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Insulin Delivery Systems: Current Topic

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Although insulin has been available for the treatment of diabetes mellitus for more than half a centry, the deficiency of conventional insulin therapy for diabetic patients have, to this date, not been satisfactorily overcome by any method. The development of potential delivery systems for insulin is highly important to prevent excessive fluctuation of plasma glucose levels, which results in long term complications in the diabetic. There are three major approaches toward development of glucose responding insulin delivery systems: A bioengineering approach is to devise mechanical components capable of releasing insulin in amounts appropriate to varying blood-glucose requirements. A biological approach relies upon cultured, living pancreatic beta cells encapsulated to constitute an insulin delivery unit. A biochemical approach is to synthesize a stable and biologically active glycosylated insulin that is complementary to the binding sites of lectin. This paper will cover several specific areas, including pancreatic transplantation(total or isolated islet cells), artificial pancreases(bioengineering or biological approach), controlled delivery system, glucose sensitive membrane systems, and a self-regulating insulin delivery system.

1. What Is Diabetes and Why Is It Necessary to Improve the Insulin Delivery Systems?

Diabetes mellitus (D.M., Diabetes) is an international disease affecting 1-2% of the populations in most countries of the world, especially in the advanced countries which are not afflicted by malaria, bilharzia, tuberculosis and gastrointestinal diseases. For example, according to the National Institute of Health (NIH) in U.S.A., 10 million Americans suffer from diabetes[1]. Diabetes is the fifth-ranking cause of death by disease, and accounted for 35,000 deaths in 1976 only. It is a contributing factor in at least 90,000 additional deaths each year.

Diabetes is a chronic complex metabolic disease. In its most fully developed state, it is characterized by a deficiency of the pancreatic endocrine hormone, insulin. This deficiency causes a defect in the glucose homeostasis system, whereby normal amounts of glucose are not able to enter the target tissue for storage and metabolism.

Clinically, diabetes exhibits an elevation of blood sugar levels (hyperglycemia), keton bodies (acetoacetate, and β-hydroxybutyrate) and ketonuria. Also, weight loss, excessive thirst (polydipsia), hunger (polyphasia), and urine excretion (polyuria), as well as a breakdown of body protein are common symptoms of diabetes.

The regulation of glucose homeostasis is a function of many variables, such as hormones, receptor sites sensitivity to hormones and nutritional state. The high degree of complexity of this system makes it difficult to ascertain the unique contribution that any one of these factors play. In diabetic, insulin is a pivotal hormone among other glucoregulatory hormones, such as glucagon, somatostatin and gastrin. From a clinical standpoint insulin is regarded as

a hormone whose major function is the moment-to-moment regulation of glucose homeostasis, exerting important effects on lipids and protein metabolism, in addition to its action on carbohydrate. The effects of insulin are directed at three primary target tissues: the liver, adipose tissue and muscle tissue. These insulin effects involve anticatabolic as well as anabolic action at each of these target tissues[2]. The diabetic, however, either does not secrete enough insulin (Type I) or cannot use the secreted insulin properly (Type II). The classifications and clinical characteristics of diabetes are listed in Table I[3].

Approximately 500,000 patients in the U.S.

Table I – *Classification of Diabetes Mellitus and Clinical Characteristics.*

Class	Former terminology	Clinical characteristics
Insulin-dependent Diabetes Mellitus (IDDM), Type I	Juvenile-onset-type diabetes (JOD), ketosis brittle diabetes, unstable diabetes.	Depends on injected insulin to prevent ketosis and to perserve life. Characterized by insulinopenia. Islet cell antibodies are frequently present at diagnosis in this type.
Noninsulin-dependent Diabetes Mellitus (NIDDM) Type II 1. Nonobese NIDDM 2. Obese NIDDM	Adult-onset diabetes Maturity-onset diabetes (MOD), ketosis-resistant diabetes, stable diabetes.	May use insulin for correction of symptomatic or persistant hyperglycemia. May develop ketosis under special circumstances, such as infection or stress. Glucose tolerance is often improved by weight loss. Hyperinsulinemia and insulin resistance characterize some patients in this type.
Other types, including diabetes mellitus associated with certain conditions and syndromes. 1. Pancreatic disease 2. Hormonal 3. Drug or chemical induced 4. Insulin receptor abnormalities 5. Certain genetic syndromes 6. Other type	Secondary diabetes.	In addition to the presence of the specific condition or syndrome, diabetes mellitus is also present.

A.[4] currently suffer from Type I or insulin-dependent diabetes mellitus (IDDM). Type I diabetes is usually characterized clinically by a rapid onset of symptoms (polyuria, polydipsia, polyphasia), insulinopenia (therefore total dependence on an exogenous insulin supply to maintain life), and proneness to ketosis. Classically, this type of disease develops before the age of 20. In IDDM patients, the pancreatic β-cells are much fewer in number than in normal persons, and produce very little or no insulin. As a result, the patient must receive one to three daily insulin injections to survive; insulin is given by injection, when taken orally it is destroyed by the body's digestive enzymes.

Type II or noninsulin-dependent diabetes mellitus (NIDDM) patients numbering approximately 5 million in the U.S. alone[5], usually produce normal (or near normal) amounts of insulin. However, they do not utilize this insulin effectively. The major cause of this phenomenon is believed to be the reduction of concentration and affinity of insulin receptors on the target cells[6-9]. Type II patients usually develop disorders after the age of 40 and the onset is gradual. The control of blood sugar levels can be achieved by carbohydrate restriction, weight reduction, in some cases insulin injection and the use of oral anti-hyperglycemic agents (mostly sulfonylurea derivatives). The oral anti-hyperglycemic agents do not stimulate the synthesis of insulin by β-cell, but instead promote the release of insulin into the blood stream. Of these 5 million type II patients, 10-20% eventually become type I[1]. As evident from the discussion so far, type I (IDDM) is the more serious form of the disease, due to the total dependence upon exogenous insulin injection to maintain life.

Although the overall survival rate of diabetics has been greatly enhanced in the last 60 years since the discovery of insulin by Banting and Best[10], the long-term complications of diabetes (esp. Type I) are now the key issue. Among the many complications of diabetes, macrovascular disease (macroan-

giopathy resulting in heartattack and strokes) and kidney disease (nephropathy) are respectively 2 and 17 times more common, among diabetics than among nondiabetics. Also the life expectancy of a diabetic from the time of onset of the disease is reduced by 30%[11]. The serious but nonlethal complications are, glaucoma, retinopathy, cataracts and eventual blindness. Diabetic patients have a 25-fold greater chance of developing blindness. The incidence of glaucoma is 5% in the diabetic population as compared with 2% in normal population[12]. In addition, significantly higher risks of myocardial and cerebral infarctions, as well as gangrene (resulting amputation of limbs) in diabetics have been reported[13]. At present, the reason why these complications occur is not clear. However, most researchers in this field believe that the long-term complicatons are related to the hyperglycemia (or wide fluctuatuon in blood glucose levels) in diabetics[14]. As clearly seen in Fig.1[15], postprandial

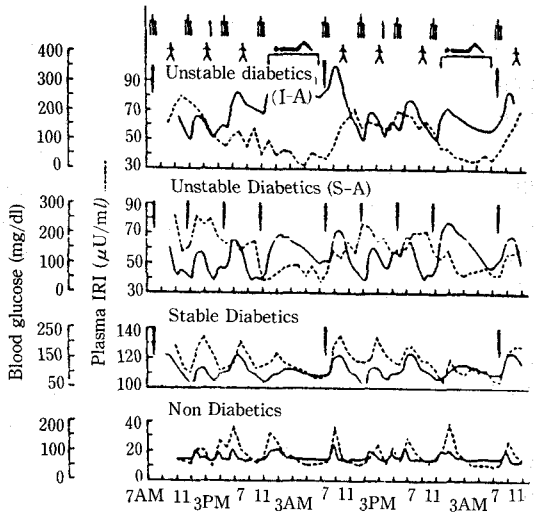

Figure 1 – Blood glucose and plasma insulin in normal, stable and unstable diabetic subjects under ambulatory, fed conditions for 48 hours. I-A refers to treatment with once a day injection of intermediate acting insulin; S-A refers to injection of short acting insulin before each meal. The syringe is the symbol for timing of the insulin treatment. The fork, spoon and knife represent a mixed meal and the single spoon represents a snack (Ref. 15).

blood glucose levels rise as high as 300 mg/dl, even with insulin injection, before they eventually return to euglycemia This hyperglycemia results in an alteration in the chemistry of hemoglobin which may play an important role in the pathogenesis of vascular disease in diabetes.

Glycosylated hemoglobins were first found to be present in the blood of diabetics by Rahbar in 1968[16]. It was also found that glucose binds nonenzymatically to hemoglobin in diabetics[17], and the degree of the glycosylation was proportional to the degree of hyperglycemia[18-20]. It should be pointed out that affinity of glycosylated hemoglobin for oxygen is somewhat enhanced[21], thus interfering with release of oxygen to the tissue in the condition of low pO_2 levels prevailing in the capillary. As a result, the glycosylated hemoglobins do not release oxygen normally, and this leads to blood vessel damage (microangiopathy) which in turn may damage the capillary in the eye (retinopathy) and lead to kidney failure (nephropathy). In addition, an increase in serum viscosity (approximately 6%) in diabetics[22,23], may be an important contributing factor to the retinopathy and nephropathy in diabetes; since altered blood flow and blood pressure may be significant factors in development of vascular complications, particularly retinopathy and nephropathy as reported[24,25].

Studies of basement membrane thickening (collagen material in the basement membrane of the ocular lens capsule, Descemet's membrane of the cornea, and the renal glomerules) have shown that the observed increase in thickness in diabetics is accompanied by an increase in the degree of collagen glycosylation, which is associated with changes in the basement membrane composition, as well as its permeability[26-29]. Therefore, the basement membrane thickening is an important contributing factor to the macro- or macroangiopathy, retinopathy and renal failure.

Although there has been an increasing amount of experimental data suggesting that

hyperglycemia and vascular disease are in some way related, it is not yet clear whether rigid control of the metabolic abnomalities (especially hyperglycemia) would prevent the long-term vascular complications[14]. However, there has been no overwhelming evidence to the contrary, that is, that vascular complications of diabetes are completely independent of hyperglycemia[14]. There are several possible reasons why this important question remains unanswered. First of all, a proper long-term clinical evaluation has yet to be done. The major reason is that through conventional treatment for diabetes mellitus (i.e., diet or exercise and intermittent subcutaneous insulin therapy), it is impossible to completely restore glucose homeostasis. Thus, diabetics rarely have completely euglycemic conditions throughout the day as shown in Fig. 1. Because of the inadequacy of conventional insulin therapy, many researchers are investigating new alternatives to the conventional modalities for the treatment of hyperglycemia in diabetes mellitus.

2. Pancreas Transplantation

(a) Total pancreas transplantation

Total pancreas transplantation was first accomplished in the 1920s by French group[30,31]. Many difficulties with this procedure have surfaced over the years, as evidenced by the wide variety of techniques that have been attempted to accomplish successful total pancreas transplantation[32]. In addition to the multiple problems associated with immune rejection, which is common in any organ transplantation, the total pancreas transplantation has several additional problem; such as vascular thrombosis, pancreatitis, and digestion of host tissue by exocrine pancreatic enzymes[32]. Therefore, pancreatic transplantation in humans is still in its early stage.

(b) Isolated islet cells transplantation

Due to the high degree of complication in total pancreas transplantation, the possibility of isolated islet cells transplantation has been investigated by Ballinger *et al.*[33] in 1972. They reported the sustained functioning of isologus islets transplanted into the peritoneal cavity of diabetic rats. Partial improvement in the rats was seen, however, they gained weight and had reduced blood sugar level and glycouria. A further improvement in the technique was made when an injection of the islet cells into the portal vein of the recipient rats[34] was used.

Najarian *et al.*[35] have attempted the transplantations of islet cell tissue in seven diabetic patients. However, hyperglycemia and glycouria continued following transplantation; also none of the patients showed an increase in circulating C-peptide levels [an indicator of insulin production since this connecting peptide (C-peptide) is removed in the conversion of proinsulin to insulin]. In addition, islet cells are not immunologically privileged and, like other tissue, are rapidly rejected when transplanted across species. Therefore, any transplantation of isolated islet cells would require immunosuppression.

3. Islet Cell Encapsulation

In 1975, Chick and his colleagues[36,37] demonstrated that beta cells (isolated islet) cultured on artificial semipermeable hollow fibers continued to synthesize and release insulin *in vitro* (Fig.2). These semipermeable membranes can also protect grafted cells from immune rejection[38]. This work was extended to alloxan induced diabetic rats, in which this "hybrid artificial pancreas" was implanted *ex vivo* as an arteriovenous shunt[39]. In this study, the use of such a device clearly showed very promising results in restoring euglycemia in diabetic rats. Also Sun *et al.*,[40] using such a device attached *ex vivo* to the vascular system of diabetic monkeys, lowered blood glucose levels into the nondiabetic range within 1 hour. More recently Sun *et al.*[41,42] encapsulated islet cells by alginate-polylysine-alginate membrane and demonstrated that pancreatic cells encapsulated in a biocompatible membrane can be used as a long-term insulin delivery system. In these studies[41,42], intraperitoneal transplant of encapsulated pancreatic

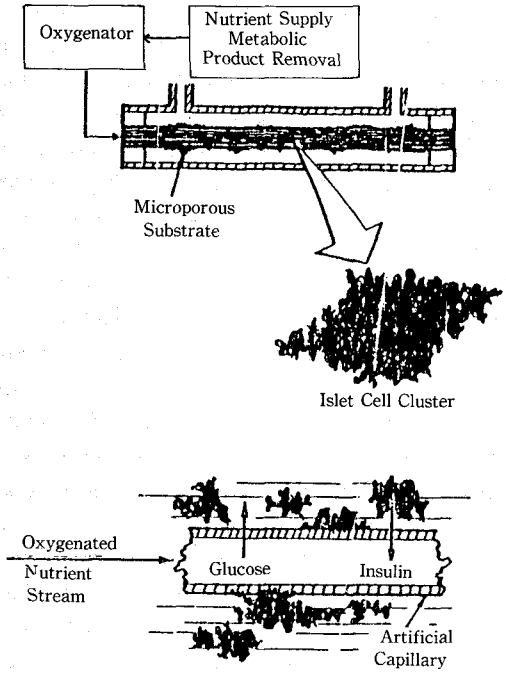

Figure 2-Beta cell culture on hollow fibers (Ref. 36).

islets reversed diabetes for over a year in rats. Furthermore, intact capsules containing islets were recovered from the peritoneal cavity 12-21 months after transplantation. Even it is very promising result for eventual clinical long-term insulin delivery, moment-to-moment regulation has not been answered yet. Therefore more investigations will be required to answer this issue.

4. Bioengineering Approach

(a) Closed-loop system

Closed-loop system is a mechanical insulin infusion pump which continuously monitors the plama glucose concentration and controls a self-contained computer unit to calculate and release insulin in proportion to the amount needed, as indicated by blood glucose level. This mechanical pump consists of glucose sensor, amplifier, computer, power supply, insulin reservoir and insulin injection pump. This device is effective in restoring euglycemia in diabetics, but it is large, nonportable, expensive and can only be used for short periods of time due to the short life span of the glucose sensor. More recently, work with wearable-type closed-loop device[43,44] has reduced its size and yielded significant progress in defining the problems in the treatment of diabetics. There are still, however, many problems to answer for real setting, such as a potential mechanical failure of device, catheter site and implantable site infection[45,46] and stability of insulin in the reservoir or in the infusion catheter[47-49]. Furthermore, even some groups[50,51] have begun evaluating hopefully stable, long-term glucose sensor, at present there is no long-term, stable glucose sensor available.

(b) Open-loop system

Because of the impracticality of closed-loop insulin infusion pump, open-loop system (absence of feedback control of blood glucose level; no glucose sensor) has been developed. Slama *et al.*[52] first showed the effectiveness (in restoring euglycemia) of this open-loop insulin infusion pump system using a continuous i.v. infusion in the absence of feedback control. This was confirmed by several other later studies[46,53-55].

However, it should be noted that the amount of insulin given in these open-loop insulin infusion pumps is predetermined in the same way as doses of conventionally administered insulin and not based on the continuous monitoring of plasma glucose concentration as is in the case of closed-loop systems. This type of treatment is only effective when used in combination with specific and carefully followed diet and exercise programs. Additionally, without home monitoring of blood sugar level, which permits patient-initiated modification of the insulin dose, this treatment would be no more effective than other conventional insulin therapy. Therefore these open-loop systems will eventually be required that some means of glucose sensing incorporated to achieve stricter control of appropriate insulin therapy. Finally the major problems related to this open-loop system are potential mechanical failure of the insulin injection pump resulting in rapid injection of

poptentially large doses of insulin (potential hypoglycemic comatose), rigid diets (due to the preprogrammed insulin release rate), frequent capillary blood sugar monitoring, and insulin aggregation in the reservoir and catheter site.

5. Controlled Delivery Systems

This technological approach relies on the use of polymeric membranes. Langer *et al.*[56,57] prepared ethylene-vinyl acetate copolymer discs (1.3cm diameter, 1mm thickness) containing 100mg of bovine pancreatic insulin and implanted subcutaneously in the lower abdomen of chemically induced (by injecting streptozotocin) diabetic rats. This polymer disc achieved euglycemia for up to one month as shown in Fig.3. This study also demonstrated that polyuria and glycouria were corrected and diabetic rats gained weight as the result of the presence of the implant. However, it should be pointed out that moment-to-moment regulation of blood glucose level cannot be achieved by sustained or zero order release of insulin since the plasma glucose levels are in dynamic state throughout a day. Thus the ability or restoring euglycemia throughout a day by this polymeric controlled release system is still questionable.

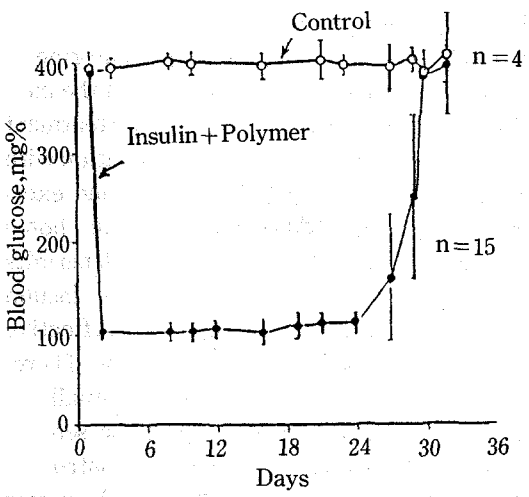

Figure 3—Implantation of single insulin containing polymers into diabetic rats. Control animals were diabetic rats receiving empty polymers or no polymers (Ref. 56).

Further improvements were made by same group[58,59] in order to solve the moment-to moment regulation by embedding small magnetic beads in the polymer matrix. These studies have demonstrated that exposure of diabetic rats with implant, containing both imbedded magnets and insulin, to an oscillating magnetic field resulted in increased insulin release and suggested the feasibility of delivering insulin at increased rats upon demand.

The other approach is to synthesize a glucose sensitive membrane which increases its permeability to insulin in the presence of glucose. Rather and his colleagues have pioneered a glucose sensitive membrane[60-63]. The glucose sensitive membrane of the type they[60,63] have developed could be employed to control insulin delivery from a reservoir containing a saturated insulin solution. The membranes consist of a hydrogel polymer (methacrylate derivatives) containing pendant amine groups and also contain entrapped glucose oxidase. As glucose diffuses into the gel, glucose oxidase catalyzes its conversion to gluconic acid and induces lowering the pH within the hydrogel microenvironment. This lowering pH induces the ionization of the pendant amine groups, thereby the electrostatic repulsion between ionized amine increases the degree of swelling and the diffusivity of insulin through the hydrogel membrane. After addition of 400 mg% glucose, the average permeabilty of insulin through macroporous HEMA/DMAEMA (hydroxyethyl methacrylate / dimethylaminoethyl methacrylate copolymer) gels containing immobilized glucose oxidase was 2.4 to 5.5 times higher than before glucose[63].

Another approach is the preparation of complex polymeric membranes which consist of two polymer membranes[64,65]. One membrane is a polyacrylamide containing glucose oxidase which acts as a sensor for glucose and produces H_2O_2 resulting from enzymatic reaction to glucose. The other membrane is a redox polymer containing a nicotinamide moiety which regulates the permeability of insulin by means of an

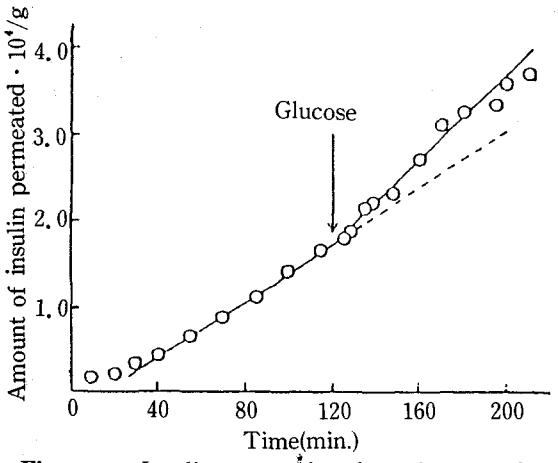

Figure 4 – Insulin permeation through a complex membrane composed of glucose oxidase immobilized membrane and 1, 4 - dihydronicotin amide -hydroxypropyl methacrylate copolymer membrane at 30℃ (Ref. 64).

oxidation reaction with the hydrogen peroxide. As shown in Fig.4, permeability of insulin increased in the presence of glucose[64]. It should be noted, however, that rapid reversal of permeability of insulin through glucose sensitive membrane is prerequisite in this system. If there is no reversibility in membranes, high permeation rate of insulin should induce hypoglycemia in diabetic patient. Unfortunately, to date this reversibility has not been proven.

6. Self-Regulating Insulin Delivery Systems.

In 1979, Brownlee *et al.*[66] reported that the release of a maltose-insulin conjugate, which is complementary to the major binding site of Concanavalin A (Con A), is proportional to the quantity of glucose present. This glucose regulation of exogenous insulin delivery has important applications in the treatment of hyperglycemia[66,67]. However, the intrinsically similar binding affinities of glucose and the maltose-insulin conjugate to Con A might result in the release of the maltose-insulin even in a hypoglycemic condition. Recently Kim and his colleagues[68-71] designed a self-regulating insulin delivery system which is based on a combination of biological feedback modulation and controlled release of a bioactive compound. The design of this system is predicated on the competitive and complementary binding behavior of Con A with the substrate, glucose and glycosylated insulin (G-insulin). The derivatized insulin (G-insulin) is bound to specific sites on Con A which are also complementary to glucose. This G-insulin is then displaced from the Con A by an excess concentration of glucose, thus providing G-insulin release is responsive to and proportional to the amount of glucose present (Fig.5). This is a form of affinity exchange chromatography and provides an inherent biofeedback control of glucose. Jeong *et al.*[70,72,74] semisynthesized seven G-insulins which exhibited bioactivity in rats by means of a blood sugar depression test and were more stable than native insulin in aggregation studies (CD and turbidity measurement)[73]. It was estimated that the binding affinities of *p* -aminophenyl- α -D-glucopyranoside and *p* -aminophenyl- α -D-mannopyranoside insulin conjugates to Con A were 80 and 400 times higher respectively than that of glucose[74]. For this reason, those G-insulins were chosen for

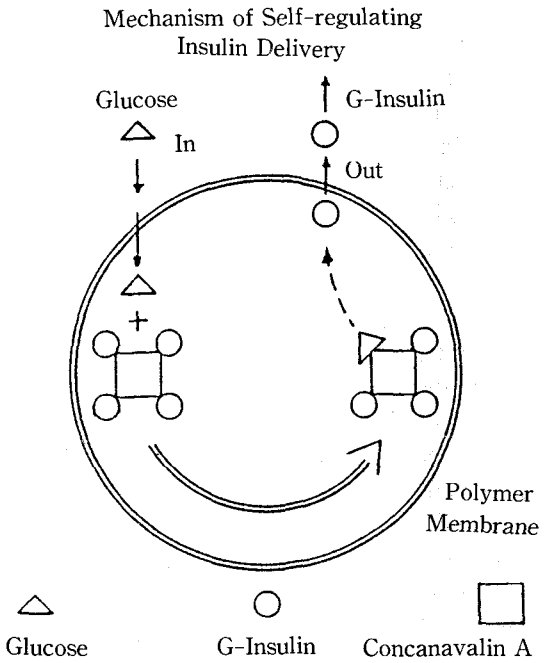

Figure 5 – Schematic diagram of self-regulating insulin delivery system (Ref. 74).

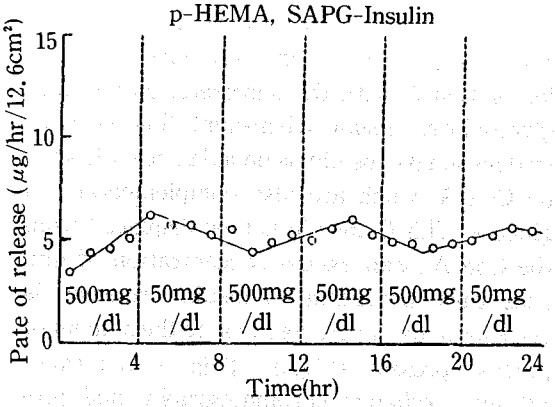

Figure 6—The response of succinylamidophenyl-α-D-glucopyranoside insulin conjugate to a step function glucose challenge through a porous poly-HEMA membrane (Ref. 73).

in vitro release studies in order to avoid G-insulin displacement in the presence of low concentration of glucose (a hypoglycemic condition). The results showed that under continuous glucose challenge, release of the G-insulin increased with increasing glucose challenge[73]. Under a step function glucose challenge through a porous p-HEMA hydrogel membrane, as shown in Fig.6, the response of G-insulin was in phase to the glucose challenge[73]. *In vivo* release study[75] using a regenerated cellulose membrane pouch containing G-insulin, implanted in peritoneum of pancreatectomized diabetic dog, has been performed. The results of the IVGTT (intravenous glucose tolerance test) on the pancreatectomized dogs, which were implanted with the G-inulin delivery system, exhibited no significant difference to the normal dogs, whereas the results of the glucose tolerance test before and after implantation in pancreatectomized dogs were significantly different (Fig. 7). Although this *in vivo* study[75] demonstrated a feasibility of self-regulating insulin delivery system for clinical use, further work will be required to address the issue of refinement, such as, achieving better insulinization both of peripheral and portal blood supplies, finding alternate polymeric membrane and design of better configuration of device.

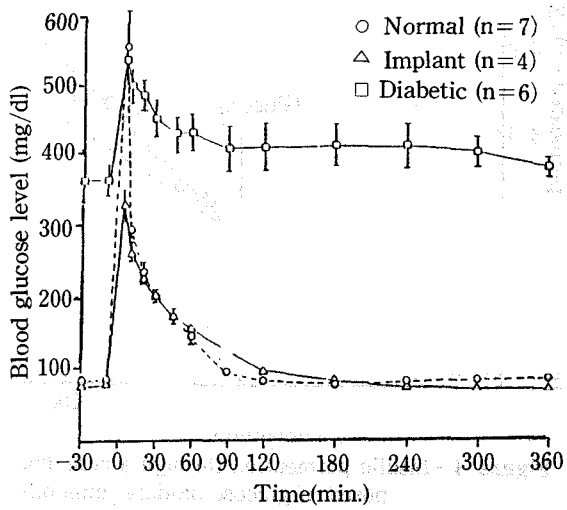

Figure 7—Peripheral blood glucose profiles of dogs administered bolus glucose (500 mg/kg) during an intravenous glucose tolerance test(TVGTT). Normal dogs had an intact pancreases, diabetic dogs had undergone a total pancreatectomy, and implant dogs had been intraperitoneally implanted with a cellulose pouch containing a Con A-G-insulin complex. Blood glucose levels at t=−30 min. show the overnight fasting level 30 min. prior to bolus injection of glucose (Ref. 75).

7. Conclusion

Treatment of IDDM or Type I diabetics by conventional daily insulin injection cannot provide tight control of glucose homeostasis. Since the blood glucose levels are highly dynamic state throughout a day (especially postprandial plasma glucose concentration) in diabetics, amounts of exogenous insulin supply should be responsive to and proportional to the blood glucose level in order to achieve a euglycemic condition. For this reason, insulin delivery systems eventually need some means of biofeedback system. Unfortunately, no imminent solution for the biofeedback is available. As discussed in the text, however, highly active research level and many approaches to improve the treatment of diabetics are currently underway. This is indicative of importance of insulin delivery systems.

Although there are much work that should be done on the insulin delivery systems, the future

for this research area to date looks promising. Eventually, many approaches for the insulin delivery system should aid the diabetic in his fight against diabetes mellitus.

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