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POTENTIAL DEVELOPMENTS IN SYSTEMIC DELIVERY OF INSULIN:

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I. Introduction

Diabetes mellitus is a disease which has been known to mankind for thousands of years. It was referred to as early as in 1500 B.C. by the famous Ebers Papyrus. It has been known for a long time that a sweet odor is present in the urine of diabetic patients. In fact, a primitive diagnostic test required the tasting of urine to determine the extent of sweetness (1). However, it was not until two hundred years ago that this sweet substance was finally identified as "glucose". The treatment for diabetic patients came much later after insulin was discovered in 1921 by Banting and Best.

With the discovery of insulin, it was expected that simple administration of insulin would be adequate to treat Type I diabetes. Unfortunately, it did not turn out to be that simple. The choice of delivery routes was fairly restricted as limited by the molecular dimension of insulin and its inherent instability, as a protein molecule. Also, the conventional methods of delivery could not simulate the precise and sophisticated feedback mechanism involved in the physiologic modulation of insulin delivery in the human body in response to the variation in blood glucose levels. Since then a tremendous amount of effort has been directed towards insulin delivery, including the recent efforts to develop self-regulating insulin delivery systems.

Each of the delivery methods and administration routes has its advantages and disadvantages and a specific route may be optimal for a given clinical application (2,3). The oral route is not a viable one since insulin is a protein molecule which is degraded easily in the gastro-intestinal tract. Parenteral routes achieve a direct entry into the systemic circulation and thus rapid onset of action, but have the drawback of a short duration of action in addition to subjecting the patients to constant pain and some psychological stress by needle insertion. The rectal route provides easy access, but it is socially undesirable. Also, most of these methods of delivery are not capable of regulating the delivery of insulin in response to the change in blood glucose levels. Additional complications are introduced by the circadian fluctuation in the basal blood glucose levels. All these factors make the systemic delivery of insulin a rather difficult and extremely challenging task. This review will discuss the various approaches that have been developed for achieving the systemic delivery of insulin and will also identify the future trends based on current research activity.

II. Physicochemical and Biomedical Considerations in Insulin Delivery

For a proper appreciation of the challenges one may encounter in achieving the systemic delivery of insulin, a brief overview of physicochemical, pharmacokinetic and physiological factors involved would be helpful.

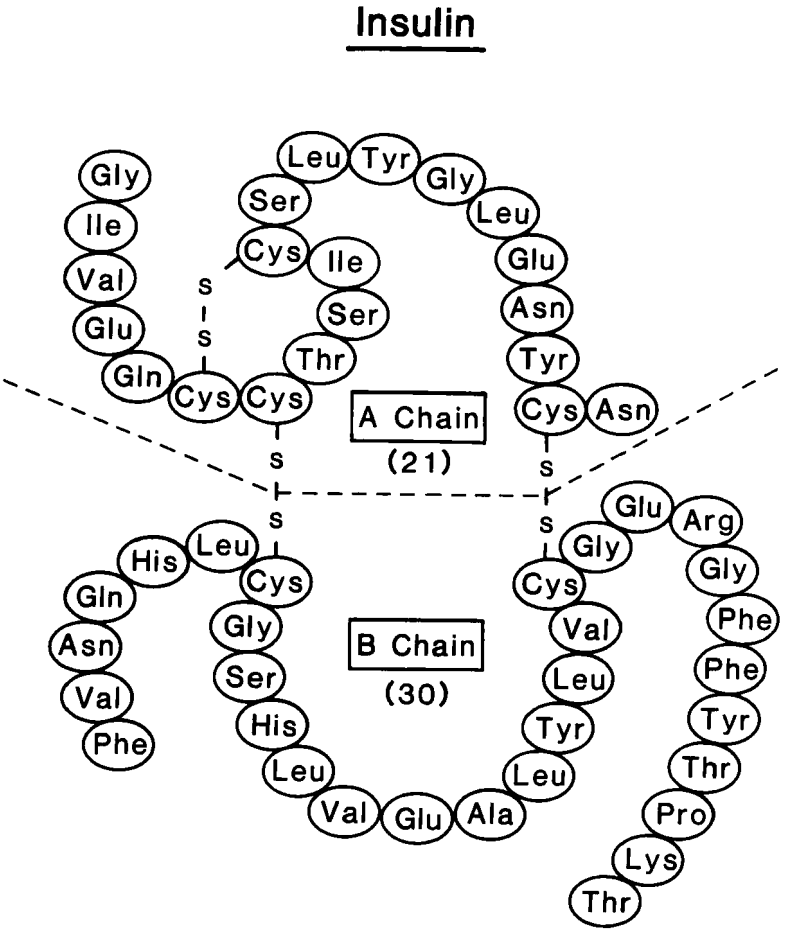

Figure 1 - Molecular structure of insulin, a protein hormone, and its amino acid sequence.

Insulin is a proteinaceous macromolecule composed of 51 amino acid residues with a molecular weight of 5,808 daltons. The beta cells of the pancreatic islets synthesize insulin from a single-chain precursor known as "proinsulin". Proinsulin contains a connecting peptide (or C-peptide) which joins the amino terminus of A chain and the carboxyl end of B chain. Upon conversion to insulin, the C-peptide is released. Insulin thus has two polypeptide chains - an A chain with 21 amino acids and a B chain with 30 amino acids. These chains are covalently connected together by two disulfide links (Figure 1). An extensive early review of the chemistry and biochemistry of

insulin was published by Klostermeyer and Humbel (4). The physicochemical stability of insulin formulations has been studied by several investigators (5-8). Unfortunately, chemical degradation of the insulin molecule is not necessarily reflected in its immunochemical or biological potency, e.g., degradation of insulin by deamidation and polymerization could not be detected by the immunochemical assay of the stored samples (5).

In addition to the needs to stabilize the molecule chemically, other potential problems in physical stability, such as self-aggregation or adsorption to container surfaces, must also be taken into consideration. Losses by adsorption can be particularly significant at low concentrations and can result in insufficient dosage for effective treatment (9). The self-aggregation of insulin molecules is a fundamental obstacle to the long-term application of many insulin infusion pumps. It has been studied by several investigators (10-15) and found to be minimized by the addition of substances, like urea (12), dicarboxylic amino acids, such as aspartic acid and glutamic acid (13), or other reagents, like glycerol (14), EDTA, lysine, Tris buffer or bicarbonate buffer (15). An extensive study of 60 additives and 1,125 formulations reported that nonionic surfactants such as Pluoronic F68 (Poloxamer 188), a polyoxyethylene-polyoxypropylene glycol surfactant, appear to be a promising stabilizer (11). Other conclusions drawn by the study were that human insulin aggregates more readily than pork or beef insulin; ionic ingredients and phenolic preservatives accelerate the aggregation of insulin, and zinc insulin is more stable than zinc-free insulin.

The pharmacodynamics of insulin can be related to the pharmacokinetic model by using a hypothetical "effect compartment" linked to the central compartment. Some earlier studies had followed the rate of disappearance of the hormone following a bolus injection and variable results were reported. However, Sherwin et al. (16) approached the problem by infusion not to a steady-state concentration, but to a steady-state blood glucose level. A three-compartment model was found adequate to fit all the data from diverse

experimental protocols. Compartment 3, which could not be sampled but in which the concentration of insulin could be calculated, was the compartment pertinent to glucose utilization. This compartment probably consisted of the interstitial fluid in the muscle and adipose tissues and was in slow equilibrium with insulin levels. Mathematical models for the pharmacokinetics and pharmacodynamics of insulin can be incorporated into computerized delivery systems for an open-loop infusion pump (17).

Basal insulin secretion in the healthy subjects also shows a circadian rhythm which must be taken into consideration in the design and operation of an insulin delivery system. It has been suggested that a larger dose of insulin is needed in the afternoon as well as at night. This may be achieved by delivering insulin via a pump which is programmable in time to mimic the physiologic circadian baseline of insulin (18). Another study (19) reached similar conclusions in both normal and diabetic rodents. Normal mice showed a circadian fluctuation in the basal blood glucose levels with a peak of 112 mg/dl at 2:30 pm. Greatest sensitivity to insulin also occurred at 2:30 pm, at which a 60% reduction in blood glucose level was observed. From 6:30 pm to 10:30 am, on the other hand, the insulin produced only a 38% decline in glucose level. Diabetic mice also showed a circadian variation with phases like that of normal mice, with basal glucose levels peaking at 438 mg/dl between 10:30 am and 2:30 pm (19).

The rate of insulin delivery from any delivery system must be characterized by a stability-indicating analytical procedure. HPLC has been suggested as being more precise in measurement of the potency than the rabbit assay (20) or the mouse blood glucose assay (21). HPLC was also found to be capable of differentiating the insulins from bovine, porcine and human, and to be both reproducible and stability indicating. For insulin and insulin injections subjected to accelerated stability tests, the HPLC method detects the decomposition that cannot be detected by either the mouse blood glucose assay or the immunochemical assay.

Insulin used in the therapeutics of diabetes mellitus may be of bovine, porcine or human origin. It is generally agreed that pork insulin is less antigenic than beef insulin, probably due to the closer chemical relationship between pork and human insulins than between beef and human insulins. Human insulin (Humulin® by Genentech-Eli Lilly) produced from E. Coli by genetic engineering (20) is the first therapeutic recombinant product approved by FDA for marketing in 1982 (22). Details of production and comparison with other insulins have been reported (20,23-25). In clinical uses, the therapeutic efficacy of Humulin® is similar to that of porcine insulin. However, the lower antigenicity of Humulin® relative to the purified porcine insulin could be of potential therapeutic value. Thus, Humulin® should be used in newly diagnosed diabetics, in patients treated intermittently with insulin, in patients with immunological insulin resistance, allergy or local reaction against animal insulin (26).

III. Systemic Delivery of Insulin

A. Approaches to Parenteral Controlled/Sustained Delivery

1. Long-acting Injectables:

Insulin can form water-soluble zinc insulin complex with zinc ion in a suitable buffer medium, which is in either crystalline or amorphous form. The crystallinity of the complex can be controlled by controlling the pH of the buffer medium (27). The zinc insulin complex has been used to formulate three long-acting insulin preparations with varying duration of normoglycemic activities: Ultralente®, Lente® and Semilente® insulin (Table I), which are still popularly used today for the treatment of diabetes.

These preparations differ with respect to their onset, duration and intensity of action following subcutaneous administration. The amorphous zinc insulin complex precipitated at pH 6-8 (semilente insulin) has a rapid onset (0.5-1.0 hour) and a moderately long duration of action (12-16 hours) as compared to regular insulin (8 hours). On the other hand, a cloudy suspension of crystalline zinc complex precipitated at pH 5-6 (ultralente insulin)

Table 1: Various Commercial Insulin Preparations and Duration of Normoglycemic Activity

Insulin Preparations	Normoglycemic Activity[1] Onset (hr)	Peak (hr)	Duration (hr)
Insulin injection, USP	0.5-1.0	2-3	6
Semilente insulin[2]	0.5-1.0	5-7	12-16
Lente insulin[2]	1.0-1.5	8-12	24
Ultralente insulin[2]	4-8	16-18	>36
Globin-Zn-insulin injection, USP	2	8-16	24
Isophane insulin suspension, USP	1-1.5	8-12	24
Protamine-Zn-insulin suspension, USP	4-8	14-20	36
Humulin® R[3]	Rapid	N/A	6-8
N[3]	Slower	N/A	24

[1]The time at which activity is evident.
[2]Developed by Novo Terapeutisk Laboratorium A/S.
[3]Codeveloped by Greentech and Eli Lilly.

Source: Compiled from Physicians' Desk Reference, 40th ed. (1986).

has a much delayed onset (4-8 hours) and also a rather long duration of action (36 hours). A mixture of crystalline (7 parts) and amorphous (3 parts) insulins (lente insulin) is intermediate in onset (1.0-1.5 hours) and intermediate duration of action (24 hours) (28,29).

Attempts have also been made to prolong the normoglycemic action of insulin by entrapping it in a liposome/collagen gel matrix for subcutaneous administration (30).

2. Novel Injectors:

A jet-type injector, which is a high-pressure device that propels a fluid through a very fine orifice, has been used for the parenteral administration of insulin. At high velocity, the fluid pierces the epidermis and spreads

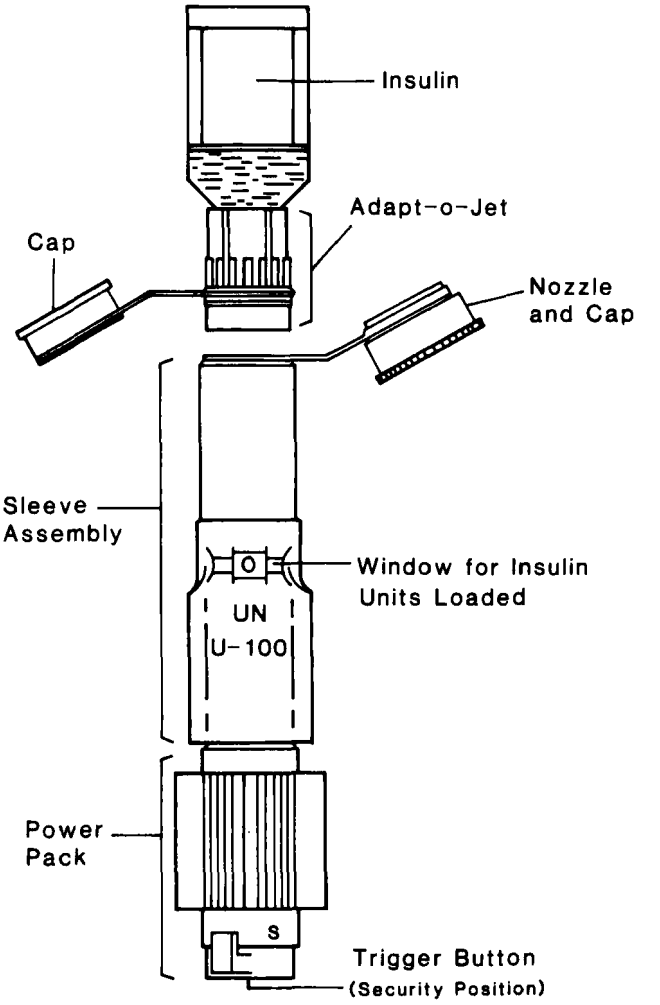

Figure 2 - Diagram showing the main components of Preci-Jet® 50 and Adapt-o-Jet (vial holder). For filling with insulin, nozzle is unscrewed and replaced with Adapt-o-Jet and insulin vial. Injector is filled by turning power rack counterclockwise until the number on small window indicates the number of insulin units required. Nozzle is then screwed back into position and pressure is generated by turning power pack clockwise until a click is heard. (Modified from Lindmayer et al., 1986)

the insulin solution into the subcutaneous tissues without the need to use a needle (31,32). A recently developed jet injector, called Preci-Jet-50® (Figure 2), has a compact design with the capability of mixing two types of insulin together during the time of delivery (33,34). A sprinkler-shaped needle for insulin injection has also been recently designed (35).

Another development has been the design of an insulin-injection pen, called Novopen®, which is a pocket-sized apparatus that resembles a fountain pen. When fitted with a disposable needle and unit-dose ampule of insulin, it becomes a portable, self-contained insulin syringe (36).

3. Infusion Pumps:

Even though continuous, subcutaneous delivery of insulin through infusion pumps, like Continuous Subcutaneous Insulin Infusion (CSII) devices, has been in practice for a long time (37-39), some concerns have been expressed on possible increase in mortality (40), morbidity due to mechanical failure (41), or lack of data on long-term safety of the treatment (42), which suggest that further long-term assessment of these devices is needed.

Recent advances in parenteral insulin administration include the development of computer-driven insulin infusion pumps, which monitor glucose concentrations in either a closed-loop or open-loop system (17). For example, intraperitoneal delivery of insulin through a steam-sterilizable micropump, called controlled release micropump (CRM), has been investigated in dogs by implantation (43,44). The CRM, which was used in conjunction with an open-loop control system, can deliver insulin at two levels: basal delivery for between meals and augmented delivery for short periods following the ingestion of meals. The rate of delivery can be adjusted to meet the insulin requirement of the respective meal. The concentration difference between the insulin reservoir in the CRM and the surrounding body fluid results in diffusion of insulin at the basal delivery rate with no application of external power source to the pump. Augmented delivery is achieved by repeated compression of the foam membrane by the coated mild steel piston. The piston is the core of the solenoid and compression is effected when current is applied to the solenoid cell (Figure 3). Development of a piezoelectric controlled micropump (P-CRM) has been recently reported (45).

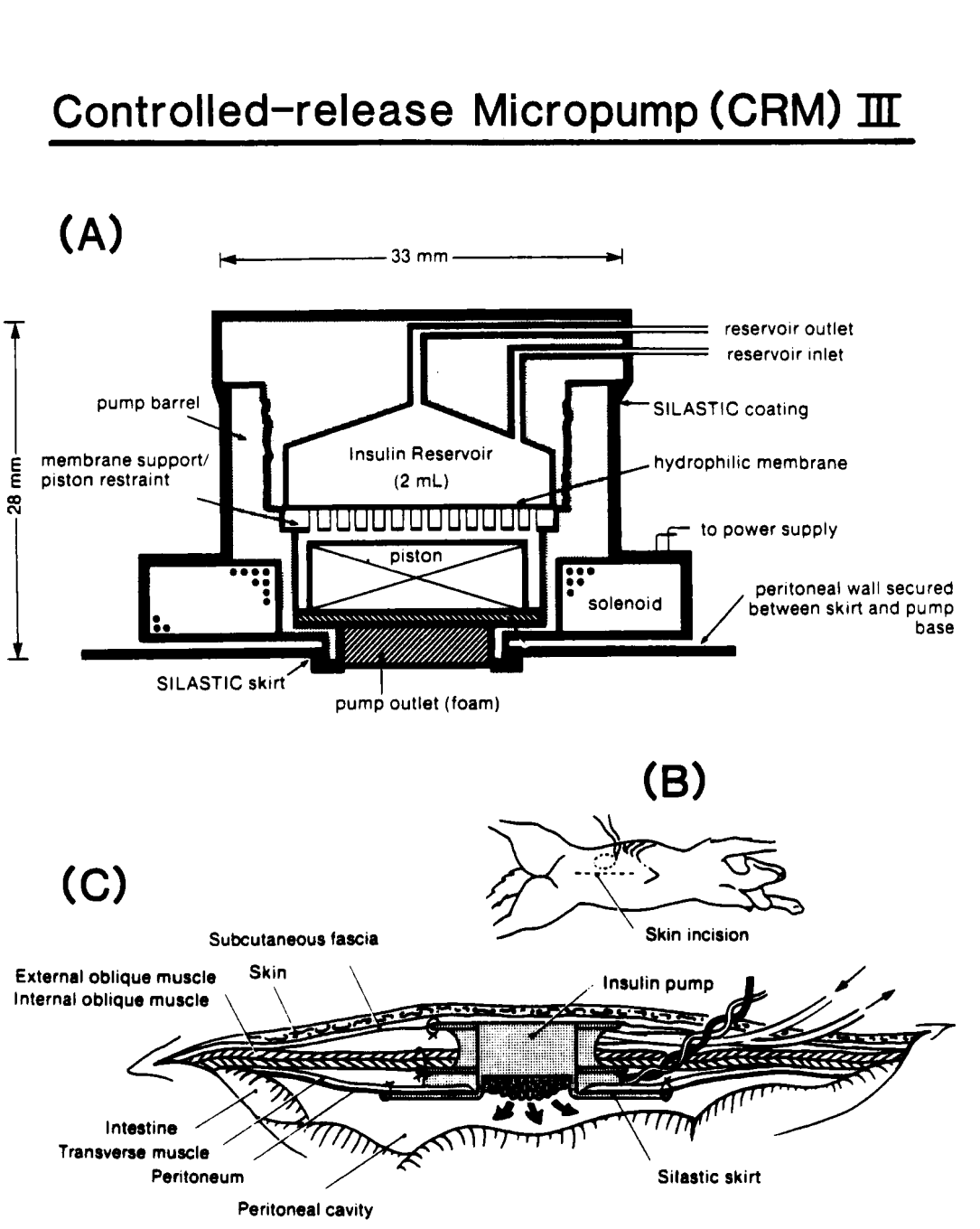

Figure 3 - Diagrammatic illustration of the controlled release micropump (A) and its intraperitoneal implantation in the pancreatectomized dogs. (Reproduced from Sefton et al., 1984)

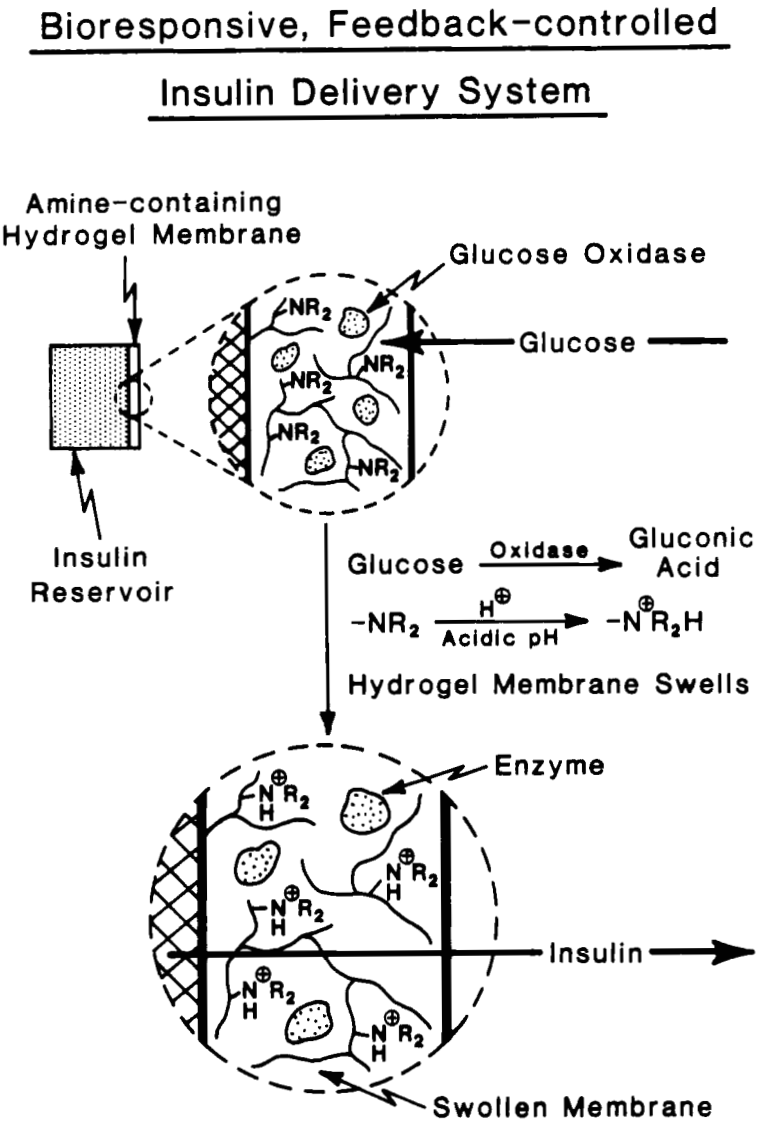

Figure 4 - Cross-sectional view of the bioresponsive insulin delivery system which applies glucose-sensitive hydrogel membrane to control the delivery of insulin in response to the influx of glucose. (Based on Horbett et al., 1983)

4. Self-Regulating Delivery Systems:

Several investigators have been actively trying to design an insulin delivery system which will have a physiological feedback mechanism so that insulin release can be self-regulating in response to changing blood glucose levels. Such a system would thus function as an "artificial" beta cell. Horbett et al. (46,47) used a glucose-sensitive membrane fabricated from a glucose oxidase-entrapped hydrogel polymer containing pendant amine groups (Figure 4). As glucose diffuses into the polymer, glucose oxidase catalyzes its conversion to gluconic acid, thereby lowering the microenvironment pH within the membrane. The reduced pH results in increased ionization of the pendant amine groups. The electrostatic repulsion between ionized amine groups increases the degree of swelling and thus increases the permeability of the hydrogel membrane to insulin contained in the reservoir. Ultimately, then, the membrane permeability to insulin is a function of glucose concentration outside the membrane and insulin delivery is accelerated by the increase in glucose level (48).

The enzymatic conversion of glucose to gluconic acid by glucose oxidase has also been utilized in the design of a closed-loop polymeric insulin delivery system. In the system, insulin was incorporated, in solid form, into EVAc matrix, so that the release of insulin was governed by its dissolution rate and diffusion rate. Feedback control was mediated by glucose oxidase immobilized to sepharose beads which were also incorporated along with insulin into the EVAc matrix. As glucose entered the matrix, gluconic acid was produced. The gluconic acid caused a fall in the microenvironment pH of the matrix, which triggered a rise in insulin solubility and, consequently, an increase in the release rate of insulin from the matrix (49).

Another potential method to achieve the self-regulating delivery of insulin is to use a biochemical approach based on the prinicple of competitive and complementary binding behavior of concanavalin (Con) A with glucose and glycosylated insulin (G-insulin) (50-54). As the glucose level increases,

the influx of glucose to the pouch increases, displacing G-insulin from Con A substrate. Increasingly displaced G-insulin in the pouch results in efflux of G-insulin to the body (Figure 5).

5. Colloidal Drug Delivery Systems:

Colloidal preparations can be administered by parenteral routes and may be useful as injectable sustained-release delivery system for insulin. Colloidal carrier system include liposomes, nanoparticles and pharmacosomes. The use of liposomes for insulin delivery will be discussed later under oral delivery (Section III-B-3). Pharmacosomes are colloidal dispersions of drugs covalently bound to lipids. A recent report (55) has described the coupling of insulin to a lipid (1,3-dipalmitoyl glyceride) through the aid of spacers on position 1 (of A-chain) and positions 1 and 29 (of B-chain). Thus, the polar hydrophilic macromolecule gets converted to a ambiphilic prodrug-type inactive insulin-ester which spontaneously forms minivesicles, called pharmacosomes, in aqueous medium. However, the hypoglycemic activity and drug delivery designs of this formulation are yet to be established.

B. Approaches to Non-invasive Systemic Delivery

The potential routes for non-invasive systemic delivery of insulin include the nasal, buccal, rectal, vaginal, transdermal, ocular, oral and pulmonary routes. A recent study (56) compared the insulin absorption from various non-parental routes of administration. By rectal delivery, insulin was found to be more efficacious than delivery through nasal, buccal and sublingual routes, when administered without an absorption-promoting adjuvant. However, the efficacy was low as compared to intramuscular administration. When sodium glycocholate, an absorption-promoting adjuvant, was co-administered, the efficacy of insulin delivered through various non-parenteral routes was enhanced with the rank order of: nasal > rectal > buccal > sublingual, whereas nasal and rectal insulin are roughly half as efficacious as intramuscular insulin. A discussion of the relative advantages and disadvantages of each

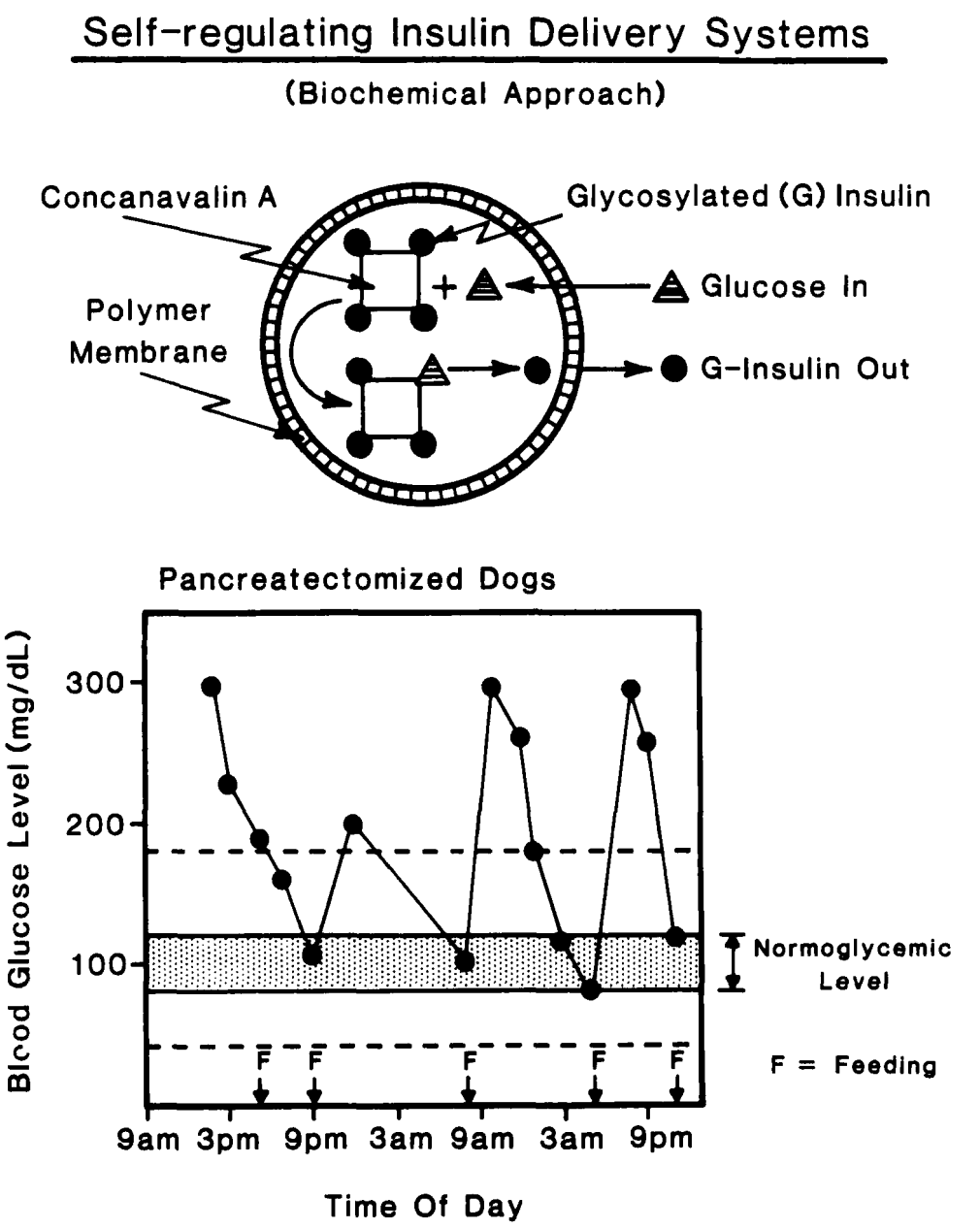

Figure 5 - Diagrammatic illustration of a self-regulating insulin delivery system which releases glycosylated insulin in response to the influx of glucose and the control of blood glucose level in the pancreatectomized dogs. (Based on Jeong et al., 1984).

of these non-parenteral routes can be found in a recent comprehensive review on the systemic delivery of therapeutic peptides and proteins (57). The potential of these routes for the delivery of insulin is discussed in the following sections.

1. Nasal Delivery:

Insulin has been extensively studied for feasibility of intranasal delivery (58-61). The potential application of nasal mucosa for systemic delivery of peptide/protein drugs, including insulin, and non-peptide drugs have been extensively reviewed (62,63). The hypoglycemic action of nasal insulin was found to be pH dependent. The transnasal permeability and nasal absorption of insulin were found to be enhanced by using permeation enhancers such as the bile salts (e.g., glyco- and deoxy-cholate) or other surfactants (Figure 6). By using these adjuvants, the therapeutically-effective plasma levels of insulin necessary for its normoglycemic effects have been achieved (64-66). Gordon et al. (67) reported 2.4 mM as the minimum concentration of sodium deoxycholate required to enhance the transnasal permeation of insulin. By varying the concentrations of sodium deoxycholate coadministered, they demonstrated that therapeutically useful amounts of insulin can be absorbed nasally in healthy human volunteers. The nasal absorption of insulin was found to correlate positively with the hydrophilicity of the bile salts with the rank order of: deoxycholate > chenodeoxycholate > cholate > ursodeoxycholate (67). Recently, Sodium taurodihydrofusidate, a novel detergent-like adjuvant, has also been demonstrated as an excellent enhancer for the systemic delivery of insulin by intranasal administration (68).

2. Buccal Delivery:

A mucosal adhesive delivery system was developed for the buccal delivery of insulin (69-72). It was found that insulin can not be effectively absorbed from a simple disk-shaped dosage form, prepared by direct compression of insulin in a mixture of hydroxypropylcellulose (HPC) and Carbomer (Carbopol 934) (CM). But, some buccal absorption was achieved by preparing a dome-shaped

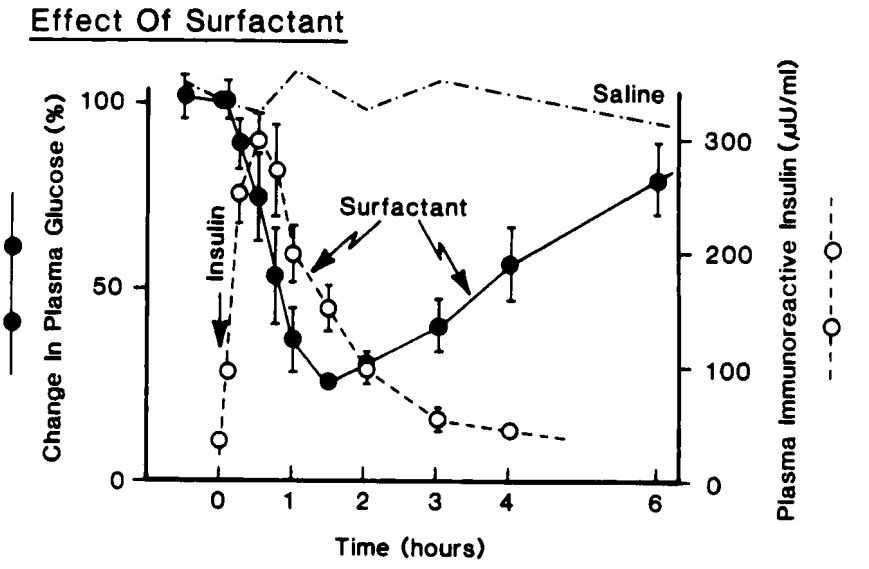

Figure 6 - Enhancing effect of surfactant on the nasal absorption of insulin and the reduction in plasma glucose levels in the dogs. (Based on Harai et al., 1978)

two-phased mucosal adhesive device (71), with an adhesive peripheral layer and an oleaginous core (Figure 7). The core was prepared by dispersing insulin and sodium glycocholate in a cocoa butter base, while the adhesive peripheral layer was made from a blend of HPC and CM. This mucosal adhesive device adhered tightly to the oral mucosa of the dogs in a gel-like swollen state, and its shape was maintained for longer than 6 hours. The systemic bioavailability of insulin, in comparison with intramuscular administration, was found to be only 0.5%. The systemic bioavailability was improved by the use of permeation enhancers, e.g., sodium glycocholate. Even though the total bioavailability was still very low, the effective plasma concentration of insulin was achieved and the blood glucose level was substantially reduced (Figure 8). Because of anatomical and physiological differences among various oral mucosal tissues, the location for buccal delivery should be carefully selected. A methodology to compare permeabilities of different oral mucosal sites has been recently reported (73).

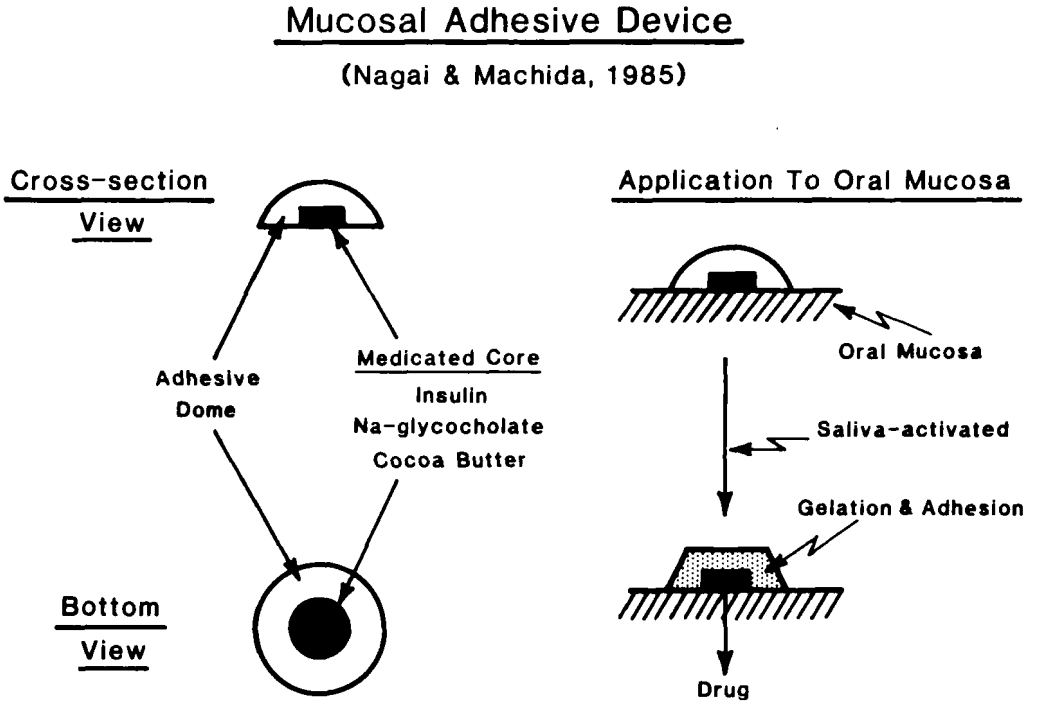

Figure 7 - Diagrammatic illustration of the dome-shaped mucosal adhesive device and its application to oral mucosa. (Based on Nagai & Machida, 1985)

3. Oral Delivery:

For an orally administered peptide to reach its site of action, it must be able to resist any chemical and enzymatic degradation in the gut lumen, and then, after penetration of the mucosal membrane, to escape the "first pass" metabolism and clearance by the gut mucosa and liver (74). Only a very small fraction of oral insulin dose becomes available for absorption through the gastrointestinal membrane (75,76). The absorption of insulin from the intestine was shown to be feasible if it is injected directly into the ascending colon with sodium deoxycholate (77). A 50% reduction in blood glucose levels could be obtained by this approach. On the other hand, a similar injection into the ileum did not result in any lowering of the blood glucose levels unless insulin is injected with a trypsin inhibitor; this effect is due to the rapid digestion of insulin by the proteolytic enzymes present in

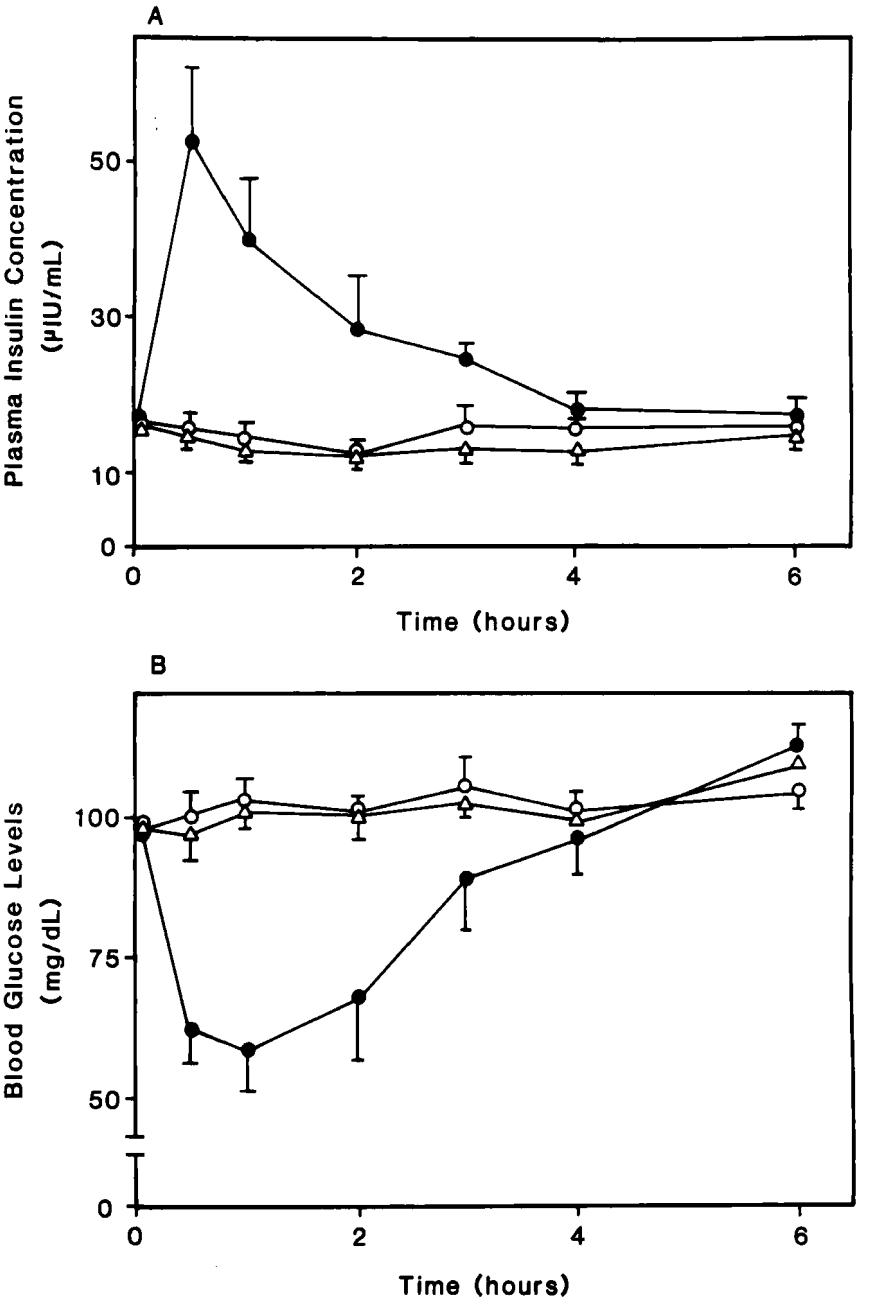

Figure 8 - Time course for the increase in the plasma insulin levels (A) and the reduction in blood glucose levels (B) in beagle dogs following the buccal administration of insulin from the mucosal adhesive device shown in Figure 7. (O) control (△) insulin (10 mg); (●) insulin (10 mg) + sodium glycolate . (Replotted from Nagai and Mahida, 1985)

the ileum. Another recent study (78) also reported that bile salts can promote insulin absorption from the large and small intestines.

One approach to circumvent the digestion of insulin in the gastro-intestinal tract is to protect insulin by coating with a polymer film which is not susceptible to the action of digestive enzymes. If this coating can be made to degrade only in the colon, then insulin will be released in a region of the intestine devoid of digestive enzymes. Such an approach was utilized by Saffran et al (79) who used polymer cross-linked with azoaromatic groups, which protected insulin from digestion in the stomach. When the azopolymer-coated insulin reached the large intestine, the microflora reduced the azo bonds, broke the crosslinks and degraded the polymer film, thereby releasing insulin into the lumen of the colon for absorption. The ability of the azopolymer coating to protect and deliver orally-administered insulin was demonstrated in rats.

The feasibility of using liposomes as a potential delivery system for the oral delivery of insulin has been extensively studied (80-83). Arrieta-Molero et al (84) suggested that oral administration of insulin entrapped in liposomes is effective in reducing the blood glucose level of diabetic animals; however, the stability and effectiveness of insulin-containing liposomes have been found to be rather unpredictable. Dobre et al (85) demonstrated a lowering of blood glucose levels in normal rats following the oral administration of insulin entrapped in phosphatidylcholine-cholesterol liposomes. However, negative results have also been reported (86,87). So, the feasibility of oral delivery of insulin by liposomal entrapment needs further work and standardization of liposome composition and stability.

Another approach for targeted enteral delivery of insulin was recently reported (88). It was developed by encapsulating insulin in a small soft gelatin capsule coated with polyacrylic polymer (Eudragit®) having pH-dependent properties. Nanocapsules of isobutyl cyanoacrylate have also been used to

encapsulate insulin (89). These biodegradable polymeric nanocapsules have been used as the oral delivery system for insulin to enhance its therapeutic efficacy. They were found to normalize hyperglycemia in diabetic rats when administered intragastrically.

Shichiri et al (90) used a water/oil/water-type multiple emulsion to deliver insulin orally to rabbits and diabetic rats via an indwelling catheter in the jejunum and observed a reduction in the urinary glucose level in the diabetic rats. It has also been suggested that oral absorption of insulin may be enhanced by simultaneous administration of an inhibitor for proteolytic enzyme with insulin.

4. Rectal Delivery:

Extensive studies have been conducted on the rectal absorption of insulin (91-97) and on the feasibility of enhancing the rectal permeability of insulin by using adjuvants (98-112). The rectal absorption of insulin delivered by a microenema was reported to be significantly promoted after coadministration of sodium 5-methoxysalicylate (SMS) (103), whereas sodium salicylate was found to be less effective as an absorption enhancer. Addition of 4% gelatin was observed to have a synergistic effect on the enhancement of rectal absorption of insulin by SMS (Figure 9). A systemic bioavailability of approximately 25% (compared to i.m. administration) was achieved. The adjuvant absorption promoting effect of SMS on the rectal delivery of insulin was recently compared with sodium 3,5-diiodosalicylate (SDS), a highly lipophilic salicylate, in rats (104). The results indicated that SMS produces a classical, sigmoidal log-dose response curve with maximal hypoglycemic effect achieved at molar concentration greater than 0.25 M, whereas SDS yields a bell-shaped log-dose response curve with equivalent, peak hypoglycemic effect attained at a lower molar concentration (0.05 M). The greater adjuvant absorption promoter efficacy of SDS could be attributed to its higher lipophilicity as demonstrated earlier by levitan and Barker (105).

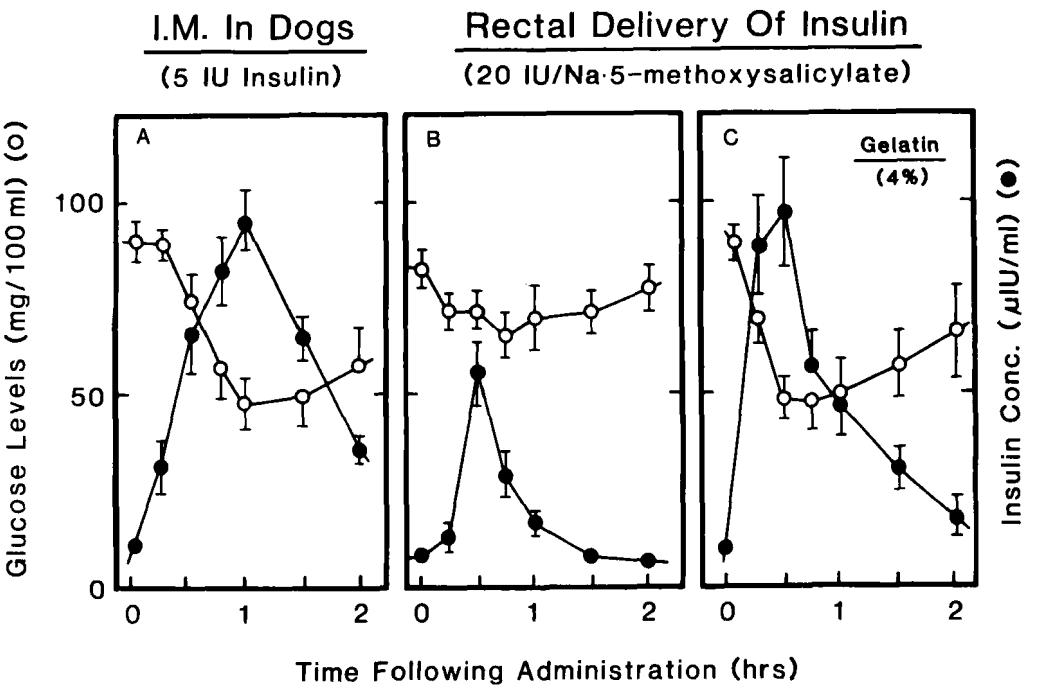

Figure 9 - Time course for the increase in plasma insulin levels (●) and the reduction in blood glucose levels (O) in dogs following intramuscular administration of insulin (5 IU; A) or rectal delivery of insulin (20 IU) via a microenema containing 150 mg of sodium 5-methoysalicylate (B) plus 4% gelatin (C). (Replotted from Nishihata et al., 1983)

Phenylglycine enamines of various diketones, e.g., ethylacetoacetate, have also been observed to be effective in promoting the rectal absorption of insulin (101,108). Touitou et al. (98) achieved hypoglycemia in the rats by administering insulin, via rectal (and vaginal) routes, in a dosage form containing polyethylene glycols and a surface-active agent. The influence of different suppository bases on the systemic bioavailability of insulin was also reported (113). Recently, it has been reported that a solid dispersion of insulin with sodium salicylate or mannitol can produce a rapid release of insulin from suppositories. Even at doses as low as 0.5 IU/Kg, a significant decrease in plasma glucose concentration was observed in dogs. The addition of lecithin to the suppository base has reportedly prolonged the effect of salicylate, as an adjuvant, due to its effect on the prolonged

release of sodium salicylate (97). Bile salts, sodium deoxycholate or sodium cholate have also been shown to enhance the rectal delivery of insulin in rats (114) and human volunteers (115).

5. Transdermal Delivery:

Transdermal delivery of insulin under passive conditions is unlikely to be successful, largely because of the large molecular size and hydrophilicity of the insulin molecule and also because of the lipophilic nature of the stratum corneum. The use of enhancers may hold some promise. However, these barriers to transdermal delivery of insulin can be surmounted by the technique of iontophoresis, which delivers ionic drugs into the body by the use of a physiologically-acceptable electric current. Iontophoretic transdermal delivery has been the subject of several recent investigations (116).

The underlying principles and the intricacies of iontophoretic drug delivery have been reviewed (116). Studies have been initiated to investigate the iontophoretic delivery of insulin (117-123) and encouraging results have been obtained. The in-vitro permeation profiles of insulin across the freshly excised hairless rat skin was substantially facilitated by iontophoresis treatment (Figure 10). In-vivo iontophoretic delivery of insulin in diabetic hairless rats and diabetic rabbits also provides the pharmacokinetic and pharmacodynamic data to demonstrate the feasibility of transdermal iontophoretic delivery of insulin (Figure 11) and its potential advantages (123-128). Recently, transdermal delivery of insulin by electroosmosis has also been reported (129). The rate of transdermal iontophoretic delivery of insulin was found to be dependent upon the physicochemical properties of the formulation, e.g., pH, ionic strength and electrolyte concentration, and the electronic variables of the iontophoretic delivery systems, e.g., current intensity, waveform, frequency, on/off ratio and treatment duration (123).

6. Pulmonary Delivery:

Absorption of insulin from the respiratory mucosa has been reported (130). An aerosol-type dosage form for insulin delivery by inhalation was

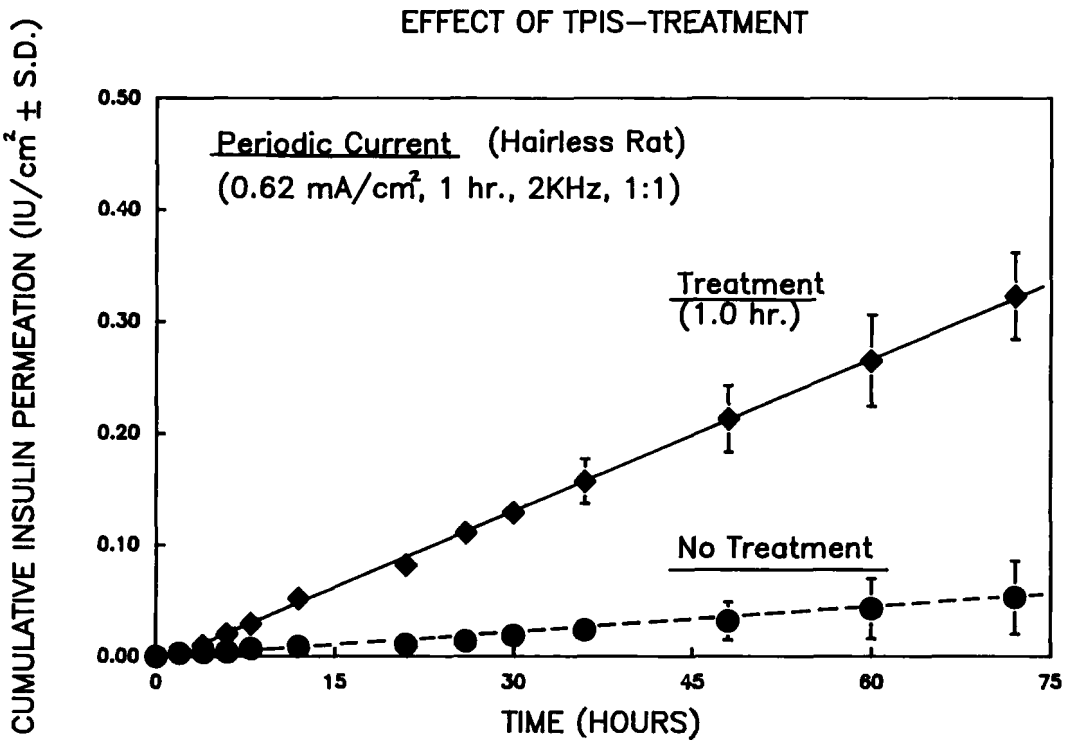

Figure 10 - The in-vitro permeation profile of insulin across hairless rat skin and the enhancement by treatment with a periodic current, delivered by transdermal iontotherapeutic system (TPIS) for one hour. (From Banga and Chien, unpublished data)

developed by suspending zinc insulin crystals in a propellant system with the aid of a dispersant like oleyl alcohol (131). No chemical incompatibilities between zinc insulin and oleyl alcohol or the propellant system were reported.

IV. A View to the Future

It is evident from the discussion so far that virtually every conceivable appraoch has been evaluated for the delivery of insulin. Several of these attempts were started and have either ended or are continuing as laboratory research, with no products reaching the market. Enthusiasm among researchers, however, has not abated as reflected by the number of recent publications

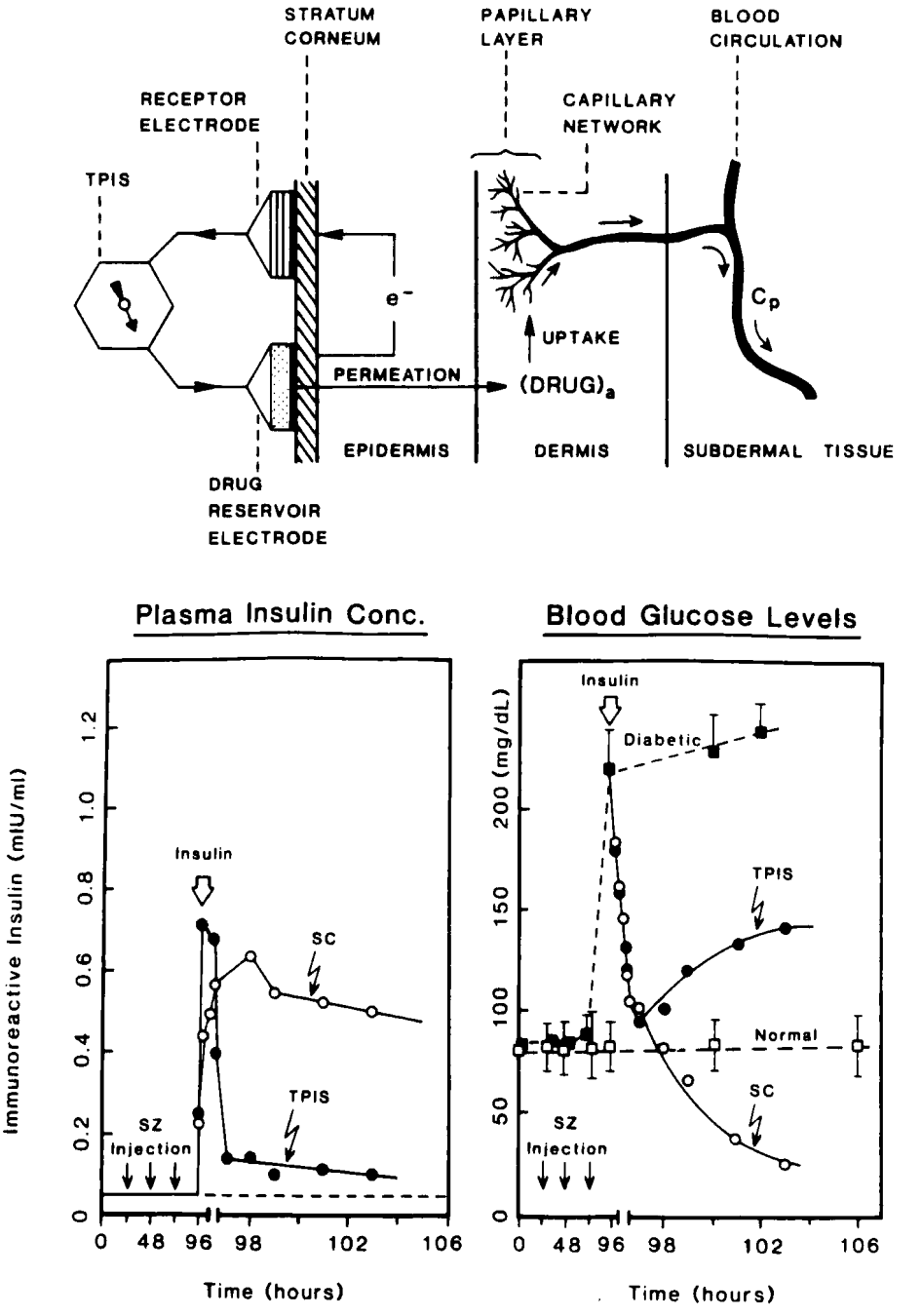

Figure 11 - Diagrammatic illustration of the TPIS-facilitated transdermal delivery of insulin and the resultant plasma insulin and blood glucose profiles in comparison with the conventional subcutaneous administration. (Reproduced from Chien et al., 1987)

in this area. The driving force for this enthusiasm includes the commercial aspect also. Even without any breakthroughs, the total U.S. market for diabetes products at the manufacturers' level is expected to grow from $961 million in 1985 to $1.37 billion by 1990.

One aspect of insulin delivery which has been ignored in most studies is the important role played by the physiologic rhythm of insulin secretion in the body. Glucose level in the blood circulation also has circadian oscillations and any insulin delivery system must take these fluctuations into account. The question of appropriate clock hour timings for insulin administration to insulin-dependent diabetics was raised almost 50 years ago but was not given due attention. This was probably because of a lack of appropriate methodology in both data gathering and analysis, leading to a poor chronophysiologic background of the insulin-mediated blood glucose control (132). A pump programmable in time which can mimic the physiological circadian baseline of insulin has been reported recently (19) as mentioned earlier.

Among the nonparenteral routes of administration, nasal delivery appears to be promising for non-invasive delivery of insulin. Therapeutically useful amounts of insulin can be delivered through the human nasal mucosa when administered as a nasal spray with bile salts as absorption enhancers. Clinical trials have demonstrated that insulin is absorbed readily into the systemic circulation when delivered intranasally in formulations containing the absorption enhancer, sodium taurodihydrofusidate (133). California Biotechnology, Inc., in conjunction with Eli Lilly Co. has begun clinical development of a metered-dose nasal spray for insulin delivery using this enhancer.

Although extensive research has been done and encouraging results have been obtained on the rectal delivery of insulin, this route is unlikely to become popular due to the social stigma attached to rectal delivery. Ocular delivery is also unlikely to be popular because ocular tissues are extremely sensitive and patient acceptance is low. Also, the systemic bioavailability

by this route is very low. Transdermal delivery by itself is unlikely to achieve systemic delivery of insulin, but a number of researchers have been successful in applying iontophoresis to enhance transdermal delivery of insulin. Although several encouraging results have been obtained (123), it is a little premature to predict the outcome at this stage. A lot will depend on the acceptance of iontophoresis as a skin permeability enhancement technique.

Among the parenteral insulin delivery systems, the most promising ones are the systems based on the concept of self-regulating delivery. A feedback system which releases insulin in response to blood glucose levels is the ultimate goal of insulin delivery. In addition to the systems that have already been discussed, an enzyme-responsive transdermal delivery system, which is still in the concept stage, has also been envisioned for insulin delivery (134). An insulin reservoir device which is attached to the skin would generate a minute pulse of electricity to open temporarily the skin pores. While the skin pores are open, the device would take a sample of the blood and process it via a glucose-oxidizing enzyme, by which the device would monitor physiologic indicators and adjust the release of insulin accordingly. A second brief electrical pulse would open the skin pores again to allow the insulin to enter the body.

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