu, A. Bueti, G. Angeletti

15:20 - 15:25 D-29 Closed-Loop Clamping of Blood Glucose Delays Growth Hormone Elevation after Insulin Administration
E. W. Kraegen, L. Lazarus, D. R. Chipps

15:25 - 15:30 D-30 Determination of Optimum Caloric Need by Means of the Biostator® System
E. Topic, M. Granic, A. Stavljenic, Z. Skrabalo

15:30 - 15:45 General Discussion

15:45 - 16:00 Coffee

16:00 - 17:50 **Closed-Loop Systems in Clinical Medicine, Part I**
Moderator: Gy. Tamas

A. Pregnancy

16:00 - 16:15 P-31 A/B Use of an Artificial Endocrine Pancreas in Diabetic Pregnancy; Continuous Blood Glucose Monitoring in Newborns, Infants and Children
Gy. Tamas, D. Bekefi, E. Baranyi, J. Szalay, J. Egyed, ZS. Banyi

16:15 - 16:25 P-32 Metabolic Control During Diabetic Pregnancy Assisted by the Artificial Pancreas
D. Desir, F. Fery, E. Von Lennep, A. Verhoeven, C. Picard, E. O. Balasse

16:25 - 16:35 P-33 Insulin and Glucose Requirements During Labor and Delivery
L. Jovanovic, R. L. Jones, C. M. Peterson

16:35 - 16:45 General Disscussion

B. Surgery

16:45 - 16:55 P-34 The Use of an Artificial Beta Cell (Biostator®GCIIS) During Surgery in Diabetic Patients
P. Drouin, D. Rousselle, G. Sery, J. Deiber, J. P. Pointel, G. Vernhes; G. Debry

16:55 - 17:05 P-35 Biostator® GCIIS Application for Surgery (Insulinoma, Open-Heart, and Vascular Surgery)
L. Kaspar, H. Kritz, H. Denck, K. Irsigler

17:05 - 17:15 P-36 Continuous Blood Glucose Monitoring and Feedback Controlled Dextrose Infusion with an Artificial Beta Cell in Diagnosis and Treatment of Organic Hyperinsulinism
Ch. Neuhaus, W. Kerner, W. Beischer, E. Heinze, Ch. Herfahrt, E. F. Pfeiffer

Discussion

17:15 - 17:20 D-37 The Utility of Feedback-Controlled Dextrose Infusion (Biostator® GCIIS) in the Diagnosis and Management of Insulinoma
C. W. Young, J. H. Karam, M. Lorenzi, A. Burns, G. M. Grodsky, P. H. Forsham

17:20 - 17:25 D-38 Dynamic Blood Glucose Regulation in Surgical In-Patients by a Closed-Loop Insulin Infusion System
J. D. Kruse-Jarres, M. Bresch, U. Lehmann, U. Letule, W. Vogel

17:25 - 17:30 D-39 Glucose Utilization in the Post-Operative Period in Severely Injured Patients
V. Hempel, H. Junger, W. Heller, U. Draski, H. Draski

17:30 - 17:50 General Discussion

SEPTEMBER 20, 1979

08:30 - 09:30 Recent Developments for Open-Loop Systems

08:30 - 08:40 P-40 Preprogrammable Micropumps with D.C. or Stepper Drives for Open-Loop Drug Delivery
A. H. Clemens

08:40 - 08:50 P-41 How to Make Miniaturized Insulin Administration Devices Safe Against Overdose
K. Prestele, M. Franetzki

08:50 - 09:00 P-42 Technical Concept of an Initial Experience with Sensorless Insulin Delivery Devices Implanted in Dogs
M. Franetzki, K. Prestele

09:00 - 09:10 P-43 Artificial Beta Cell Development Studies
W. J. Spencer, G. A. Carlson, R. P. Eaton, D. C. Schade

Discussion

09:10 - 09:15 D-44 A Sophisticated Programmable Miniaturized Pump for Insulin Delivery
J. C. Klein, G. Slama

09:15 - 09:30 General Discussion

09:30 - 10:30 Route Assessment for Open-Loop Systems
Moderator: A. H. Clemens

09:30 - 09:40 P-45 Comparison of Peripheral Venous, Portal Venous, Subcutaneous and Intraperitoneal Routes for Insulin Delivery in Diabetic Dogs
R. A. Rizza, F. J. Service, R. E. Westland, L. D. Hall, G. S. Patton, M. W. Haymond, J. E. Gerich

09:40 - 09:50 P-46 Preprogrammed Peripheal and Portal Insulin Infusions in Unrestrained Diabetic Dogs
A. M. Albisser, Y. Goriya, A. Bahoric

09:50 - 10:00 P-47 Comparison of Insulin Administration via Intravenous, Subcutaneous, or Intraperitoneal Routes in Insulin-Dependent Maturity Onset Diabetics
K. Irsigler, H. Kritz

10:00 - 10:15 General Discussion

10:15 - 10:30 Coffee

10:30 - 10:40 Impact on Diabetes Management
Moderator: K. Irsigler

10:40 - 12:05 A. Closed-Loop Determination of Open-Loop Programs and Injections Schedules

10:40 - 10:50 P-48 Normoglycemic Control with a Portable Insulin Minipump in the Initial Phase of Treatment after Diabetes Onset - Remission
H. Kritz, L. Kaspar, C. Najemnik, K. Irsigler

10:50 - 11:00 P-49 Physiological Control of Meal Intake by the Artificial Pancreas
G. Slama, J. C. Klein, A. Delage, E. Ardila, H. Lemaignen, L. Papoz, G. Tchobroutsky

11:00 - 11:10 P-50 Plasma Glucose and Free Insulin Responses to a Meal using Combined Preprogrammed and Feedback-Controlled Insulin Administration
[illegible] J. F. Granger, M. Nattrass, [illegible]

[illegible] - 11:20 P-51 [illegible]on of Optimum Doses of Insulin by Means of Artificial Pancreas in the Treatment of Diabetes Mellitus
M. Granic, E. Topic, A. Stavljenic, Z. Skrabalo

Discussion

11:20 - 11:25 D-52 The Artificial Beta Cell in Determination of Insulin Requirements for an Open-Loop System
K. Kolendorf, J. S. Christiansen, J. Bojsen, P. A. Svendsen

11:25 - 11:35 D-53 A/B Improved Metabolic Control by Combined Insulin Injections and Infusions/ The Role of the Artificial Beta Cell (Biostator® GCIIS) in the Correction of Conventional Insulin Treatment
W. Bruns, K. P. Ratzmann, P. Steinborn, L. Meyer, E. Zander, R. Muntel, P. Aber[illegible]

11:35 - 11:40 D-54 Diurnal Variation in Closed-Loop Insulin Requirements in Fasting Insulin Dependent Diabetics - Probable Role of the Adrenal Pituitary Axis
W. Clarke, N. White, T. Melton, J. Santiago

11:40 - 11:45 D-55 Application of an Artificial Endocrine Pancreas in Clinico-Pharmacological Studies
Gy. Tamas Jr., J. Bojta, M. Guoth, Zs. Banyai, E. Kovacs, F. Enzmann

11:45 - 11:50 D-56 Efficacy of an Insulin Regimen Preplanned with the Use of Artificial Pancreas in Brittle Diabetics
P. Vague, E. Altomare, J. P. Moulin, N. Lopez

11:50 - 12:05 General Discussion

12:05 - 14:00 Lunch

14:00 - 15:20 B. Open-Loop Applications
Moderator: K. Irsigler

14:00 - 14:10 P-57 Subcutaneous Continuous Insulin Infusion (S.C.I.I) Using Variable Augmented Infusion Rates in the Management of Diabetic Pregnancy
J. M. Potter, J. P. D. Reckless, D. R. Cullen

14:10 - 14:20 P-58 Improved Clinical Management with the Help of Miniaturized Infusion Systems
R. Renner, K. D. Hepp, H. Mehnert, M. Franetzki

14:20 - 14:30 P-59 Preprogrammation of an Open-Loop System of Insulin Infusion
J. L. Selam, T. C. Pham, D. Chenon, J. Mirouze

14:30 - 14:40 P-60 Long-Term Continuous Subcutaneous Insulin Infusion in Outpatient Diabetics
J. C. Pickup, H. Keen, M. White, E. M. Kohner, J. A. Parsons

14:40 - 14:50 P-61 Use of a Semi-Closed Loop Computer-Assisted Insulin Infusion System (CAIIS) for Control of Hospitalized Diabetics
D. J. Chisholm, E. W. Kraegen, D. R. Chipps, M. McNamara, D. Bell, L. Lazarus

Discussion

14:50 - 14:55 D-62 Continuous Subcutaneous Insulin Infusion in Management of Insulin Dependent Diabetes Mellitus
M. Champion, G. Shepherd, N. W. Rodger, J. Dupre

14:55 - 15:00 D-63 Normalization of Circadian Profiles of Plasma Glucose, Immunoreactive Glucagon, and Immunoreactive C-Peptide in Diabetics with Computer-Operated Portable Insulin Infusion Systems
R. Kawamori, T. Morishima, R. Tohdo, M. Shichiri, H. Abe

15:00 - 15:05 D-64 Studies with the Biostator® Closed-Loop System and a Portable Open-Loop Pump in a Patient with Abnormal Handling of Insulin Given Subcutaneously
J. V. Santiago, R. Gingerich, N. White, W. Clarke, J. Gavin

15:05 - 15:20 General Discussion

15:20 - 15:40 Coffee

15:40 - 16:10 Closed-Loop Systems in Clinical Medicine II
Moderator: J. Santiago

15:40 - 15:55 P-65 Autoregulation of Endogenous Insulin Secretion: A Protective Mechanism against Hyperinsulinemia due to Errors in Secretion of Constants in Algorithms for Insulin Delivery
J. V. Santiago, W. L. Clarke, D. M. Kipnis

A. Renal Dialysis

15:55 - 16:05 P-66 Application of an Artificial Endocrine Pancreas during Haemodialysis in Diabetic Patients
J. Bojta, J. Juhasz, L. Koranyi, J. Makoandgy, G. Tamas Jr.

Discussion

16:05 - 16:10 G. Slama

B. Glycemia and Hemodynamics

16:10 - 16:20 P-67 Hypercoagulation and Blood Glucose Control in Patients with Diabetes Mellitus -- Rapid Reversibility as Monitored and Controlled by the Artificial Beta Cell
R. L. Jones, L. Jovanovic, C. M. Peterson

16:20 - 16:30 P-68 Dynamic Study of Whole Blood Viscosity and Related Factors of Insulin Requiring Diabetics, using an Artificial Pancreas
P. Drouin, D. Roussele, J. P. Pointel, J. Deiber, Ph. Voisin, S. Gaillard, J. F. Stolz

16:30 - 16:40 P-69 Normalization of Erythrocyte Filtrability after Correction of Hyperglycemia by an Artificial Pancreas in Insulin Dependent Diabetics
I. Juhan, P. Vague, M. Buonocore, E. Vovan

16:40 - 17:00 General Discussion

17:00 - 18:00 Panel Discussion:
Benefits and Limitations of Closed-Loop versus Open-Loop Systems
Moderator: A. H. Clemens

A NEW EQUIPMENT FOR CONTINUOUS BLOOD GLUCOSE MEASURING WITHOUT BLOOD LOSS

A. Qvarnstrom, U. Nylen, B. Schersten, P. Hagander, T. Lindholm, H. Thysell, D. Heinegard, L-G Ohlsson, H. Hakansson, C-A Gullberg
Lund, Sweden

A mobile bedside system is developed for continuous blood glucose monitoring (CGM). A micro extracorporeal circuit is established by pumping blood from a venous or arterial catheter at a constant flow on the outside of a semipermeable membrane in the form of a capillary and then returning the blood to a vein. An isotonic sodium chloride solution is pumped inside the capillary. The membrane contact area and the flow rates are chosen, so that the glucose concentration in the dialysate is less than 2% of the concentration in the blood. As the dialysate is formed exclusively by a pressure independent diffusion process there is a linear relation between the dialysate and the blood glucose concentrations. The system is to some extent temperature dependent but the error is made less than 1% by electronic temperature compensation. The dialysate passes at a steady flow rate through an enzyme reactor, with immobilized glucose oxidase, immediately followed by an oxygen electrode. In order to determine the oxygen concentration in front of the enzyme reactor, this is bypassed at predetermined intervals. The consumption of oxygen in the reactor, and thus the glucose content is calculated from the electrode readings. The glucose values are presented by a microcomputer with a delay time of less than 60 seconds. The CGM-system was successfully used in animal and patient investigations. In some cases the system was combined with an algorithm for automatic glucose control by insulin infusion.

A NEW AUTOMATED GLUCOSE-CONTROLLED INSULIN INFUSION SYSTEM BASED ON A PHYSIOLOGICAL ALGORITHM AND ITS APPLICATION IN ANIMAL AND HUMAN DIABETES

F. Salzsieder, E. Jutzi, G. Albrecht, W. Wilke, E.-J. Freyse and U. Fischer
2201 Karlsburg, DDR

Based on a linear relationship between the glucose concentration and its rate of change and the calculated insulin secretion rate an automatic insulin infusion system was developed. The system consists of a computer and an infusion pump control unit. The computer calculates the insulin dosage for periods of 5 minutes in relation to the actual glucose concentration course. On the one hand the pump controller converts the calculated insulin dosage into a pulse like control signal and on the other hand it divides the dose in a glucose controlled period and in a constant "basal" period of 2.5 minutes. The five essential infusion parameters of this system are preselectable in a wide range and therefore we can choose the parameters individually for each diabetic patient or animal. The very simple structure of the whole infusion system allows easily a miniaturization.

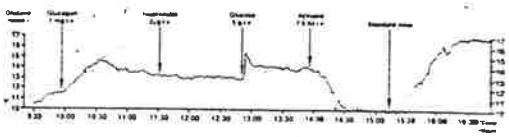
In our experiments we have connected the system with the Beckman Glucose-Analyzer (Beckman Instruments Inc., USA) and the infusion pump Infumat LS 212 (MTA Kutesz, Hungary). In investigations with experimental diabetic dogs we used the system to fit the parameters of the mathematical algorithm under special test situations [illegible] the fitted parameters we obtained a concrete formalization of the glucose concentration course of a day or longer. In patients the apparatus was applied to improve the conventional insulin therapy and to compare their own findings with results received by other systems.

CLINICAL EXPERIENCE OF A NEW EQUIPMENT FOR CONTINUOUS GLUCOSE MEASURING

B. Schersten, P. Hagander, U. Nylen, A. Qvarnstorm, C-A Gullberg
Lund, Sweden

Plasma glucose was continuously monitored with a time delay of less than 60 seconds by using a closed circuit in which blood is returned to the patient after flowing through a microdialyser. The dialysate passes an enzyme reactor containing glucose oxidase, and the glucose concentration is calculated from the corresponding oxygen consumption determined by an oxygen electrode. Five independent security systems built into the apparatus assured a high degree of safety.

The equipment was used for long term glucose monitoring in order to reach an optimization of diabetic therapy. The glucose kinetics was studied in response to intravenous injections of glucagon, isoprenalin, glucose and insulin, and in response to standardized meals. Blood was sampled separately in these studies for determination of insulin, C-peptide, glucagon, growth hormone, and cortisol.



The diagram shows how the four insulin stimulators were used to study the insulin secretion capacity of a not insulindependent 50 years old diabetic on oral treatment. The glucose profile is a [illegible]

CIRCADIAN RHYTHMS OF GLUCOSE AND OF INSULIN IN DIABETIC DOGS ON GLUCOSE-CONTROLLED INSULIN INFUSION

U. Fischer, E. Jutzi, G. Albrecht, E.-J. Freyse, P. Abel, W. Unger, M. Heil,
Central Institute of Diabetes, Karlsburg, GDR

The circadian rhythms were analyzed in dogs using power spectra and cross correlation analysis. Normally the acrophase of plasma glucose was early in the morning and that of IRI was in the evening. This pattern is suggested to be the expression of physiological regulatory events at least in carnivora. - The same dogs were made diabetic (partial pancreatectomy and streptocotozin into the A. pancreaticoduodenalis sup.) and got glucose controlled insulin infusions. The algorithm used resulted from multiple linear regression analysis of the normal glucoseinsulin relationship. - During these infusions there were almost normal mesor values of the two parameters; but they exhibit acrophases concomitantly in the evening. In time-dependent insulin dosage (like an open-loop system) acrophases of plasma glucose were in the evening, too. - It is concluded that the normal circadian rhythms in carbohydrate metabolism result both from that of B-cells and of insulin responsiveness. But in artificial B-cell application (closed-loop system) the circadian pattern is determined by insulin responsiveness only.

RELATIONS BETWEEN INSULIN HALF LIFE AND THE NEED OF INSULIN IN GLUCOSE-CONTROLLED INSULIN INFUSIONS (GCI)

E.-J. Freyse, G. Albrecht, E. Jutzi, U. Fischer,
Central Institute of Diabetes, Karlsburg, GDR

In GCI an algorithm was used resulting from regression analysis between glucose curves and simultaneous insulin secretion rates. They were calculated from peripheral IRI curves of normal dogs using half life (τ) and distribution space (IS) of insulin. - Both in normal and diabetic dogs (no insulin antibodies, no resting insulinogenic function) the injection of MC-insulin results in a monoexponential IRI-decrease. τ and IS do not significantly differ between normal (2.5 ± 0.9 min., 103 ± 44 ml/kg) and diabetic animals (3.2 ± 0.6 min., 160 ± 20 ml/kg). There are no systematic variations e.g. in dependence on the day-time or on the duration of diabetes. The variations observed are mainly due to the different basal IRI levels. - The algorithm parameters depend exponentially on τ and on IS as a multiplier. In the same animal a_0 (basal glucoseindependent dose), a_1 (proportional control), and a_2 (differential control) vary by a factor <2 in dependence on the real τ and IS values. The more rough the time pattern (2.5 min in these experiments) the more pronounced is the influence of τ. - Since there was no system in the variations, the algorithm parameters can be estimated using statistically proved values of τ and IS.

D-11

STUDIES IN ORDER TO OPTIMIZE CONSTANTS USED IN THE ALGORITHMS OF THE BIOSTATOR®GCIIS

J. Sandahl Christiansen, P. Aaby Svendsen, E. Mathiesen, P. Rubin and B. Ronn

Using a set of constants recommended by Miles, a surplus of 24-hour insulin consumption in the machine compared to normal clinical dose was noted - in accordance with several reports.

In C-peptide negative juvenile-onset insulin-dependent diabetics repeated OGTT were performed using still higher values for QI and lower values for KR until the set of values giving the smallest amount of insulin still capable of maintaining normal glucose tolerance was found. Further weakening of constants resulted again in higher insulin consumption, but now producing OGTT-curves resembling those of maturity-onset diabetics.

Using the optimized set of constants, 24-hour insulin requirement in Biostator® GCIIS were found equal to the clinical dose.

It is concluded that the Biostator GCIIS with the constants described can be valuable in determining clinical insulin dose in insulin-dependent diabetics without endogenous insulin secretion.

D-10

KINETIC MODEL OF INSULIN CONTROL ON GLUCOSE METABOLISM

T. Deutsch, M. Schulz, Gy. Tamas - Budapest, Hungary

For modeling glucose homeostasis determination of blood glucose (BG) and IRI are necessary. Our investigation on structural identifiability of insulin-glucose system in 3 diabetics with no insulin production (proved by C-peptide det.) showed the possibility of calculating both parameters of glucose- and insulin subsystem as well by measuring BG only. Analyses of 6 insulin tolerance tests permitted us to define a formal mathematical model containing 2 insulin- and 2 glucose compartments. At the beginning of the tests a pulse injection of crystalline insulin were given intravenously (16 U Actrapid and 16 U porcine des Phe B1-insulin; HOE 01S resp. in two-day intervals). Starting BG averaged 420 mg/dl.BG was measured continuously. Glucose production was supposed to be inhibited by high BG and high insulin level induced by insulin administration.

Following parameters can be calculated: rate constants of insulin and glucose transport ($K12=0.19\pm0.11$; $K21=1.70\pm0.66$; $K34=0.68\pm0.41$; $K43=7.68\pm2.08$ /hr); insulin metabolic rate constant ($K10=1,90+0,15$); peripheral insulin sensitivity ($S=1.08\pm1.21$ U./h). The different operating modes and control parameters of Biostator® GCIIS (Miles) made it possible to get values for calculations. Comparing results found in diabetics to those of the model the data fit well ($r=0.97$). In our opinion using an artifical endocrine pancreas the above mentioned characteristics of glucose-insulin system in insulin dependent diabetics can be calculated even without determining insulin by measuring blood glucose only.

D-29

CLOSED-LOOP CLAMPING OF BLOOD GLUCOSE DELAYS GROWTH HORMONE ELEVATION AFTER INSULIN ADMINISTRATION

E. W. Kraegen, L. Lazarus and D. R. Chipps Sydney, Australia

Studies using the glucose infusion facility of a closed-loop control system (artificial pancreas) enable direct effects of insulin to be differentiated from those due to lowering of blood glucose (BG). We have used such a system to examine growth hormone (GH) and cortisol (C) secretion after insulin administration.

After 30 minutes rest insulin (0.1U/kg) was delivered by I.V. bolus to 6 healthy fasting volunteers. BG was then maintained in the euglycaemic range (glucose clamp). Integrated samples were taken for GH and C. A mean of 0.67 ± 0.08 (SE) g/kg body weight of glucose was required to maintain basal euglycaemia. (BG 3.5-5.5 mmol/L.) This blocked the GH and C response to hypoglycaemia during the first 2 hours post-insulin. All subjects however showed a significant elevation ($p<0.025$) in GH initially apparent at 171 ± 9 min post-insulin and reaching a peak of $20.0\pm3.1\mu U/ml$ at 211 ± 6 min. No significant rise in C were observed ($P>0.10$). The GH rise followed the reduction to negligible rates of I.V. glucose required to maintain BG. In control studies ($n=4$), substituting saline for insulin, no similar GH rises were observed.

CONCLUSION: There is no immediate direct effect of insulin on GH or C secretion during the euglycaemic glucose clamp but there is a late rise of GH at 3-4 hours after the glucose clamp. We suggest that this rise is not stress-related (no accompanying rise in C) but is a response to altered glucose turnover. A change in BG level is not necessary to elicit this response.

P-15

BIOSTATOR® GCIIS FOR CHARACTERIZATION OF INSULIN SENSITIVITY IN EARLY DIABETES

B. Schulz, K. P. Ratzmann, P. Abel, H. Goraczka Karlsburg, German Democratic Republic

Insulin sensitivity may be assessed by monitoring changes of plasma glucose concentrations in response to an intravenous bolus injection or infusion of insulin. Obviously, the relatively small decrease of blood glucose levels without hypoglycemic symptoms does not allow an exact determination of insulin sensitivity in early diabetes. Reaven's group has circumvented this arduousness by using combined insulin-glucose infusions during inhibition of endogenous insulin secretion by epinephrine and prapranolol. However, a real assessment of insulin sensitivity is rendered more difficult because of interfering effects of epinephrine, betaadrenergic agents, and insulin on the metabolism of glucose-utilizing tissue. The purpose of the present studies was to investigate insulin sensitivity using the GCIIS (BIOSTATOR®; Mode 6:1). 5 healthy subjects and 5 non-obese asymptomatic diabetics (A.D.) were studied over 24 hours after an overnight fast. They were continously infused with 2 mg/kg/min glucose constant RD) without receiving any nutrients orally. Blood samples were taken before, at ½; 1;2;3;6 and 24 hours after the beginning of the investigation for assay of C-peptides levels. The amount of insulin (BC-Actrapid) needed to keep glycemia at fasting levels (constant BI) served as an index of insulin sensitivity. Under these conditions the endogenous insulin secretion was not stimulated. In comparison to normal subjects A.D. required significantly higher doses of insulin. Moreover, a diurnal rhythm of insulin sensitivity could be observed in all subjects. In conclusion, the GCIIS is suitable to assess insulin sensitivity which is reduced in non-obese A.D.