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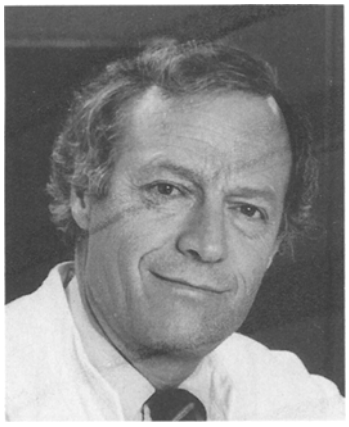

Karl Dietrich Hepp was born in 1936 in Munich, Germany. He studied medicine at the University of Munich and Freiburg, Germany and obtained his M.D. in 1960. Dr. Hepp was an intern at the Muhlenberg Hospital, Plainfield, N.J., USA from 1961–1962. He then became a resident in internal medicine, surgery and obstetrics and gynaecology in Munich. From 1963–1965 Dr. Hepp was a research fellow in clinical biochemistry at the University of Munich and from 1965–1967 he was senior research fellow and instructor in medicine at the University of Washington, Seattle, Wash., USA, In 1970 Dr. Hepp became head of the Division of Clinical Research, Diabetes Research Unit and consultant in endocrinology, Schwabing City Hospital, Munich. In 1972 Dr. Hepp obtained a board certificate and privatdozent in internal medicine from the University of Munich. In 1974 Dr. Hepp was visiting physician, Department of Endocrinology and Internal Medicine, Mayo Clinic, Rochester, Minn., USA. In 1976 he became Director of Medical Education, Schwabing City Hospital, and in 1978 became Professor of Medicine. In 1979 Dr. Hepp became head of the Department of Internal Medicine Oberföhring City Hospital, Munich. In 1984 he became head of the Third Department of Medicine (Endocrinology and Metabolism, Angiology) Bogenhausen City Hospital and head of the Clinical Diabetes Center of Bogenhausen City Hospital. Since 1968 Dr. Hepp has been an associate of the Diabetes Research Unit in Munich. Dr. Hepp has been a member of many professional societies and been involved with several medical publications. His research interests are in insulin therapy, insulin delivery systems, neuropathy and nephropathy.

Implantable insulin pumps and metabolic control

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Summary The development of implantable, remote-controlled insulin pumps dates back to the early 1970's when it was recognized that conventional insulin therapy may be inadequate to control microvascular complications. For the first prototypes the intraperitoneal access route was favoured because of a physiological portal/peripheral insulin gradient. With intraperitoneal insulin delivery excellent metabolic control can be obtained with glycohaemoglobin values close to the upper normal range. Although long-term studies in insulin-dependent diabetic patients show comparable results with respect to glycaemic control and intermediary substrate levels with intensive conventional therapy, the advantage of intraperitoneal insulin delivery may lie in the low rate of hypoglycaemic episodes. [Diabetologia (1994) 37 [Suppl 2]: S108–S111]

Key words Implantable insulin pumps, intraperitoneal insulin delivery, metabolic control.

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A number of European studies and the Diabetes Control and Complications Trial (DCCT) [1, 2] have now put an end to the lengthy discussion on the causal relationship between metabolic control and dia-

betic complications. Yet despite the ongoing discussion, many clinicians decided some time ago that they should provide the best possible metabolic control for their patients. In the early 1970s it was recognized that conventional subcutaneous insulin injection was in many cases inadequate, and new technologies were investigated.

Development of insulin delivery systems

In 1972 we began our cooperation with a group of medical engineers from Siemens AG (Erlangen, Germany). Although the first reports on glucose sensors had already appeared [3], it was clear that the time was not ripe for a miniaturized glucose-controlled system for insulin delivery. We therefore embarked on a project of programmable and patient-controlled devices for continuous insulin infusion with the purpose of developing an implantable insulin delivery system. The first step was a programmable bedside infusion apparatus consisting of a steering unit and a syringe pump for continuous intravenous insulin infusion. A circadian pattern of different infusion rates was programmed with the aim of imitating a physiological profile of insulin secretion [4].

The first trials showed surprisingly good glycaemic control even in patients with brittle diabetes who could not be sufficiently treated by conventional methods [4, 5]. Subsequently, a miniaturized insulin pump was developed by Franetzki and co-workers at Siemens. The first results with this portable, patient-controlled pump were presented by Renner et al. in 1977 [6].

With a view to potential implantation, the system consisted of two parts: a steering unit and an infusion device with an insulin reservoir. Thus, an external pump seemed to be only a transient step on the way to the implantable version. Unfortunately, further progress was considerably hampered by the instability of the insulin preparations which tended to form aggregates that precipitated in pumps and catheters. It took some years of investigation in basic insulin chemistry until this problem was solved by the group at Hoechst AG [7].

In the meantime a more pragmatic solution for continuous subcutaneous insulin infusion with an external pump was shown to be successful [8] and went into widespread clinical use. However, the work on implantable insulin delivery systems continued. Two different access routes were investigated, the intravenous, with the advantage of an immediate response to insulin, and the intraperitoneal route which was shown to deliver the hormone essentially to the portal system and which was likely to have less clinical complications [9].

In 1981–1982 the first prototypes of remote-controlled insulin pumps were implanted, including the Promedos system developed by Siemens [10–13]. Apart from these programmable pumps, gas pressure pumps of the Metal Bellows type which provided only one delivery rate, were also under study [14]. In 1985 the Point Study, the first collaborative (open) study with an implantable remote-controlled insulin delivery system, was started in order to test the clinical safety and efficacy of the Promedos E1 system [15].

Since adequate glycaemic control can be achieved with a multiple injection regimen or continuous subcutaneous insulin infusion which are both less invasive and less expensive, the benefit of an implantable pump is questionable. However, apart from the rare absolute indication in patients with subcutaneous insulin degradation [16] and considerations of quality of life and freedom from injections, intraperitoneal insulin application seems to be the major advance.

Intraperitoneal insulin delivery

First attempts at the intraperitoneal route of insulin delivery were made in diabetic patients undergoing peritoneal dialysis. By this route insulin is preferentially absorbed into the portal system and delivered to the liver [17]. It is evident that this approach is more physiological than either subcutaneous injection or intravenous infusion. Studies in experimental animals and man have shown that insulin given intraperitoneally is mainly absorbed via the portal circulation [18–20] and that 40–60 % is degraded during its first pass through the liver [18]. Consequently, peripheral insulin levels were found to be lower as compared with subcutaneous or intravenous application [21]. In view of the possible atherogenic effect of hyperinsulinaemia, this was felt to be an important argument in favour of intraperitoneal insulin [22]. However, we did not observe a significant difference of post-prandial insulin levels after 1 year of euglycaemic control in insulin-dependent diabetic patients, treated either with intensive conventional therapy or intraperitoneal insulin infusion [23]. However, if one compares peritoneal delivery with peripheral injection, a more rapid and consistent absorption and a more predictable delivery to the circulation can be shown [17, 18]. Thus, a better synchronisation of the insulin peak with postprandial hyperglycaemia and a more rapid onset of insulin action is obtained. In view of the future development of implantable glucose sensors experiments have been conducted with the aim of glucose-controlled feedback regulation of intraperitoneal insulin delivery. Although the general feasibility has been demonstrated, the quality of postprandial control was not convincing unless hybrid infusion regimens were used. These consisted of a pre-programmed pre-meal dose with subsequent feedback control [24]. One of the main arguments in favour of in-

traperitoneal insulin delivery is its possible advantage with respect to glucose control and the regulation of hormones and metabolites.

Effect of intraperitoneal insulin on metabolic control

Studies with variable rate, remote controlled implantable dosing systems have shown excellent metabolic control in C-peptide negative, insulin-dependent diabetic patients [14, 25, 26]. More recently, the EVA-DIAC-Survey on 227 patients (342 patient years) observed a mean HbA_{1c} of 7.01 % at 12, and 7.25 % at 24 months, respectively for intraperitoneal insulin delivery with three types of programmable implantable pump [27]. We have compared intensive conventional therapy with intraperitoneal insulin delivery over 12 months in matched pairs where the mean HbA_{1c} was 6.7 % in intensive conventional therapy, and 6.8 % with intraperitoneal therapy [23]. Thus, long-term control with intraperitoneal delivery results in metabolic regulation equivalent to a factor of 1.09–1.2 of upper normal glycohaemoglobin [15, 25–27] and in this respect, is clearly not superior to other forms of intensified insulin therapy.

If one takes the standard deviation of the mean blood glucose as a measure of instability, values between 2.3–3.4 mmol/l are observed [23, 26, 27]; again we found no significant difference when compared to intensive conventional therapy [23]. A different picture emerges with respect to the incidence of hypoglycaemia. Severe hypoglycaemic episodes, requiring external help were found to be frequent in the DCCT (0.62 per patient/year in the intensive conventional therapy-group [2]), and the conclusion was that euglycaemic control is achieved with the imminent danger of severe hypoglyceamia. However, the EVA-DIAC-Survey with 0.03 events per patient year shows a much lower rate [27] and would be a strong argument in favour of the implantable pump.

Hormones and substrates

Although lower plasma insulin levels were thought to be characteristic of the intraperitoneal access route, we [23] and others [28] could not confirm this under clinical conditions. Glucagon is reduced (perhaps reflecting partial alpha-cell failure in these patients) while growth hormone is elevated in comparison with a healthy control group [23].

The intermediary substrates non-esterified fatty acids, glycerol, β-hydroxybutyrate, lactate and alanine were found to remain in the normal range and the same applied to the lipid values (cholesterol, triglycerides, HDL-, LDL-cholesterol, apolipoprotein A_1 and B [23]. So far the available data show that glycaemic control close to the normal range results in normal levels, but not necessarily normal turnover of relevant substrates [29].

Primary and secondary prevention of diabetic complications

Even before the DCCT, a number of prospective studies had shown the beneficial effect of near-normoglycaemia on retinopathy, nephropathy and neuropathy in insulin-dependent diabetes [for review see 1]. The common problem in these types of trials, however, including the DCCT, is the inability to achieve glycaemic regulation within the normal range. Theoretical estimates would put the levels of HbA_{1c} at least in primary prevention, very close to the normal range, i.e. perhaps under a factor of 1.1 of the upper normal level [2, 30]. Although there is now sufficient evidence for a causal relationship between control and complications, we may not be able to achieve the quality of metabolic control that is necessary to fully prevent or halt complications. Insulin pumps so far have been shown to be the tool for the best long-term control [31], and implantable systems, after improving technical function and insulin dosing, may come closest to the goal of euglycaemic control.

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