chapter four

*Implants in drug delivery**

Contents

I. Introduction

Although most current controlled drug delivery systems are designed for transdermal, subcutaneous, or intramuscular uses, others (e.g., implants) can also deliver drugs into the bloodstream. This approach to drug delivery has become quite appealing for a number of classes of drugs, particularly those that cannot be given via the oral route.[1] Implantable drug delivery

* Adapted from Ranade, V.V., Drug delivery systems. 4. Implants in drug delivery, *J. Clin. Pharmacol.*, 30, 871, 1990. With permission of *J. Clin. Pharmacol.* and J.B. Lippincott Publishing Company, Philadelphia, PA.

systems are designed to transmit drugs and fluids into the bloodstream without the repeated insertion of needles. These systems are particularly well suited to the drug delivery requirements of insulin, steroids, chemotherapeutics, antibiotics, analgesics, total parenteral nutrition, and heparin.

Implantable drug delivery systems are placed completely under the skin — usually in a convenient but inconspicuous location. The patient is aware of only a small bump under the skin. Because the device is completely subcutaneous, with no opening in the skin, there is little chance of infection or interference with daily activities. Some of the critical questions for ongoing research on implants have been concerned with the reproducibility of erodibility, irritation/carcinogenicity, dose dumping, duration, and pulses.

While it is possible to surgically implant and remove drug-concentrating devices or polymeric matrices, the requirement for such intervention could have a significant negative impact on the acceptability of a product candidate. Two approaches to this problem seem possible. The first is the use of implanted electrically driven pumps which can be refilled by simple injection of the drug through a septum into the pump reservoir. An advantage of such pumps is that the pumping rate can be regulated by microprocessor control (it can be reliably programmed and altered via radio signals). The major disadvantages are the large size of the devices and the need for surgical implantation with the possibility of infection. The second approach is the use of erodible implants. Here, the requirements are for a system that will be safe and whose erosion rate can be sufficiently well controlled to give a reproducible and precise drug-release rate over the entire lifetime of the implant.

The desire to build into polymers precise zero-order surface erosion, without alteration of the structural integrity of the inner structures, has been difficult to achieve. Thus, although surface erosion can account for a significant portion of the release process, diffusion of the drug out of the device or solvent into the polymer ultimately contributes to the drug-release process and causes unpredictable changes in release rate, some of which may not be desirable. The future use of polymeric systems as implants requires greater input from polymer chemistry and related fields.[2]

Polymers that are used in medicine can be divided into two groups: those that are introduced for a chronic period of time and polymers whose presence is transient. The first case includes the use of polymeric materials in cardiovascular surgery, orthopedics, plastic surgery, and otolaryngology. Such applications impose high demands on the stability of the materials used. An implant must retain the properties necessary for its functioning throughout its lifetime, and the structure is chosen so that degradative changes are minimal.

To be able to fully assess the biological properties of polymers, it is necessary to know their chemical composition, ingredients, and fabrication methodologies. All too often, it is the additives or fabrication parameters that influence the behavior of material in contact with blood. Blood-contacting applications pose severe requirements on materials. While clotting and

thrombosis are the most obvious evidences of blood incompatibility, they are only the end products of a complex series of events when materials come in contact with blood.

Most, if not all, synthetic materials adversely affect plasma proteins, enzymes, and clotting factors, as well as formed blood elements, namely platelets, erythrocytes, and leukocytes. To what extent these processes can cause serious problems in the body will be influenced by the relative surface area to which blood is exposed, the duration of implantation, and the individual physiological and biochemical responses elicited by the implant. Prolonged periods of implantation may conceivably lead to carcinogenesis induced by chemical or physical mechanisms. Materials in contact with blood should not cause thrombus formation, either on the surface of foreign materials or embolization elsewhere in the circulatory system, or at distant organ sites as the result of endothelial damage and platelet injury.

In addition to not producing thrombosis, there are a number of other requirements that polymeric implants must meet for clinical applications. First, they must not cause injury or sensitization to any of the formed blood elements leading to hemolysis and aggregation of leukocytes in the microvasculature. Second, they must neither alter plasma proteins to any considerable extent, nor cause adverse responses by the activation of either the classical or alternate pathways of the complement system. In addition, they must not cause cancer. Finally, polymeric implants must be sterilizable without degradation or changes in their surface properties.

Implantable polymeric miniature pumps have made contributions to numerous areas of biomedical research, in particular, to drug delivery systems. The examples that will be reviewed in this chapter deal with the process of drug scheduling, toxicology, targeted delivery, and patterned administration.

II. Insulin delivery as a model implant pump system

Conventional controlled-release formulations are designed to deliver drugs at a predetermined, preferably constant, rate. Only under special circumstances are these formulations modified to provide variable-rate delivery. Some clinical situations, however, necessitate either external control of the drug delivery rate or a volume of drug that is beyond the capabilities of existing controlled-release formulations. Implantable drug delivery pumps have been devised to meet these situations.

A pump can be distinguished from other controlled-release dosage forms in that the primary driving force for delivery by a pump is not the concentration difference of the drug between the formulation and the surrounding tissue, but, rather, a pressure difference. This pressure difference can be generated by pressurizing a drug reservoir, by osmotic action, or by direct mechanical actuation.

The primary impetus for the development of such pumps has been the experience of electromechanical devices for the control of hyperglycemia in

insulin-dependent diabetes — the "artificial pancreas." The limitations of the miniaturized syringe or peristaltic pumps that are currently used to deliver insulin to diabetics in clinical trials are becoming apparent, which is generating an interest in implantable devices. While some implantable pumps have been used for other applications, it is the difficulty of delivering insulin that has received the most attention and has underscored the problems and limitations of such devices.

Sefton[3] has summarized the characteristics for the ideal pump. The pump must deliver a drug within a range of prescribed rates for extended periods of time. It should include features such as reliability; chemical, physical, and biological stability; and be compatible with drugs. The pump must be noninflammatory, nonantigenic, noncarcinogenic, nonthrombogenic, and have overdose protection. The pump must be convenient to use by both the patient and the health professional, have long reservoir and battery life, easy programmability, and be implantable under local anesthesia. There must also be a simple means to monitor the status and performance of the pump, and both the interior and exterior of the pump must be sterilizable.[4,5]

Implantable pumps are expected to reliably deliver a drug at a prescribed rate for extended periods of time. The delivery-rate range of the pump must be sufficiently wide to provide both basal and enhanced delivery of the drug as dictated by the clinical situation. Alternately, there must be a capability for providing bolus injection of a drug in addition to basal delivery. A wide range of delivery rates is also needed to meet the expected patient-to-patient variability in demand for a drug and the individual patient's changes in drug need during the course of therapy.

Accuracy and precision of delivery must be maintained over extended periods of time. To justify the surgery associated with the implantation of a pump, this period must be at least 2 years or, preferably, 5 years. This implies a reliability for both the pump and (implanted) electrical components since neither is easily replaceable. Sufficient biological, physical, and chemical stability of the drug within the pump are also required.

The goal of an implantable pump is to improve existing therapeutic methods of drug delivery and not be a lifesaving measure. However, the device also must be safe. In addition to the normal concerns of an implant, the implantation of a large quantity of a drug poses the additional danger of "dose dumping." While in some situations, delivery of less than the required amount of a drug on the prescribed schedule can be considered dangerous, this can be corrected for by reverting to conventional therapy. Overdoses, however, are not as easily correctible. An insulin overdose, for example, could result in severe hypoglycemia, coma, and death if not corrected with a rapid administration of glucose.

An overdose can occur in a number of ways when drug delivery is by an implantable pump. For example, the life of a peristaltic pump is typically limited by the life of the tubing, which is repeatedly compressed. Splitting of the tube can result in contamination of nonhermatically sealed electrical components, electrical failure of the pump, and a drug overdose if there is a

leak in the pump housing. This restriction is particularly severe in implantable pumps since it is not possible to change the tubing routinely, as in the case of portable devices. Mechanical trauma may pierce the reservoir, also resulting in drug overdose if the pump is not sufficiently well protected. Mechanical failure of a pump, particularly one that uses valves to regulate an otherwise high delivery rate, can result in delivery at a higher than desirable rate. Thus, mechanical failure is an important consideration because it not only affects the performance of the pump, but also is a safety concern.

The presence of a finite reservoir life, a finite battery life, patient-to-patient variability in drug demand, or long-term changes in an individual patient's drug demand require that the implantable device be convenient to use. This is in addition to any requirement for a simple means to adjust the delivery rate in accordance with the physiological effects of the drug.

The reservoir of an implantable pump should be as large as possible. The total volume of a pump that can be implanted at a single site is limited to approximately 200 to 300 $cm,^3$ of which a maximum of 50 cm^3 can be set aside for the drug reservoir. Reservoir life is determined by the drug requirement and the maximum concentration of the drug that can be used, as dictated by the constraints of viscosity, drug stability, or availability. In the event that reservoir life is less than 2 to 5 years, then a simple means to refill the reservoir is required.[6,7]

Battery life should also be more than the 2- to 5-year pump life. This means that pump energy requirements should be within the range of the available battery systems. Alternatively, rechargeable batteries or a transcutaneous energy-transmission system can be used to supply the required power. These alternatives must obviously be designed with the safety and convenience of the user in mind.

The pump must also be easily programmable. Simple methods are required for initial programming of the pump in order to meet the delivery needs of the individual patient and for choosing among various delivery profiles during the course of therapy. Also, initial programming should allow for adjusting the delivery profiles to the changing needs of the patient.

The location for the pump can be the anterior subcutaneous tissue of the chest or abdomen, depending on the route of administration, since these sites are well protected and the implant is well concealed under the clothing. The abdomen is the preferred site for i.p. delivery since placement of the delivery catheter requires only limited dissection.[8]

Implicit in meeting the stated criteria is a need for a means of continuous monitoring of the current status and performance of the implanted device. Parameters may include current delivery rate, accumulated drug delivered, and amount of drug remaining in the reservoir. Warning indicators need to be developed in the event of too low or too high a delivery rate, low battery power, low reservoir content, or any mechanical or electrical failure.[9,10]

The difficulty of sterilizing complex electromechanical devices should not be overlooked. Since the patient could ultimately be exposed to microorganisms inside the pump, conventional sterilization methods may be inad-

equate if only the outside of the device is sterilized. Furthermore, the effect of sterilization on the materials used within the pump should be considered since the associated changes in these materials may be serious.[11,12]

Implantation of a pump introduces design constraints that are not present in corresponding portable devices. Refilling or replacing the reservoir and recharging the battery are matters of convenience in a portable device, while reservoir and battery life assume more importance in an implanted device, which has restricted access. A drug reservoir should be able to deliver a reasonably large volume of drug if implanted. However, now the potential of leakage of the drug becomes a significant safety concern that is not present in a portable device. Similarly, the design of the transcutaneous energy-transmission system to drive the pump or to recharge the implanted batteries is a necessity for smaller size and biocompatible materials.[13,14]

Although pumps based on a conventional peristaltic mechanism have been implanted in humans, many implantable pumps based on unusual or unconventional driving mechanisms have also been described. These include fluorocarbon propellant, osmotic pressure, piezoelectric disk benders, or the combination of a concentration gradient with an oscillating piston.

A. Peristaltic pumps

Sandia National Laboratories has developed[15] a rotary, solenoid-driven peristaltic pump, which has been implanted in diabetics. It is based on the principle of a portable pump. Each electrical pulse to the motor produces 10 rotations of the pump head, with delivery of 2.1 μl against a pressure head of up to 30 psi. While not as efficient as DC motors, rotary or stepper motors cease operation as soon as the power is removed, thus making them capable of more accurate delivery in stop-and-start situations. They are also safer since no drug can be delivered in a case of electrical malfunction.[16]

Although originally housed in a 0.7-mm-thick, type-304, stainless-steel casing, a laser-welded titanium chamber is currently used to house the pump, electronics, and battery in order to provide a hermatic seal. The housing is further coated with silastic for enhanced biocompatibility. Internal components are either nickel-plated or made from corrosion-resistant materials. Flat silicone rubber pouches are used as reservoirs. The 0.5-mm-thick walls can withstand more than 60 psi without rupture. These reservoirs are percutaneously refilled through a silicone rubber septum in a refill port made from 2-mm-thick polypropylene. Polypropylene prevents the needle from puncturing the wall of the reservoir. Silicone rubber tubing is used to connect the reservoir to the pump, and a silicone rubber Codman Hydrocephalus shunt is used as the catheter for i.p. delivery of insulin, for example. The wall of this catheter is reinforced with a stainless-steel helix to prevent kinking and has a low-pressure valve at the distal end to prevent retrograde flow of peritoneal tissue into the catheter.[17]

The flow controller is carried externally, and two-way communication is achieved by induction coupling at 30 kHz. The operator of the pump can

define delivery rates, initiate bolus or basal delivery, or initiate an audible signal to check on battery voltage and pump operation.[18,19] Protection from external electrical noise is provided. Readout capability on the external module includes program data, accumulated dose, remaining dose to be delivered, and whether the unit is operating in basal or augmented delivery mode.

Summers[20] has prepared an implantable prototype version of their Promedos El portable pump. The implantable dosing unit consists of the stepper motor-driven peristaltic pump, lithium battery, control electronics for regulating a 10-ml insulin reservoir, and a septum for percutaneous refilling of the insulin reservoir. All components are hermatically encapsulated in a titanium pacemaker casing, which is at a lower pressure than the exterior to minimize the effect of a pump, reservoir, or septum leak.

An implantable, three-roller, peristaltic pump that is driven by a rotatable magnet located outside the body has also been described by Summers.[20] A visual signaling system has been incorporated into the implanted unit. An implanted light source is energized during each revolution of the pump rotor to indicate that the pump is operating and to provide a measure of the administered dose. The pump delivers a drug from a percutaneously refillable, silastic bladder lined with an impervious layer of latex rubber.

The most sophisticated of the emerging implant delivery technologies is the noninvasively programmable drug administration device (DAD, Medtronic, Minneapolis, Minnesota). The device's titanium housing contains a 20-cm^3 refillable reservoir, an electronic control module, an integral battery, and a peristaltic drive pump that provides drug delivery with an accuracy of ±15%. A catheter routed to the site of administration is secured to the device. As with venous access ports, the reservoir is refilled or evacuated by percutaneous insertion of a syringe-mounted hypodermic needle through the device's self-sealing septum. The inert properties of the titanium and silicone DAD containment and drug delivery surfaces allow the use of a wide variety of drugs (see Figure 4.1).

The DAD contains an audible alarm system that alerts the patient and physician to low battery power, low reservoir volume, or memory error. For most applications, the entire system is implanted using only local anesthesia. The procedure is performed on an outpatient basis.

The DAD can deliver continuous infusion rates ranging from 0.025 to 0.9 ml/h or single or multiple boli. The physician can reset the rate at any time using an office-based programming system. Communication between the DAD and the program is accomplished by a radio wave-like telemetry link. Automatic security codes are exchanged between the implanted electronics and the programmer system to verify that proper and appropriate transfer of information has taken place. In addition, programming can be accomplished only in the presence of a strong magnetic field produced by the programming wand. These security measures ensure that spurious environmental signals or other causes do not inadvertently reprogram the DAD.

The DAD's delivery capabilities allow considerable clinical flexibility. Dosage titration and schedule revision can be accomplished conveniently

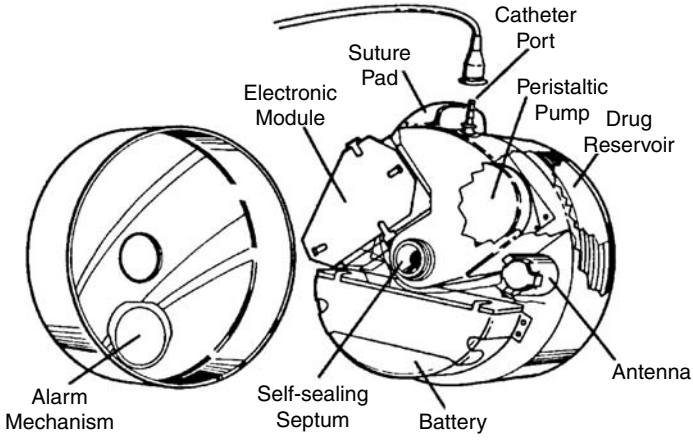

Figure 4.1 Cross-sectional view of the DAD showing key components. (From *Pharm. Technol.*, The Latest Developments in Drug Delivery Systems, Conf. Proc., 1987, 20. With permission.)

without reformulating the drug concentrations or exchanging the device for another with a different flow rate. The peristaltic drive pump, with its delivery accuracy, enables potent substances or agents with narrow therapeutic indices to be delivered precisely. The risk of infection is reduced since the entire system is fully implanted. One model of the DAD contains a bioretentive filter in the reservoir fluid outlet path. This filter enables substances to be delivered directly to the intrathecal space and to the brain, effectively bypassing the blood–brain barrier. Thus, the DAD is the first fully implanted system that provides convenient chronic, site-targeted, rate- and pattern-controlled drug delivery.

B. Fluorocarbon propellant-driven pumps

Blackshear et al.[21–23] have devised a unique "no external energy," constant-rate, implantable pump that, appropriately modified, has also been used for variable-rate insulin delivery. The basic constant-rate pump (Infusaid) consists of a hollow titanium disk that is divided into two chambers by freely moveable titanium bellows. The inner chamber contains the drug solution, while the outer chamber contains a fluorocarbon liquid that exerts a vapor pressure well above atmospheric pressure at 37°C. The inner drug chamber is refilled through percutaneous injection by means of a self-sealing silicone rubber and Teflon septum. The pressure of the injection causes expansion of the inner chamber and compression of the fluorocarbon. Once filled, the fluorocarbon vaporizes and compresses the inner chamber. The drug solution is then forced through fine-bore Teflon capillary tubing, which acts as a flow regulator, and subsequently through an intravascularly located silicone-delivery catheter. Bacterial filters are included in the refill and delivery lines.[24,25]

Flow rate can be modified by changing the length of the capillary tubing or by changing the viscosity of the drug solution (e.g., high-molecular-weight dextran). According to the Poiseuille equation, flow through the pump is inversely related to the capillary length or solution viscosity. These pumps can deliver insulin or heparin solutions at constant flow rates in the 1 to 5 ml/day range. Drug delivery rate is altered by adjusting drug concentration. The primary advantage of this type of device is the absence of any need for external power. It has been found to be reliable in long-term animal studies as well as in human clinical trials.

The fluorocarbon-driven pump has been modified for insulin delivery at two infusion rates by connecting a three-way valve to the pump assembly so that a portion of the flow-restricting capillary can be bypassed when the valve is opened. A 15-fold increase in flow rate can be obtained since flow is shunted through 1/10 the length of the capillary tubing. The flow is directed through the remaining 9/10 of the capillary when the valve is closed. The valve has been modified so that it can be actuated by placing a small permanent magnet outside the body at a distance of 2 to 3 cm from the valve. The delivery rate can be maintained between maximum and minimum rates by cycling the valve on and off to provide an intermediate rate determined by the fraction time that the magnet is held near the valve and the valve is open.

In newer designs, the valve is housed in a module attached to the side of a pump along with an infusion regulator to compensate for the effects of changes in ambient pressure and temperature; it also has an auxiliary injection port and associated check valve to provide direct access to the cannula. A pressure transducer and transmitter can also be incorporated to make pressure data available for flow rate and reservoir-volume computation. In this design, machine-grooved capillaries replace the Teflon tubing restrictor. The external magnetic controller consists of an electronic timer that rotates a permanent magnet over the pump site to cycle the valve on and off.[26]

Without the infusion regulator, these pumps are sensitive to changes in ambient temperature and pressure since they are implanted near the skin. The vapor pressure of the fluorocarbon liquid increases and the viscosity of the infused fluid decreases with increasing temperature. This is important in febrile conditions or if there are significant changes in the skin temperature. Similarly, the lowering of ambient pressure causes a similar decrease in delivery rate.

In humans, the pump has been implanted in a subcutaneous pocket under the infraclavicular fossa and sutured to the underlying fascia for heparin therapy or in a subcutaneous pocket in the abdominal wall for chemotherapy. For heparin administration, the cannulae are threaded through a tributary of the subclavian vein into the superior vena cava. Cannula plugging due to thrombosis has been noted in nine of the clinically implanted pumps and generally occurs after one year of heparin infusion when the heparin is replaced with bacteriostatic water. A check valve is also incorporated at the end of the catheter to prevent the backflow of blood.[27]

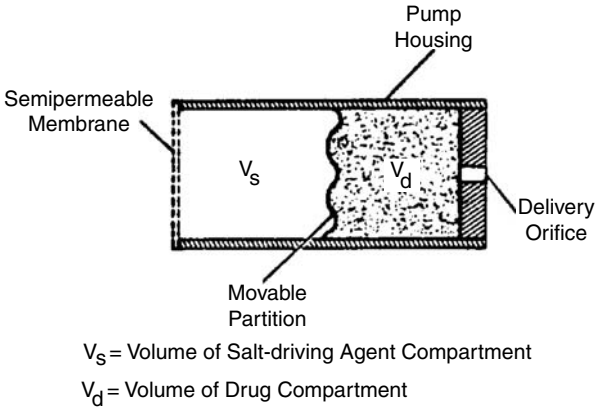

Figure 4.2 Schematic representation of a generic osmotic pump. (From *Pharm. Tech.*, June 1987, 98. With permission.)

C. *Osmotic pumps*

The Alza osmotic minipump (Alzet) has been used in a wide variety of experimental situations for constant-rate delivery and preprogrammed delivery of a biological agent.[28,29] This minipump consists of a flexible, impermeable diaphragm surrounded by a sealed layer containing an osmotic agent at a particular concentration, which, in turn, is contained within a cellulose ester semipermeable membrane. A stainless steel tube or a polyethylene catheter is inserted into the innermost chamber for delivery. When the filled pump is placed in an aqueous environment, water diffuses into the osmotic agent chamber at a rate determined by the permeability of the surrounding membrane and the concentration of the agent. The absorbed water generates a hydrostatic pressure that acts on the flexible lining to force drug through the pump outlet. The pump is filled with sterile solution with a separate filling tube; the pump itself is presterilized (see Figures 4.2 and 4.3).

An osmotic-pressure actuated, constant-rate pump has also been described with a freely moveable piston rather than a rubber diaphragm. The piston is used to maintain a constant pressure in a low osmotic pressure solution reservoir, which is separated from the high osmotic pressure fluid by a semipermeable membrane. Movement of solvent across the membrane increases the pressure on that side of the membrane, forcing drug solution out of a chamber, which is separated from the high osmotic pressure solution by a second freely moving piston. The freely moving piston on the low osmotic pressure side moves to lower the volume of that reservoir as the solvent moves across the membrane. It is assumed that the piston is exposed to a source of atmospheric pressure on its other side. A device conforming to these requirements has been made from two concentric tubes, one inserted part way into the other.[30, 31]

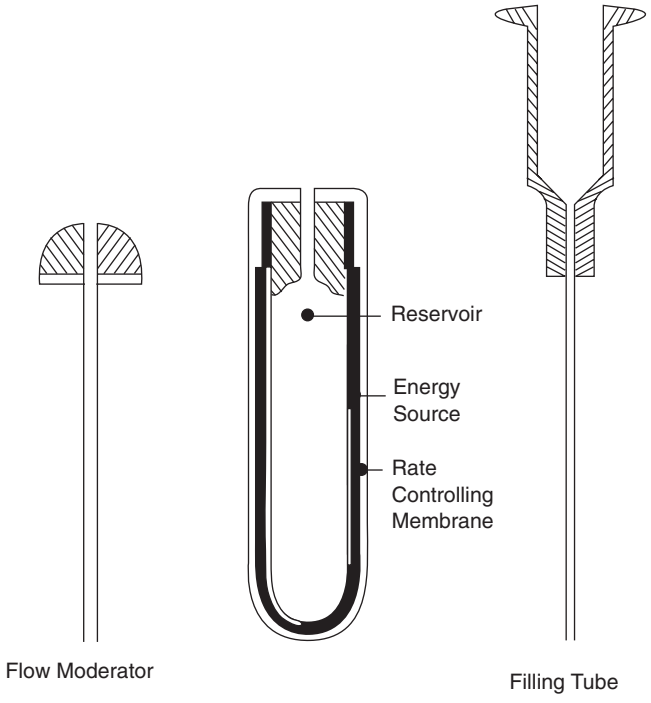

Figure 4.3 Miniature osmotic pump with flow moderator. (From *Pharm. Tech.*, June 1987, 98. With permission.)

D. Miniosmotic pumps: systemic delivery

The work of Nau and his colleagues exemplifies the value of using osmotic pumps as subcutaneous drug delivery devices in toxicology.[32] Nau studied the effects of the antiepileptic drug valproic acid on fetal development in pregnant mice. Nau compared the effects of giving the dose by two different administration regimens: a once-daily subcutaneous injection and a constant subcutaneous infusion from an osmotic pump.[33,34] With constant infusion, an order of magnitude higher total dose was required to produce fetal resorptions and encephaly comparable to that obtained with the once-daily injection bolus regimen. Despite the large difference between mouse and man in the half-life of valproate, miniosmotic pumps can produce plasma concentrations in mice that are bioequivalent to concentrations achieved by conventional dosing in man.[35,36]

Another pattern of drug dynamics is illustrated by the work of Sikic et al. with bleomycin.[37] This antineoplastic drug was administered for one week to tumor-bearing mice by three different dosing schedules: twice-daily injections, an injection on the first and third day, and a continuous infusion by osmotic pump. Over the course of all three schedules, the same total dose was administered. Efficacy was measured by reductions in tumor size, and

toxicity was measured by hydroxyproline content of the lung, an indicator of pulmonary fibrosis. Therapeutic doses given by infusion achieved significantly greater reductions in tumor size than identical doses given by either of the injection schedules. In contrast, at a given dose, the infusion regimen resulted in significantly less pulmonary fibrosis than either of the injection schedules. Thus, bleomycin appears to be a drug in which the infusion dose-response curve for one effect is shifted to the left, while the infusion dose-response curve for another effect is shifted to the right. These concomitant shifts have the net effect of widening the therapeutic index of bleomycin.

Bleomycin is thus safe and more effective when given by infusion in this model. Such pharmacodynamic work is drug-specific. Constant drug delivery is not *a priori* the superior regimen. For example, it appears that gentamicin and cyclophosphamide are drugs that are better given by injection rather than by infusion. It has been advocated that both injection and infusion regimens should be investigated during drug screening programs.

E. Miniosmotic pumps: local delivery

A catheter can be attached to the exit port of an implantable osmotic pump to perfuse a discrete location distant from the site of implantation.[38] In this manner, drug solutions may be delivered into solid tissue or against arterial pressures without measurable reduction of flow. The miniature osmotic pump is capable of changing local drug concentrations around the catheter tip without influencing the rest of the body. Flows of 0.5 to 1.0 µl/hr appear to be low enough that hydraulic damage or edema is minimal in the microperfused region.

Sendelbeck and Urquhart[39] have investigated the spatial distribution of the polar drugs (relatively non-lipid-soluble)^{14}C-dopamine hydrochloride (DA), ^{3}H-sodium methotrexate (MTX), and the lipid-soluble drug ^{14}C-antipyrine (AP) during continuous intracerebral microperfusion. Following microperfusion, DA and MTX remained concentrated in brain tissue whereas the more lipid-soluble AP escaped across the blood–brain barrier and was removed by the circulation. From a therapeutic perspective, these results indicate that brain tissue can sequester polar drugs directed from a catheter while minimizing drug levels elsewhere. Such targeted administration might maximize local effects and limit side effects in adjacent tissues or other areas of the body.

Another example of targeted administration has been reported in the studies by Ruers et al.[40] Their work indicates that continuously infused prednisolone (an immunosuppressant) to kidney-transplant patients is superior to bolus treatment in prolongation of survival time and kidney function. The longer survival of allografts with continuously infused versus bolus-injected intraperitoneal prednisolone confirms the earlier results of Proovst et al.[41] in studies on cardiac allograft survival. Continuously infused prednisolone has superior immunosuppressive action, dose for dose, compared to bolus-injected prednisolone.

F. Miniosmotic pumps: patterned delivery

Although miniosmotic pumps operate at a constant rate, they can be readily adapted to deliver drugs according to a variable time schedule. Time-varied drug administration is accomplished by coupling the miniosmotic pump to a catheter displacement tube containing a predetermined program of sequential drug infusions. The pump is filled with an inert liquid, and the displacement catheter containing the drug sequence can be thermoformed into a tight coil around the pump, thereby forming a compact package that is readily implanted.

If the catheter is loaded with a sequence of drug solution segments, alternating with segments of an inert drug-free spacer solution (which is immiscible with the drug solution), a time-based, on-off sequence is created. Thus, a linear array of alternating segments of drug solution and drug-free spacer solution in the catheter creates a pulsatile sequence of drug infusions. Other patterns of administration may be achieved by varying the concentration of drug in the segments or the length of the drug segments or spacers. More complexity is achieved if multiple drugs or multiple drug concentrations are used in the segments.

Adaptation for time-varied drug administration allows for investigation of the pharmacodynamics of time-varied drug administration patterns and the generation of synthetic circadian rhythms. Cronan et al.[42] used this time-varied method of drug administration to mimic the effects of human drug use patterns in rats. Lynch et al.[43] have investigated the artificial induction of circadian melatonin rhythm in pinealectomized rats. Temporally programmed delivery has also been used in reproductive studies. Lasley and Wing[44] successfully stimulated ovarian function in several exotic female carnivores with pulses of gonadotropin-releasing hormone (GnRH).

Miniosmotic pumps, although preprogrammed at discrete volumetric rates, allow the researcher freedom in the selection of drug and drug delivery rate. Although osmotic pumps deliver drugs by volume displacement, they deliver at low flow rates that allow undisturbed targeted tissue or organ perfusion. Catheter attachments to such pumps can be loaded with varying patterns of drugs for patterned drug delivery. Such systems appear to have unique value for polypeptide drug delivery.[45]

G. Positive-displacement pumps

Bessman and Layne[46] have described one of the early developments of an implantable, positive-displacement, insulin pump made from piezoelectric disk benders. Two 1-in. diameter thin wafers of piezoelectric material, bonded to brass, were glued to a ring of Lexan tubing. Upon applying a voltage, the piezoelectric wafers, unable to shrink or expand in diameter because of the brass disk, bend in the middle to form spherical surfaces (bellows). The bender-bellows are connected via a three-way, solenoid-driven valve to a drug reservoir. Using an appropriately shaped voltage

signal, the valve can be opened and closed in sequence with the flexing inward or outward of the disk benders-bellows. Flexing outward causes suction of drug through the valve into the bellows, while a voltage signal of the opposite polarity causes flexing inward, forcing drug through the valve and delivery catheter. Control of the pulse train results in control of the delivery rate.

Another early piezoelectric bellows pump has been prepared with piezoelectric valves. Piezoelectric disks epoxied to two titanium disks are used as valves in a modified diaphragm pump driven by a propellant gas.[47,48] The piezoelectric disks lie on either side of a ceramic disk to close off a hole separating a pressurized insulin reservoir from the body. Activation of the reservoir-side piezoelectric disk causes fluid to move from the reservoir into the space between the ceramic and piezoelectric disk because of the displacement of the piezoelectric disk. Deactivation of that disk, and activation of the piezoelectric disk on the other side of the ceramic disk, draws fluid through the hole in the ceramic disk and into the body. A 24-hour clock and control package are designed to operate from a 5-V power supply and are contained, along with a refillable reservoir, in a hermatically sealed can.

Andros, Inc. has designed a solenoid-driven, positive-displacement, diaphragm pump. When the solenoid is energized, the insulin in the pump chamber is pressurized by a rubber diaphragm driven by the solenoid. Fluid pressure opens the multiple, redundant-outlet valves to the delivery catheter, while an inlet valve prevents backflow into the reservoir. The reservoir is refillable through a self-sealing septum. Another implantable positive-displacement pump utilizes fail-safe pneumatic valves under microprocessor control to assure delivery safety. Other positive-displacement pumps for insulin delivery are under development elsewhere (St. Jude/Coratomic).

H. Controlled-release micropump

An implantable pump has been developed utilizing diffusion across a rate-controlling membrane for basal delivery, which can be augmented by a rapidly oscillating piston acting on a compressible disk of foam.[49] Without an external power source, the concentration difference between the drug reservoir and the delivery site is sufficient to cause diffusion of the drug to the delivery site (basal delivery). Augmented delivery is achieved without valves by repeated compression of the foam disk by a coated piston. The piston is the core of a solenoid, and compression is affected when current is applied to the solenoid coil (see Figure 4.4). Interruption of the current causes the membrane to relax, drawing more drug into the foam disk for the next compression cycle. The basal rate is determined by the magnitude of the concentration or pressure difference and by the permeability of the rate-controlling membrane and other diffusion resistances between the reservoir and the outlet. The augmented rate is a function of the elastic properties of the foam, the force applied by the solenoid piston, and the frequency of compression.

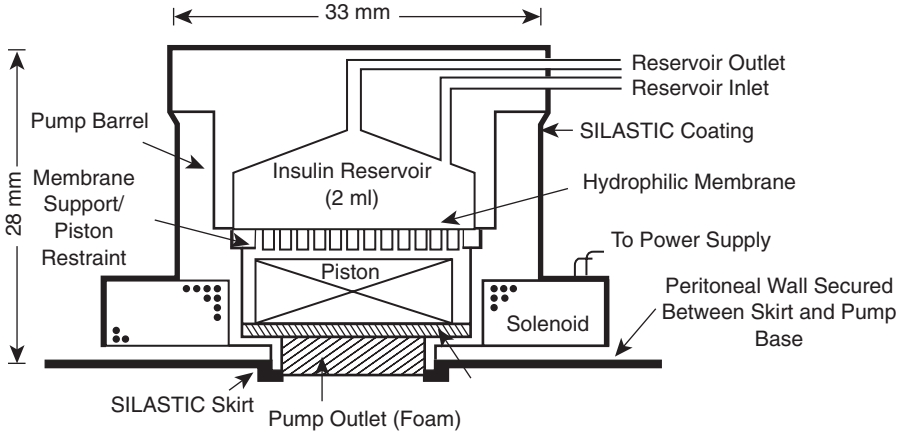

Figure 4.4 Schematic illustration of prototype VIII of the controlled-release micropump (CRM) with a solid piston. (From Anderson, J.M. and Kim, S.W., Eds., *Recent Advances in Drug Delivery Systems*, Plenum Publ. Corp., New York, 1984, 351. With permission.)

The actual mechanism of augmented delivery is unclear, since there are no valves to impose a preferred direction for augmented delivery. It is presumed that augmentation arises from a pressure difference superimposed during piston movement on the basal-concentration gradient or from a mixing effect associated with piston movement. In short-term experiments performed to date with insulin and hydrophilic membranes, no problem with deposition has been noted. This is in distinct contrast to the experience with hydrophobic membranes used in an earlier prototype in which delivery rate decreased within 2 to 3 h of operation due to deposition of insulin crystals.

Although the capability for operation with high-concentration/low-volume reservoirs is the primary advantage of the controlled-release micropump (CRM), two inherent fail-safe mechanisms are also important. Augmented delivery is achieved without valves. Therefore, the mechanical unreliability associated with the inadvertent opening and sticking of valves with complex motors or with the peristaltic action of a rotating metal component on a soft plastic tube is avoided. The long-term stability of the foam membrane after repeated compression is also important. *In vitro* results indicate that a life of one year can be expected under normal use. In the CRM, basal delivery is not achieved by regulating a large flow rate, as is done in valve-operated systems. Failure of the CRM, therefore, cannot result in uncontrolled delivery at the maximum rate and cause an inadvertent insulin overdose, for example. Furthermore, the presence of a membrane in the CRM eliminates the effect of sudden acceleration or deceleration, which can result in overdoses in other pumps.

The need to minimize diffusion resistance limits the location of the implant to the delivery site. This introduces greater emphasis on the biocompatibility of the pump exterior, particularly, the pump outlet. The devel-

opment of a fibrotic capsule, for example, can change tissue perfusion and interfere with the absorption and subsequent distribution of any drug from the delivery site. Furthermore, the fibrotic capsule can act as an uncontrollable diffusion-resistance factor and adversely affect the performance characteristics of the pump. The tissue-implant interface is a major focus of current animal studies.[50]

I. Other devices

Various electrochemical methodologies have been proposed for implantable pumps, particularly for the delivery of insulin.[51,52] An electrolytic pump, utilizing the pressure of gases evolved at the electrodes of an electrolytic cell, has been described. However, it is not clear how the evolved gases will be collected, vented, or recombined to cause the driving pressure to be reduced and to slow the pump.[53] Another group of investigators has proposed using electroosmosis to drive water across a cation-exchange membrane to pressurize an appropriate drug reservoir. Although aqueous flows of the appropriate magnitude for insulin delivery have been developed in repeated fashion over long periods of time, and with little power consumption, the necessary valve and reservoir arrangements have not yet been devised. Such devices are of interest because of their low power and particularly low voltage requirements. Whether they can ultimately be powered with a glucose fuel cell in a closed-loop fashion or not still remains to be explored.[54,55]

III. Implants for contraception

A. Biodegradable

Biodegradable polymers are the most recent developments in contraceptive drug delivery systems. They appear to be an excellent contraceptive strategy since they can provide a programmed rate of release of steroids, thereby possibly eliminating menstrual abnormalities associated with constant steroid levels. Following implantation or injection, the devices can be used for three months and longer.

The primary mechanisms of steroid release are erosion, diffusion, cleavage of covalent linkage, or a combination of these processes. The most investigated polymer materials are poly(lactic acid), poly(glycolic acid), and poly-(ε-caprolactone). The steroids used are primarily norethisterone and levonorgestrel. The mode of action at high blood levels may involve central inhibition of ovulation, while at low levels, it may involve alterations in cervical mucus, sperm migration, ovum transport, and implantation.[56,57]

Little human clinical work has been reported in this area. The most extensively examined system is composed of norethisterone in microcrystals of DL-poly(lactide-co-glycolide) or DL-poly(lactic acid). A saline suspension of microspheres — 25% w/w norethisterone in DL-poly(lactic acid) — was

injected intramuscularly at a dose of either 200 mg or 400 mg. The release of steroid occurred over 6 months. The treatment was well tolerated with no adverse effects except spotting and irregular menstrual cycles. It was concluded that doses of 1.33 to 3.45 mg/kg are necessary to inhibit ovulation for six months. Due to a problem of DL-poly(lactic acid) accumulation with continuous injections, the release of norethisterone from a copolymer DL-poly(lactide-co-glycolide) was examined. This copolymer was reported to have similar kinetics of steroid release, but degrades at a faster rate than DL-poly(lactic acid).[58,59]

Several other methods of steroid release from biodegradable polymers are also currently under examination. Poly(ε-caprolactone), which is permeable to levonorgestrel, is believed to release the drug for at least a year at a constant diffusion-controlled rate, after which the device erodes. Subdermal implantation of poly(ε-caprolactone) capsules containing levonorgestrel into the lateral hip suppressed ovulation in all subjects without any serious adverse effects.[60,61]

Norethisterone has been prepared as compressed pellets with cholesterol. It has been covalently bonded to polyN-(3-hydroxypropyl)-L-glutamine to produce an implant that erodes rather than relying on diffusion. Another approach involves the use of a poly(orthoester) known as Chromoner as a matrix for a suspension of norethisterone and levonorgestrel with a stabilizing buffer. This product has been shown to release norethisterone in a fairly constant manner until the 32nd week after implantation.

B. Nonbiodegradable

One of the methods of steroid release involves the use of a nondegradable polymer, silastic. The polymer is shaped into capsules or rods, which are implanted subdermally. The advantages of these devices are that their effectiveness does not depend on patient compliance, the duration of action is longer, and the effects can be terminated by removing the implant. The usefulness of such implants, however, may be limited by the occurrence of menstrual abnormalities and systemic side effects. A primary disadvantage with their use is the need for medical personnel to implant and remove them. Additional concerns are the possibility of the implants migrating, thus making retrieval difficult. Possible toxicological effects of the polymers also represent a concern.[62]

The Norplant device has been the most extensively examined implant. It consists of medical-grade silastic capsules 34 mm long containing levonorgestrel. Six capsules are placed subdermally into the inner aspect of the upper arm in a fan shape through a 5-mm incision within 1 week of the onset of menses. The implant is designed to be used for approximately 5 years.

This device operates by interfering with ovulation or luteal function. The rate of anovulation ranges from 25 to 80%, being highest in the first year

of treatment. In a 3-year study, Norplant was found to have excellent contraceptive effectiveness and demonstrated a significantly lower pregnancy rate than the TCu 200 IUD. Menstrual abnormalities occur with both devices, but patients using the implant show higher blood hemoglobin levels. In Norplant users, the dominant medical complaints leading to removal are those associated with progestational contraceptive agents (primarily bleeding irregularities). Capsule migration was found to be minimal.[63]

Other steroids that have been used within implants are estradiol and ST 1435 (a 19-norprogesterone derivative) that is seven times more potent as an ovulation inhibitor than levonorgestrel.[64]

IV. Delivery of chemotherapeutic agents using implants

The size of a potential market often drives drug development; the larger the market, the greater the competition. Hypertension, diabetes, cancer, and arthritis markets, for example, have attracted a number of companies because of the number of patients in these market populations.[65–67] Diabetes and cancer have been identified by companies involved in a myriad of different technologies. Both implantable and external ambulatory infusion devices are currently in use, providing controlled delivery of insulin and chemotherapeutic agents via various types of catheters and access devices.[68–70]

Work has progressed in several laboratories around the world in which implanted insulin-infusion pumps are used. The objective is to establish a safe and effective approach to "open-loop" insulin delivery from an implanted system. Open-loop means that the pump itself does not sense blood glucose; rather, the patient must monitor blood glucose and, in some way, signal the pump with a command describing when and how much insulin to infuse.

The Programmable Implantable Medication System (PIMS) was developed at The Johns Hopkins University Applied Physics Laboratory.[71] The implanted unit is a disk approximately 3 inches in diameter and 0.78 inches thick, surgically placed beneath the skin in the left side of the abdomen. It delivers pulses of insulin via a catheter, the tip of which is placed deep in the peritoneal cavity. The pump spaces its pulses to deliver a basal release rate, which is programmable and recycles every 24 h. The patient then uses an external transmitting unit (a box about $6 \times 4 \times 2$ in.) to command the pump to deliver any of a variety of insulin doses.

A major step in the future will be the development of a continuous glucose sensor. This has been a difficult problem over the years. The ideal sensor should have long life, be sensitive to small changes in glucose, be rapid in its response rate, remain in contact with either blood or a body fluid that reflects blood glucose, and, above all, be reliable.

Insulin, like other medications, can be bound to various polymers and implanted as a pellet under the skin. It can then slowly leach off the pellet

and find its way into the bloodstream. This relatively simple approach would be of limited use, however, because it would require repeated implantations of the pellet and would provide only a continuous infusion of insulin and would not give physiologic variations needed to control both between-meal and after-meal changes in blood glucose. More elegant approaches are under development that could allow modification of the rate of insulin release from insulin products, such as proinsulin, for example, by an external device that alters an electrical field.[72,73]

The capabilities of the programmable drug administration device (DAD) make it a useful device for chronotherapy.[74,75] Chronotherapy is based on the fact that the efficacy of a drug can change when administered at different times during the circadian cycle. This fact, explored for more than three decades, has been demonstrated in laboratory and clinical trials. For commonly used cancer chemotherapeutic drugs, animal studies have shown that both efficacy and toxicity to the host are related to the time of administration. The susceptibility of normal tissues to these powerful drugs varies rhythmically, with tumor cells displaying a different time-related response. Therefore, the timing of drug delivery via a DAD can be important in achieving therapeutic specificity.

The preferred objective is to deliver the chemotherapeutic agent when normal cells are least susceptible and when cancer cells are more susceptible. Chronic evaluation of these principles is difficult in large numbers of patients because of the complex, nonlinear dosing patterns required for rhythm-based chronotherapy. Current medical practice cannot readily and consistently achieve the dosing patterns on either an inpatient or outpatient basis. The DAD, however, may be capable of implementing these protocols automatically and over an extended period of time.

The DAD has been used clinically in several patients in three primary application areas: terminal cancer pain management, intractable spasticity management, and cancer chemotherapy. The DAD's longevity is a function of the capacity of the power source and the dispensing rate of the drug. Depletion of the power source is affected principally by the cumulative amount of drug administered by the pump. The expected longevity of an implanted pump is 3 to 5 years, depending on the application and the amount of drug delivered.[76]

In cancer pain management, clinically effective relief of intractable cancer pain has been obtained with the DAD using morphine sulfate delivered intrathecally in 60 patients for whom oral medications had failed. The majority of the patients judged pain relief to be good to excellent. Respiratory depression was not a problem. In comparison to previous methods of administration, the patients were more alert and active and did not experience many of the secondary complications of chronic narcotic administration, such as lethargy, confusion, and constipation.[77] Although the development of tolerance is a concern during intrathecal administration, it was not an overwhelming clinical problem with programmable delivery. According to Penn et al.,[78] only 2 out of 43 patients with implanted pumps

developed significant tolerance. Its ability to alter dosage noninvasively makes the DAD a convenient system for meeting patients' changing needs. The DAD also conveniently accommodates a broad patient range of initial dosage levels.

Spasticity caused by spinal cord trauma or multiple sclerosis is often treated with oral baclofen (an analog of the inhibitory neurotransmitter gamma aminobutyric acid). The goal is to reduce muscle tone to normal levels and to suppress spasms. The major side effects of the drug are drowsiness and, in some cases, confusion. The DAD has been used to administer baclofen intrathecally to patients with severe spasticity who are refractory to oral baclofen.[79] As with pain patients, noninvasive programmability is clinically useful for initial-dose titration and for accommodating changes in dosage requirements. No drowsiness, confusion, or weakness was experienced at dosage levels adequate to suppress symptoms.

As noted previously, studies have demonstrated that drug toxicity, side effects, and therapeutic results are affected by the timing of cancer chemotherapy drug delivery during the circadian cycle. However, the nonequal dosing regimens needed to obtain chronotherapeutic results simply do not readily lend themselves to conventional therapy. The use of the DAD in cancer chemotherapy by Hrushesky[75] illustrates the therapeutic effect of implanted programmable drug infusion. In one series of patients with carcinoma of the kidney, constant-rate intravenous infusion of floxuridine (FUDR) was compared with time-modified administration. The time-modified schedule consisted of four dosage intervals: low-level administration in the early morning quadrant, a stepwise dosage increase from late morning into early afternoon (second quadrant), peak delivery rates from late afternoon into early evening, and a decrease in dosage to second quadrant levels in the final interval. Results of this study were encouraging and support the usefulness of DAD. Oncologists currently believe that the amount of drug administered, as well as adherence to monthly treatment schedules, are important to the ultimate success of chemotherapy. In the intravenous FUDR groups studied, 40% of the patients receiving constant-rate infusion required treatment delays compared to 6% of the time-modified group. Reductions in dosage were necessary in 60% of the former group, while only 12% of the time-modified patients required reduction because of drug-related symptoms.[80,81]

In conclusion, programmable implantable drug delivery is an emerging technology. Its clinical benefits include improved drug efficacy, dynamic dosing, noninvasive prescription modification, reduced side effects, improved quality of life, and cost-effectiveness compared to traditional in-hospital therapies. These benefits accrue principally from ambulatory targeted delivery and from programmability — particularly as it relates to complex dosing patterns. This and similar systems are expected to be used in the delivery of genetically engineered substances, which have inherent problems in delivery.

V. *Recent advances in implants and related devices (excluding inserts)*

In veterinary applications, implants are commercially available for estrus synchronization via delivery of hormones. COMPUDOSE is a polymeric controlled-release device for the delivery of estradiol to improve both growth rate and feed efficiency in beef cattle. The product is composed of a non-medicated silicone rubber core coated with a thin layer of medicated silicone rubber containing estradiol. COMPUDOSE is implanted subcutaneously in the ear of beef cattle.[82]

For peptides contained in film-coated implants, degradation can occur inside the implant while crossing the rate-limiting membrane or in the bathing solution. As part of a program using coated implants to deliver peptides, it has been found that conjugated peptides ranging in molecular weight from 1200 Daltons through 30,000 Daltons were degrading during *in vitro* testing.[82]

Ouabain-induced ventricular tachycardia in the dog has been converted to normal sinus rhythm via controlled release drug delivery of lidocaine from a polymeric matrix directly into the ventricular myocardium. This therapeutic effect was achieved as rapidly as an intravenous bolus, but with comparatively lower plasma levels. Antiarrhythmic drug delivery implants may prove to be a useful approach to optimize efficacy while minimizing untoward effects.[82]

The development of inexpensive, biocompatible, subcutaneous implants for the controlled delivery of peptides has been undertaken. The release of peptides from Eudragit NE30D coated implants using an incubating medium was studied. *In vivo*, the implants containing LHRH have been used to induce ovulation and mating in anestrus sheep.[82]

Studies have been carried out in an effort to develop implants for the controlled delivery of a synthetic growth hormone-releasing peptide (His-D-Trp-Ala-Trp-D-Phe-Lys-NH) for sustained periods to ruminants. Various polymeric materials have been employed as coating agents to modify the surface area of the implants, thereby affecting the release profile. Formulation and surface area modifications were combined to obtain the desired uniform release rates and optimum release period. *In vivo* release profiles were obtained for several sets of implants, which correlated well with the *in vitro* profiles.[82]

An elastomer matrix implant providing release for a period in excess of one year of an agonistic analogue of leutenizing hormone-releasing hormone (LH-RH) has been developed. The compound is a decapeptide, and the system was targeted for reversible suppression of estrus, reversible chemical castration, and treatment of sex-hormone-dependent conditions in companion animals. The system is biocompatible and nondegradable. At the end of one year of therapy, or when it is otherwise desired to discontinue the therapy, the implant may be removed via a minor surgical procedure. A new device may be implanted at this time and therapy continued. Formulation

factors are critical to both rate and duration of delivery of the compound, and their appropriate manipulation allows design of this extremely prolonged release system.[82]

The feasibility of incorporating insulin into an osmotic pump whose pumping rate is dependent on blood glucose has been evaluated.[83] Such a pump could contain insulin in virtually any liquid or semisolid form, and its release rate would be independent of the formulation. The approach has been to develop a semipermeable membrane whose aqueous permeability increases with blood glucose concentration. The membrane consists of two layers: the first layer contains immobilized glucose oxidase, which converts glucose to gluconic acid, thereby lowering the local pH, while the second layer consists of a cross-linked, hydrophobic, polybasic hydrogel. This hydrogel absorbs little water at physiologic pH, but becomes quite hydrated as pH is lowered.

Bioerodible implants have been investigated using polylactides, caprolactone polymers or copolymers, solid solutions in polylactic acid, and cyclazocine, norethidrone, and d-norgestrel, respectively.[83] Permeable implants have also been studied using polysiloxane grafted with N-vinyl-pyrrolidone, hydrophilic acrylate or methacrylate polymers and ACTH hormone, and norethandrolone (Nilevar), respectively.[83]

Dedrick et al.[84] have developed a device called a diffusion cell for release of methotrexate, while Schopflin[85] used silicone rubbers and norethisterone acetate as the medicinal agent.

An implanted apparatus that dispenses a drug over a prolonged period of time has been developed by Ellinwood.[86] A self-powered dispensing device stores one or more substances in powdered, liquid, or other dispensable form and uses a compressible container (i.e., bellows, for withdrawing substances from the reservoir and dispensing to the body). The dispensing operation may be on a fixed schedule or may be controlled by monitoring single or multiple sensors implanted in the body and evaluating the sensed data in order to control the conditions under which dispensing takes place, as well as the kind of dispensing. Dual dispensers and dual medication also may be used. The types of application used with evaluation of biological signals according to this process include chemical transducers and feedback, such as detection of glucose and pH, as well as ionic change detection; temperature, pressure, or mechanical transduced changes (e.g., blood pressure, blood flow, gut motility); and electrical activity, as might be measured in an electrocardiogram or electroencephalogram.

An implantable dosing device composed of a medication reservoir, a propellant chamber, and flow control has been described by Kuhl and Luft.[87] The release of the medication to the body can be controlled or regulated and thus adapted to demand at any time. This is achieved by providing an electroosmotic regulatory control valve with an ion-exchange diaphragm arranged between two porous electrodes for flow control. In such a valve, liquid is transported through the electrodes and through the ion-exchange diaphragm when current flows. For example, negative charges are fixed at

the pore walls of the ion-exchange diaphragm, and the mobile positive ions, which are necessary for reasons of electroneutrality, then travel in the electric field and take along the liquid by friction.

In addition to the advantage that this implantable dosing device can be controlled or regulated, the device is also uninfluenced by changes of body temperature insofar as its operation and effectiveness are concerned. This is because the transport of the medication, due to the gas pressure of a propellant in the propellant chamber, is superimposed (i.e., regulated by the amount of liquid passing through the ion).

In the process described by Wichterle,[88] long-term tubular outlets through the skin are replaced by an implant introduced into a subcuticular ligament immediately below the skin. The implant is generally in the shape of a capsule or pouch and formed of a wall construction that substantially retains its shape both when filled and empty. This defines a hollow interior cavity of substantially constant volume in which the liquid may be stored and is easily filled through injection with a hypodermic needle. The capsule is provided with at least one channel, which may be connected to an implanted tube leading to the body organ or organ substitute, even though it may be remote from the skin or the location of the capsule.

Wichterle[88] has also developed an implant for infusion consisting of a hollow body with one wall formed by a thin, permeable membrane with a chamber inside the body, the chamber being connected by at least one channel with the outside. This system enables essentially unidirectional diffusion of the active substance directly to the affected tissue and maintenance of arbitrary changes of the concentration of the active agent. This device is useful for directing drugs into the location of nonoperable tumor diseases.

A self-powered, vapor-pressure delivery device for the controlled and continuous dispensing of an active agent has been developed by Michaels et al.[89] This device uses vapor pressure as the motive force, and it may be used for administering drugs internally in the body of an animal or human. Michaels and colleagues have also described a device comprising an expandable laminate surrounding a collapsible container filled with drug and positioned in a rigid housing chamber. When in operation, the device releases a drug in response to the laminate imbibing fluid and expands, thereby exerting pressure on the container, which then collapses and delivers a drug from the device.[89]

Epicardially implanted D-sotalol polyurethane composite matrices for preventing ischemic ventricular arrhythmias have been studied in open-chest dogs. D-sotalol was combined with a polyureapolyurethane (3:7) in solvent-cast films, which were characterized *in vitro* for their drug release. Placement of 200-mg D-sotalol matrices in the nonischemic zone was ineffective for significantly reducing the occurrence of ventricular arrhythmias. Furthermore, D-sotalol controlled-release matrices were ineffective for preventing ventricular fibrillation (VF) regardless of dose or placement site. It was concluded that epicardial D-sotalol controlled-release matrices inhibited ischemic ventricular arrhythmias, but not VF, if placed in the left ventricular

ischemic zone during repeated left anterior descending coronary artery (LAD) occlusions.[90]

Novel biodegradable implants have been designed for extended delivery of effective levels of the growth-promoting agent17-β estradiol to steers. The initial burst of release from poorly entrapped drug on the surface of the implant was found to be minimized by reducing the drug loading in the terminal active compacts, which tend to contribute disproportionately to the initial surface area of the device. Prolonged dissolution testing on single compacts and composite implants facilitated selection of implant designs that showed the desired increase in active release.[91]

A microcapsule for implantation that reduces immune response has been described. Active material was encapsulated within a semipermeable barrier, the outermost layer of which contained an alginate substantially composed of alpha1-guluronic acid. Islets of Langerhans from rats were suspended in a concentrated aqueous solution of the acid and then injected into aqueous calcium chloride to form cross-linked microcapsules. Capsules were subsequently soaked in sodium alginate solution to form an outer alginate membrane.[92]

Schindler and Hollomon[93] have prepared random copolymers of caprolactone containing 5 to 25 mol% trimethylene carbonate. Copolymers can be shaped into tubular containers and used for sustained drug delivery after subcutaneous implantation. In one preparation, they dissolved trimethylene carbonate and stannous octoate in caprolactone and then heated it to 140°C. They cast the resulting copolymer as a thin film from chloroform and rolled it at 80°C. The resulting tube was shaped into capsules and filled with levonorgestrel for testing.

French researchers have developed a cellular implant-based targeted delivery system that may have potential in the treatment of cancer. Although cytokines are of increasing interest in the treatment of cancer, they are rapidly broken down in the body, and a more targeted approach is needed. Several research teams have tried using genetically modified cancer cells to secrete IL-2 locally in mice. The implants stimulate the immune system in two ways: they are histocompatible, and the IL-2 they secrete activates natural killer cells. To make the method more lasting and specific, the plan is to insert into the implants other genes coding for specific tumor antigens as well as the IL-2 gene. This approach could be a viable alternative to the use of viral or retroviral vectors.[94]

Alza's tetracycline peridontal implant, developed in conjunction with On-Site Therapeutics, Inc., has been targeted for a potentially large market. A survey in the mid-1980s conducted by the National Institute for Dental Research indicated that as many as eight out of ten Americans have some form of periodonitis. Therefore, this product could be well recognized in oral care as well as in the area of dental consumer products.

Biodegradable materials have been successfully utilized for guided tissue regeneration (GTR) and local delivery systems as they are biocompatible, less cytotoxic, and do not require removal. The regenerative effect of 25%

doxycycline-loaded biodegradable GTR membrane was evaluated in dogs. The results suggested that doxycycline-loaded membrane might have beneficial effect on osteogenesis to favor peridontal regeneration. Repeated estrus synchronization of beef cows with intravaginal progesterone implants and the effects of a GnRH agonist buserelin following implant insertion was investigated.[98]

The release characteristics of antibiotics from *in vivo*- and *in vitro*-processed morselized cancellous bone have been compared. The results indicate that this bone can act as a carrier of antibiotics. The elution profiles of netilmicin-, vancomycin-, clindamycin-, and rifampicin-impregnated cancellous bone were similar.

Ceramic hydroxyapatite implants have been used in dentistry for their unique compatibility with alveolar bone. Bisphosphonates may be beneficial in preventing alveolar bone destruction associated with natural and experimental periodontal disease. It also prevents resorption of alveolar bone following mucoperiosteal flap surgery. Effects of highly bisphosphonate-complexed hydroxyapatite implants on osteoconduction and repair in rat tibiae were investigated, and it was found that normal osteoconduction and repair did occur on and around the tibiae.[99]

The controlled delivery of toremifene citrate from subcutaneously implanted silica xerogel carrier has been evaluated. Toremifene citrate was incorporated into hydrolyzed silica sol, and the implants were tested *in vivo* and *in vitro* in mice. The silica xerogel discs showed a sustained release of toremifene citrate over 42 days, and toremifene-related changes in the uterus were detectable at all studied time points. These findings suggest that silica xerogel is a promising carrier material for implantable controlled drug delivery systems.[100]

The effect of bone morphogenic protein (BMP) on the bond strength of titanium implants at the bone-implant interface was evaluated. It was concluded from this study that the use of BMP-atelopeptide type I collagen mixture is an effective means of obtaining greater bond strength at the bone-implant interface within a shorter time period than the titanium implants without BMP.[101]

Resistance of antibiotics, such as rifampicin-, vancomycin-, and gentamicin-bonded gelatin-coated polymer meshes to *Staphylococcus aureus* in a rabbit subcutaneous pouch model, was studied. At the time of explanation, none of the antibiotics-soaked meshes were infected, while all of the untreated meshes were infected. These results indicate that antibiotic soaking evidently prevents perioperative infection of gelatin-coated knitted polymer meshes in this experimental model.[102]

Bioprosthetic heat valves made from glutaraldehyde-fixed porcine aortic valves or bovine pericardium have been shown to have some advantages over mechanical valves. However, their durability is low due to calcification and immunological rejection. Studies on immunogenicity play an important role in understanding the biocompatibility of materials. For example, the effect of polyethylene glycol on pericardial calcification has been investi-

gated. The authors studied the complement activation potential and the contribution of complement factors on the calcification of polyethylene glycol (PEG)-grafted pericardium samples and compared the results with standard glutaraldehyde-treated pericardium samples. Based on the results, the authors selected activated PEG-grafted bovine pericardium using glutaraldehyde and carbodimde for further studies.[103,104]

VI. Future prospects

Among implants, ambulatory drug delivery technology represents one of the fastest growing areas in the health care market. Vascular access ports are particularly important because of their compatibility with current economic trends aimed at reducing the length of hospital stays and moving adaptable therapies to more profitable settings in the hospital, such as the outpatient surgery unit, outpatient clinic, or home health department.[95]

Perhaps the most promising market segment for ambulatory long-term infusion therapy is chemotherapy. This segment alone is projected to increase at a rate of 30 to 40% annually during the next decade. In addition, other relatively new markets for these devices, such as long-term antibiotic therapy, total parenteral nutrition, and pain management, will expand greatly as infusion therapy is moved to ambulatory settings, such as the outpatient clinic, the home, and the physician's office. In the near future, pediatric and epidural venous access systems will undoubtedly be introduced, and additional products serving the dual lumen market will probably be developed. But the most interesting opportunities for growth lie in the area of dedicated port and pump systems.[83,96,97]

Based upon the established work on implantable delivery vehicles, it is probable that these or related devices may well be in widespread clinical use within the next 10 to 20 years. Availability of devices that can provide not only insulin infusion, but also delivery of chemotherapeutic agents, is not too far in the future. It would be highly desirable to combine an insulin-delivery device with a totally implanted glucose sensor, thereby achieving the development of a completely "closed-loop" implantable artificial beta cell. Although sensor development has been under study for 15 to 20 years, there still appears to be none ready for combination with an insulin-delivery device to make a completely "closed-loop" artificial beta cell. Several serious problems in sensor technology, including electrode drift and problems with standardization in a totally implanted device, as well as changes in sensor function with overgrowth of tissue cells, have made this an extremely difficult problem to solve. Whatever the eventual outcome, it seems clear that the next two decades will be an active time for research into insulin-delivery devices of all kinds and their clinical evaluation. Most important, these future implantable delivery systems will perhaps offer the patient greater freedom and thus improved quality of life.

References

1. Bruck, S.D., Evaluation of blood compatibility of polymeric implants. In *Controlled Drug Delivery*, Vol. 2, Clinical Applications, Bruck, S.D., Ed., CRC Press, Inc., Boca Raton, FL, 45–64, 1983.
2. Lawrence, W.H., Acute and chronic evaluations of implanted polymeric materials. In *Controlled Drug Delivery*, Vol. 2, Clinical Applications, Bruck, S.D., Ed., CRC Press, Inc., Boca Raton, FL, 1–44, 1983.
3. Sefton, M.V., *Implantable Pumps in Medical Applications of Controlled Release*, Vol. 1, Langer, R.S. and Wise, D.L., Eds., CRC Press, Inc., Boca Raton, FL, 129–158, 1984.
4. Hsieh, D.S.T., Langer, R., and Folkman, J., Magnetic modulation of release of macromolecules from polymers, *Proc. Natl. Acad. Sci.*, 78, 1863, 1981.
5. Merrill, E.W., U.S. Patent 3,608,540, 1981.
6. Leininger, R.I., Polymers as surgical implants, *CRC Crit. Rev. Bioeng.*, 1, 1973.
7. Williams, D.F., Ed., *Biocompatibility of Clinical Implant Materials*, Vols. 1 and 2, CRC Press, Inc., Boca Raton, FL, 1981.
8. Schade, D.S. et al., Future therapy of the insulin-dependent diabetic patient — the implantable insulin-delivery system, *Diabetes Care*, 4, 319, 1981.
9. Soeldner, J.S., Treatment of diabetes mellitus by devices, *JAMA*, 70, 183, 1981.
10. Blackshear, P.J. et al., Control of blood glucose in experimental diabetes by means of totally implantable insulin-infusion device, *Diabetes*, 28, 634, 1979.
11. Marliss, E.B., Caron, D., Albisser, A.M., and Zinman, B., Present and future expectations regarding insulin-infusion systems, *Diabetes Care*, 4, 325, 1981.
12. Buchwald, H. et al., Intraarterial infusion chemotherapy for hepatic carcinoma using a totally implantable infusion pump, *Cancer*, 45, 866, 1980.
13. Ellinwood, E.H., U.S. Patent 3,923,060, 1975.
14. Spencer, W.J., A review of preprogrammed insulin-delivery systems, *Trans. Biomed. Eng.*, BME28, 237, 1981.
15. Schade, D.S., Eaton, R.P., Edwards, W.S., Doberneck, R.C., et al., Successful short-term implantation of a remotely programmable insulin-delivery system in man, *JAMA*, 247, 1848, 1982.
16. Carlson, G.A. et al., A new low-power high-reliability infusion pump., *Proc. Seventh N. Engl. Bioeng. Conf.*, Ostrander, L.E., Ed., 193, 1979.
17. Carlson, G.A. et al., Development of an artificial beta cell suitable for animal implantation, *Trans. Am. Soc. Artif. Intern. Organs*, 26, 523, 1980.
18. Love, J.T. and Goana, J.L., An implantable insulin-delivery system. In *Frontiers of Engineering in Health Care*, Cohen, B.A., Ed., 51, 1981.
19. Spencer, W.J. et al., Some engineering aspects of insulin-delivery systems, *Diabetes Care*, 3, 345, 1980.
20. Summers, G.D., U.S. Patent 3,527,220, 1970.
21. Blackshear, P.J., Dorman, F.D., Blackshear, P.L., Varco, R.L., and Buchwald, H., The design and initial testing of an implantable infusion pump, *Surg. Gynaecol. Obstet.*, 134, 51, 1972.
22. Blackshear, P.J., Dorman, F.D., Blackshear, P.L., Buchwald, H., and Varco, R.L., U.S. Patent 3,731,681, 1973.
23. Blackshear, P.J., Rohde, T.D., Varco, R.L., and Buchwald, H., One year of continuous heparinization in the dog using a totally implantable infusion pump, *Surg. Gynaecol. Obstet.*, 141, 176, 1975.

24. Perkins, P.R. et al., Design and initial testing of a totally implantable transcutaneously controllable insulin-delivery device, *Trans. Am. Soc. Artif. Intern. Organs*, 24, 229, 1978.
25. Buchwald, H. et al., A totally implantable drug-infusion device: Laboratory and clinical experience using a model with single flow rate and new design for modulated insulin infusion, *Diabetes Care*, 3, 351, 1980.
26. Rohde, T.D., Blackshear, P.J., Varco, R.L., and Buchwald, H., Chronic heparin anticoagulant in dogs by continuous infusion with a totally implantable pump, *Trans. Am. Soc. Artif. Intern. Organs*, 216, 510, 1975.
27. Loughheed, W. and Albisser, A.M., Insulin delivery and the artificial beta cell: Luminal obstruction in capillary conduits, *Int. J. Artif. Org*., 3, 50, 1980.
28. Alzet miniosmotic pump bibliography, Alza Corporation, Palo Alto, CA, 1981.
29. Lynch, H.J., Rivest, R.W., and Wurtman, R.J., Artificial induction of melatonin rhythms by programmed microinfusion, *Neuroendocrinology*, 31, 106, 1980.
30. Theeuwes, F., Elementary osmotic pump, *J. Pharm. Sci*., 64, 1987, 1975.
31. Stolzenberg, S.J. and Linkenhermer, W.H., U.S. Patent, 3,604,417, 1971.
32. Nau, H., Trotz, M., and Wenger, C., Controlled-rate drug administration in testing for toxicity, in particular, teratogenicity, towards interspecies bioequivalance. In *Topics in Pharmaceutical Sciences*, Breimer, D.D. and Speiser, P., Eds. Elsevier Press, Inc., New York, 143–157, 1985.
33. Nau, H., Zierer, R., Spielmann, H., Neubert, D., and Gansau, C.H., A new model for embryotoxicity testing: teratogenicity and pharmacokinetics of valproic acid following constant-rate administration in the mouse using human therapeutic drug and metabolic concentrations, *Life Sci*., 29, 2803–2814, 1981.
34. Nau, H., Teratogenic valproic acid concentrations: infusion by implanted minipumps versus conventional injection regimen in the mouse, *Toxicol. Appl. Pharmacol*., 80, 243–250, 1985.
35. Ray, N. and Theeuwes, F., Implantable osmotically powered drug delivery systems. In *Drug Delivery Systems, Fundamentals and Techniques*, Johnson, P. and Lloyd-Jones, J.G., Eds., Ellis Horwood, VCH Publishers, Chichester, 120–138, 1987.
36. Theeuwes, F. and Yum, S.I., Principles of the design and operation of generic osmotic pumps for the delivery of semisolid or liquid drug formulations, *Ann. Biomed. Eng*., 4, 343–353, 1976.
37. Sikic, B.I., Collins, J.M., Mimnaugh, E.G., and Gram, T.E., Improved therapeutic index of bleomycin when administered by continuous infusion in mice, *Cancer Treat. Rep*., 62, 2011–2017, 1978.
38. Urquhart, J., Fara, J., and Willis, K.L., Rate-controlled delivery systems in drug and hormone research, *Ann. Rev. Pharmacol. Toxicol*., 24, 199–236, 1984.
39. Sendelbeck, S.L. and Urquhart, J., Spatial distribution of dopamine, methotrexate, and antipyrine during continuous intracerebral microperfusion, *Brain Res*., 328, 251–258, 1985.
40. Ruers, T.J.M. et al., Local treatment of renal allografts, a promising way to reduce the dosage of immunosuppressive drugs, *Transplantation*, 41, 156–161, 1986.
41. Proovst, A.P., de Keyzer, M.H., Kort, W.L., and Wolff, E.D., Superiority of continuous infusion of prednisolone over daily injections in the prolongation of heart allograft survival in rats, *Transplantation*, 34, 221–222, 1982.

42. Cronan, T., Conrad, J., and Bryson, R., Effects of chronically administered nicotine and saline on motor activity in rats, *Pharmacol. Biochem. Behav.*, 22, 897–899, 1985.
43. Lynch, H.J., Rivest, R.W., and Wurtman, R.J., Artificial induction of melatonin rhythms by programmed microinfusion, *Neuroendocrinology*, 31, 106–111, 1980.
44. Lasley, B.L. and Wing, A., Stimulating ovarian function in exotic carnivores with pulses of GnRH, *Ann. Proc. Amer. Assoc. Zoo. Vet*., 14–14, 1983.
45. Phillips, J.A., Alexander, N., Karesh, W.B., Millar, R., and Lasley, B.L., Stimulating male sexual behavior with repetitive pulses of GnRH in female green iguanas lguana-lguana, *J. Exper. Zool*., 234, 481–484, 1985.
46. Bessman, J.P. and Layne, E.C., Implantation of a closed-loop artificial beta cell, *Abstr. Am. Soc. Artif. Intern. Organs*, 67, 1981.
47. Schubert, W., Baurschmidt, P., Nagel, J., Thull, R., and Schaldach, M., An implantable artificial pancreas, *Med. Biol. Eng. Comput*., 18, 527, 1980.
48. Schapiro, G.A., Implantable insulin-delivery system, *Med. Electron*., 55, 1979.
49. Sefton, M.V. and Burns, K.J., Controlled-release micropumping of insulin at variable rates, *Ind. Eng. Chem. Prod. Res. Dev.*, 20, 1, 1981.
50. Anderson, J.M., Niven, H., Pelagalli, J., Olanoff, L.S., and Jones, R.D., The role of the fibrous capsules in the function of implanted drug-polymer sustained-release systems, *J. Biomed. Mater. Res*., 15, 889, 1981.
51. Nalecz, M., Lewadonski, J., Werynski, A., and Zawicki, I., Bioengineering aspects of the artificial pancreas, *Artif. Org*., 2, 305, 1978.
52. Uhlig, E.L.P., Graydon, W.F., and Zingg, W., The electroosmotic activation of implantable insulin micropumps, *J. Biomed. Mater. Res*., 17, 931, 1983.
53. Lougheed, W.D., Woulfe-Flanagan, H., Clement, J.R., and Albisser, A.M., Insulin aggregation in artificial delivery systems, *Diabetologica*, 19, 1, 1980.
54. Schade, D.S., Eaton, R.P., and Spencer, W., Implantation of an artificial pancreas, *JAMA*, 245, 709, 1981.
55. Sefton, M.V., Allen, D.G., Horvath, V., and Zingg, W., Insulin delivery at variable rates from a controlled-release micropump. In *Recent Advances in Drug Delivery Systems*, Anderson, J.M. and Kim, S.W., Eds., Plenum Publishing Corp., New York, 349–365, 1984.
56. Benagiano, G. and Gabelnick, H.L., Biodegradable systems for the sustained release of fertility-regulating agents, *J. Steroid Biochem*., 11,449–455, 1979.
57. Bengiano, G., Ermini, M., and Gabelnick, H.L., *Hormonal Factors in Fertility, Infertility, and Contraception*, Vander Molen, H.J., Klopper, A., Lunefeld, B.L., Neves e Castro, M., Sciarro, F., and Vermeulen, A., Eds., Excerpta Medica, 141–147, 1982.
58. Beck, L.R. et al., Clinical evaluation of injectable biodegradable contraceptive systems, *Am. J. Obstet. Gynecol*., 140, 799–806, 1981.
59. Beck, L.R. et al., Poly(DL-lactide-co-glycolide)/norethinsterone microcapsules: an injectable biodegradable contraceptive capsule, *Biol. Reprod*., 28, 186–195, 1983.
60. Pitt, C.G., Marks, T.A., and Schlinder, A., *Natl. Inst. Drug Abuse Res. Monogr. Ser*., 28, 232–252, 1980.
61. Ory, S.J., Hammond, C.B., Yancy, S.G., Hendern, R.W., and Pitt, C.G., The effect of a biodegradable contraceptive capsule (Capronor) containing levo-norgestrel on gonadotropin, estrogen, and progesterone levels, *Am. J. Obstet. Gynecol*., 145, 600–605, 1983.

62. Croxatto, H.B., Diaz, S., Pavez, M., Miranda, P., and Brandeis, A., Plasma progesterone levels during long-term treatment with levo-norgestrel silastic implants, *Acta. Endocrinol*, 101, 307–311, 1982.
63. Sivan, I. et al., Three-year experience with Norplant subdermal contraception, *J. Fertil. Steril*., 39, 799–808, 1983.
64. Faundes, A., deMejias, V.B., Leon, P., Robertson, D., and Alvarez, F., First-year clinical experience with six levo-norgestrol rods as subdermal contraception, *Contraception*, 20, 167–175, 1979.
65. Blackshear, P.J., Implantable pumps for insulin delivery: current clinical status. In *Drug Delivery Systems, Fundamentals and Techniques*, Johnson, P. and Lloyd-Jones, J.G., Eds., Ellis Horwood, VCH Publishers, Chichester, 139–149, 1987.
66. Blackshear, P.J., Rohde, T.D., Prosl, F., and Buchwald, H., The implantable infusion pump: A new concept in drug delivery, *Med. Prog. Technol*., 6, 149–161, 1979.
67. Blackshear, P.J., Implantable drug-delivery systems, *Sci. Am*., 241, 66–73, 1979.
68. Blackshear, P.J. and Rohde, T.D., Artificial devices for insulin infusion in the treatment of patients with diabetes mellitus. In *Controlled Drug Delivery*, Vol. 2, Bruck, S.D., Ed., CRC Press, Inc., Boca Raton FL, 111–147, 1984.
69. Blackshear, P.J., Implantable infusion pumps: Clinical applications. In *Methods in Enzymology*, Vol. 112, Colowick, S.P. and Kaplan, N.O., Eds., Academic Press, Inc., New York, 520–530, 1985.
70. Blackshear, P.J., Wigness, B.D., Roussell, A.M., and Cohen, A.M., Implantable infusion pumps: Practical aspects. In *Methods in Enzymology*, Vol. 112, Colowick, S.P. and Kaplan, N.O., Eds., Academic Press, Inc., New York, 530–545, 1985.
71. Fischell, R.E. et al., A programmable implantable system (PIMS) for the treatment of diabetes, *Artif. Organs*, 7A, 82, 1983.
72. Blackshear, P.J., Rupp, W.M., Rohde, T.D., and Buchwald, H., A totally implantable constant-rate insulin-infusion device: Preliminary studies in Type II diabetic subjects. In *Artificial Systems for Insulin Delivery*, Brunnetti, P., Alberti, K.G.M.M., Albisser, A.M., Heff, K.D., and Mussin Benedetti, M., Eds., Raven Press, New York, 131–139, 1983.
73. Citron, P., Benefits of programmable implanted drug administration. In *The Latest Developments in Drug Delivery Systems*, *Conf. Proc. Pharm. Tech*., 20–22, 1987.
74. Halberg, F. et al., Toward a chronotherapy of neoplasis: tolerance of treatment depends upon host rhythms, *Experientia*, 29, 909–934, 1973.
75. Hrushesky, W., Circadian timing of cancer chemotherapy, *Science*, 228, 73–75, 1985.
76. Levi, F. et al., in *Chronobiology: Principles and Applications to Shifts in Schedules*, Scheving, L.E. and Halberg, F., Eds., Sijthoff and Noordhoff, The Netherlands, 481–511, 1980.
77. Roemeling, R.V. et al., Time of day modified continuous FUDR infusion, using an implanted programmable pump, improves therapeutic index. Abstract from *ASCO Proceedings*, 1986.
78. Penn, R.D. et al., Cancer pain relief using chronic morphine infusions: early experience with a programmable implanted drug pump, *J. Neurosurg*., 61, 302–306, 1984.

79. Penn, R.D., Drug pumps for treatment of neurological diseases and pain, *Neurologic Clinics*, 3, 439–451, 1985.
80. Penn, R.D. and Kroin, J.S., Long-term baclofen infusion for treatment of spastcity, *J. Neurosurg*., 66,181–185, 1987.
81. Roemeling, R.V. and Hrushesky, W., Circadian shaping of FUDR infusion reduces toxicity even at high-dose intensity, Abstract from *ASCO Proceedings*, 1987.
82. Lee, P.I. and Leonhardt, B.A., *Proc. 14th Int. Symp. Control. Rel. Bioact. Mater.*, August 2–5, 1987, Toronto, Canada.
83. *Program and Abstracts of the 15th Int. Symp. Control. Rel. Bioact. Mater.*, August 15–19, 1988, Basel, Switzerland.
84. Dedrick, R.L., Lutz, R.J., and Zaharko, D.S., U.S. Patent 3,946,734, 1976.
85. Schopflin, G., U.S. Patent 4,012,497, 1977.
86. Ellinwood, E.H. Jr., U.S. Patent 4,003,379, 1977.
87. Kuhl, D. and Luft, G., U.S. Patent 4,140,122, 1979.
88. Wichterle, O., U.S. Patents 3,971,378, 1976 and 3,896,806, 1975.
89. Michaels, A.S., Bashwa, J.D., and Zaffaroni, A., U.S. Patent 3,901,232, 1975; Michaels, A.S., U.S. Patent 3,788,322, 1974.
90. Labhasetwar, V., Kadish, A., Underwood, T., Sirinek, M., and Levy, R.J., The efficacy of controlled-release D-sotalol-polyurethane epicardial implants for ventricular arrhythmias due to acute ischemia in dogs, *J. Control. Rel*., 23/1, 74, 1993.
91. Deasy, P.B., Finan, M.P., Klatt, P.R., and Hornkiewytsch, T., Design and evaluation of a biodegradable implant for improved delivery of oestradiol-17 beta to steers, *Int. J. Pharmaceut*., 89, 251–259, 1993.
92. Skjak-Barek, G. et al., Canadian Patent CA 2,034,641.
93. Shindler, A. and Hollomon, M., PCT Int. Appl. (WO)91 16, 887, *Pharm. Technol.*, March 1993, 178.
94. SCRIP No. 1841, July 27th, 1993, 23.
95. Eckenhoff, B., Theeuwes, F., and Urquhart, J., Osmotically actuated dosage forms for rate-controlled drug delivery, *Pharm. Technol.*, June 1987, 96–102.
96. Theeuwes, F. and Bayne, W., Dosage form index, an objective criterion for evaluation of controlled-release drug delivery systems, *J. Pharm. Sci*., 66, 1388–1392, 1977.
97. Urquhart, J., Methods of drug administration. In *Proc. National Academy of Sciences,* Institute of Medicine, Conf. on Pharmaceuticals for Developing Countries, 329–348, 1979.
98. Chang, C.Y. and Yamada, S., Evaluation of the regenerative effect of a 25% doxycycline-loaded biodegradable membrane for guided tissue regeneration, *J. Periodontal*., 71, 1086–93, 2000.
99. Denissen, H. et al., Normal osteoconduction and repair in and around submerged highly bisphosphonate-complexed hydroxyapatite implants in rat tibiae, *J. Periodontal*., 71, 272–8, 2002.
100. Kortesue, P. et al., Silica xerogel as an implantable carrier for controlled drug delivery: Evaluation and tissue effects after implantation, *Biomaterials*, 21, 193–8, 2000.
101. Bessho, K. and Carnes, D.L., BMP stimulation of bone response adjacent to titanium implant *in vivo*, *Clin. Oral Implants Res*., 10, 212–8, 1999.

102. Goeau-Brissonniere, O. et al., Resistance of antibiotic-bonded gelatin-coated polymer meshes to *Staphyloccus aureus* in a rabbit subcutaneous pouch model, *Biomaterials*, 20, 229–32, 1999.
103. Aravind, S. et al., Polyethylene glycol (PEG)-modified bovine pericardium as a biomaterial: A comparative study on immunogemicity, *J. Biomater. Appl.*, 13, 158–65, 1998.
104. Witso, E. et al., Cancellous bone as an antibiotic carrier, *Acta. Orthop. Scand.*, 71, 80–4, 2000.