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Overview of Delivery Systems for the Administration of Contraceptives to Wildlife

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Abstract: Successful contraception in wildlife requires both an efficacious and safe contraceptive agent and an efficacious and safe method of delivering that agent to the animal. Remote delivery systems (RDS)—mechanical devices capable of administering a single dose to an unrestrained animal, usually by means of a ballistic projectile—can target specific animals and facilitate the administration of contraceptives on a body weight basis. Liquid, solid, and semisolid formulations can be delivered via RDS, and sometimes treatment costs can go down with this methodology. Disadvantages of RDS include the fact that many of them can be used only on larger animals and RDS' inherent complexity increases the probability of administration failure.

Most RDS use a powered gun to deliver either a dart or biobullet containing the contraceptive product. Biobullet RDS are capable of treating many animals rapidly. Both darts and biobullets can be designed to deliver different formulations to provide controlled release of contraceptives at a predetermined rate for a given period. The four general classes of controlled release systems (mechanical pumps, osmotic pumps, chemically controlled systems, and diffusional systems) are discussed. Chemically controlled and diffusional systems comprised of biodegradable polymers offer the most promise for single-dose, prolonged contraceptive release that can be remotely delivered to wildlife.

Keywords: controlled release, drug delivery, wildlife contraception, polymers

Introduction

There are two fundamental components required for the successful use of contraceptives in wildlife: (1) an efficacious and safe contraceptive agent and (2) an efficacious and safe method of delivering that agent to the animal. Many delivery systems are available to administer contraceptives to wildlife, ranging from surgically implanting devices into individual animals (Bell and Peterle 1975, Matschke 1980, Plotka et al. 1992) to dispersing oral baits over a wide area to an entire population (Matschke 1977, Roughton 1979).

Traditionally, the term "drug delivery system" has resided in the domain of human medicine, where it refers to mechanical or chemical methods to protect drugs from immediate degradation (e.g., in the stomach) or to prolong or control their release. The efficacy of these systems does not depend on first getting one's hands on the subject; the patient is seen as a willing partner in the process. Obviously, wild animals cannot be counted on to cooperate with biologists. So drug delivery systems take on a different meaning when applied to wildlife.

There are at least two facets of drug delivery of importance relative to wildlife contraception: (1) getting the contraceptive agent into the animal and (2) controlling the release of the drug in a manner that either maximizes or prolongs its efficacy. This chapter will describe devices for remotely delivering contraceptives to individual, unrestrained animals. Technologies for drug release *into* the animal will also be reviewed as they must work in concert with any primary delivery device.

Remote Delivery Systems

For purposes of this discussion, remote delivery systems (RDS) will be defined as mechanical devices capable of administering a single dose to an unrestrained animal, usually by means of a ballistic projectile. In their most elemental form, RDS consist of a gun and a dart containing a product. Although the bulk of this discussion will focus on these ballistic systems, other technologies will be reviewed because they may contribute to the development or administration of wildlife contraceptives.

Remote drug delivery dates to pre-Columbian times, when aboriginal natives of Africa and South America dipped arrows, spears, and blow darts in preparations of muscle-paralyzing drugs derived from plant and animal sources (Bush 1992). Modern delivery systems have their genesis in the 1950's, when the first projectile dart capable of delivering a liquid drug was reported (Crockford et al. 1957). This dart became the predecessor of darts still used today.

Many types of delivery systems were developed in the following 3 decades, but only a few proved reliable and versatile enough to survive competition in a limited market (Harthoorn 1976, Jones 1976, Kock 1987).

The operational definition of RDS implies administration to an individual animal. This may appear to be antithetical to wildlife *population* management; however, RDS can solve many wild animal population problems. In many situations, wildlife populations functionally exist as if they were confined to islands. Such populations have limited opportunities for immigration/emigration and are usually not subject to the population-control factors of predation and hunting. In these situations, populations usually thrive and increase until the forage base is depleted, and then disease and starvation lead to population reduction. Many of these populations are also generally visible and accessible by road or trail systems. Examples include natural areas within urban settings, airports, military arsenals, parks, and zoos.

Use of RDS need not be limited to such confined settings, however. Many species are accessible because they inhabit open environments such as deserts, prairies, or tundra. Such species can usually be approached from the air so that selected individuals or entire herds can be treated. Examples include feral horses, mountain goats, and polar bears.

Advantages and Disadvantages

Using RDS to administer contraceptives offers at least six advantages:

1. *Specific animals can be targeted.* Animals can selected and treated based on sex, size, age, or status.

2. *Contraceptives can be administered on a body weight basis.* Biologists familiar with a species can often estimate body weights of free-ranging animals quite accurately. Fairly precise doses can then be administered under field conditions if necessary for research purposes or efficacy.

3. *Different formulations can be employed.* Solid, semisolid, or liquid formulations can be delivered by RDS.

4. *A wide range of volumes can be delivered.* Depending on the projectile type and volume, liquid doses ranging from a few microliters to as much as 25 mL and solid doses up to 300 mg can be delivered.

5. *Some RDS can both treat and mark individual animals.* Some projectiles can be equipped with marking dyes and others can deliver electronic identification devices along with the contraceptive.

6. *The treatment cost per animal can be low.* When compared to contraceptive delivery methods requiring capture of the animal (e.g., implants), RDS greatly reduce the cost of treating each animal (but see #1 below). Some RDS can treat large numbers of animals rapidly, reducing costs as much as 60 percent when compared to capturing and treating individuals.

At least six disadvantages of using RDS to administer contraceptives merit consideration:

1. *The treatment cost per animal can be high.* Depending on the circumstances and taking into account all costs, such as labor hours and helicopter time, it can cost several hundred dollars to treat one animal using RDS.

2. *The target animal must be first located and then approached closely.* Under most circumstances, animals must be within 75 m of the shooter for projectile-RDS to be effective. Many species are secretive and extremely difficult to locate, let alone approach closely.

3. *Many RDS can be used only on larger animals.* Those RDS using projectiles are not terribly accurate, and the preferred target area on smaller animals may only be a few square centimeters. If the shot is misplaced, it may injure or kill the animal outright. Even if placed correctly, the impact energy or penetration depth could be injurious or lethal to smaller animals. As a working rule, only animals weighing > 15 kg (33 lb) should be targeted when powered (e.g., CO_2 or .22-cal. systems) RDS are used.

4. *RDS are inherently complex.* Many system variables can fail or affect successful delivery. A working maxim could well be, "Everything that can possibly go wrong with RDS eventually will!"

5. *Many RDS are noisy.* Some RDS may spook other animals after the first shot is fired, rendering subsequent shots at other animals difficult or impossible.

6. *Training and experience are necessary.* RDS should not be used without some degree of formal instruction by experienced practitioners of remote delivery techniques, and RDS should never be used without fairly intense practice by the user in order to assess the performance of the device prior to using it on an animal.

Longbows/Crossbows

Projectiles containing drugs or biologics have successfully been delivered using blowpipes, longbows, crossbows, pistols, shotguns, and rifles. Arrows or crossbow bolts can be modified to administer a liquid product up to 5 mL upon impact (Anderson 1961, Short and King 1964, Hawkins et al. 1967). Longbows and crossbows, though, have generally fallen out of favor because of impact trauma. If used at all, they are usually limited to larger animals shot at long ranges. I believe there are no commercial manufacturers of longbow or crossbow RDS in North America.

Blowpipes

There are several makes of blowpipes on the market today. Most of them consist of one- or two-piece aluminum tubes measuring up to 2 m. Most propel 10-mm darts (measured by their diameter) having a maximum capacity of 3 mL. Blowpipes are silent and fairly accurate, but their effective range is limited (< 20 m). Darts propelled by blowpipe cause very little impact trauma to the animal, so they are generally safe for use on smaller species. With the appropriate equipment, animals as small as 3 kg (6.6 lb) can be treated. Blowpipes are used primarily on captive animals but can be used effectively on free-ranging animals under the right circumstances, such as treed animals or animals approached closely by vehicle (Brockelman and Kobayashi 1971, Haigh and Hopf 1976). Prices range from $75 to $160 (all monetary figures in this chapter are expressed in 1995 U.S. dollars).

Powered Blowpipes

Powered blowpipes or "blowpipe guns" are blowpipes modified to use compressed air to extend their effective range. Blowpipe guns consist of the blowpipe aluminum tube connected to a pistol grip containing a metering device. Air is compressed by a foot pump connected by a hose to the pistol grip. After the desired pressure has been built up in the reservoir, the hose can be disconnected. When the trigger is pulled, the compressed air is released, propelling the dart. Similarly, some powered blowpipes use CO_2 cartridges that feed into a reservoir that can be adjusted to either increase or decrease the amount of pressure. Because the dart flight distance is proportional to the pressure built up in the reservoir, these devices have a wide effective range (from 1 to 40 m). Blowpipe guns propel the same type of lightweight darts (10–11 mm in diameter and 1–3 mL in volume) as do blowpipes, and these guns are silent and safe for use on smaller animals. Prices range from $225 to $375.

Dart Guns

The most widely used RDS are dart-shooting guns. Some dart guns have been constructed by modifying existing shotguns, rifles, pistols, pellet rifles, or pellet pistols; other guns are almost entirely custom designed and manufactured for this purpose. Dart guns propel darts by either the gas generated from a .22 caliber blank cartridge, compressed CO_2, or compressed atmospheric air. Dart-firing guns are the most versatile of the RDS. Effective ranges can reach 100 m for larger animals having larger target areas. Dart volumes can be as much as 25 mL, although these larger, heavier darts drop rapidly after leaving the barrel, making longrange, accurate shots difficult. All darts, of course, begin falling as soon as they leave the barrel, but small darts (1–2 mL) traveling at higher velocities shoot flatter and go farther than large darts. Guns can be equipped with a variety of sights, including adjustable iron sights, rifle scopes, laser aiming devices, and light-intensifying scopes (night vision or starlight scopes). Prices range from $300 to $1,650.

Table 1. Characteristics of powered remote delivery systems

Category	.22-caliber Blank	CO_2	Compressed air
Maximum effective range (m)	75	50	50
Volumes (mL)	1–25	1–10	1–10
Availability of propellant	High	Medium[1]	Low[2]
Temperature sensitivity	None	Medium	None
Impact injury	High[3]	Medium	Medium–Low
Report	Medium–High	Medium–High	Medium–High
Maintenance	High	Low	Low
Performance reliability	Medium	High[4]	High
Ease of use	High	High	Low
Overall versatility	High	Medium	Low

[1] There are two general types of CO_2 cartridges: threaded and unthreaded. Most sporting goods stores carry the smaller, unthreaded CO_2 cartridge, but the larger, threaded CO_2 cartridge may be very difficult to procure when working in rural areas.

[2] This rating refers to systems using compressed air tanks only and does not apply to systems using foot pumps. Most fire departments can fill air tanks but are reluctant to do so because of liability concerns. Welding shops may have compressed air, but not always. Scuba shops have air compressors, but they usually do not have the necessary fittings required for the tanks used with dart guns.

[3] Twenty-two-caliber blanks come in a variety of strengths. Charge strengths are coded by different colors, usually brown, green, yellow, or red, with red being the most powerful. Darts propelled with either yellow or red charges are capable of causing significant injury or death.

[4] CO_2 cartridges generally provide consistent performance except when the propellant runs low. There is only a subtle drop in performance between the last acceptable shot and the next shot where the dart drops precipitously due to a rapid drop in pressure. Experienced shooters often allow only a fixed number of shots per cartridge before changing cartridges even though some shots remain.

Table 1 lists the advantages and disadvantages of the three types of dart-gun propulsion systems. Ten criteria have been analyzed.

Maximum Effective Range—This is the maximum distance at which the dart can be safely and effectively delivered. The range of most guns can be decreased from this maximum either by using a built-in metering device which directs little or all of the gas to the dart, by using different strengths of propellant (i.e., different sizes of .22 blanks), or by pushing the dart farther down the barrel to reduce its velocity and thus its range.

Volumes—Dart volumes range from 1 to 25 mL; however, not all systems are capable of delivering this full range of dart sizes.

Availability of Propellant—This category rates the ease of obtaining the propellant from local suppliers.

Temperature Sensitivity—The vapor pressure of some gases (e.g., CO_2) is temperature dependent. At cold temperatures, darts travel less far due to decreased vapor pressure. In extremely cold conditions, some guns may barely function without some means of warming the gas.

Impact Injury—The impact energy of the dart striking the animal is a function of its mass and velocity ($KE = 1/2\ MV^2$). Table 2 compares the relative muzzle kinetic energy of three darts of the same volume but from different manufacturers. Even on a large animal struck correctly, the dart can cause hemorrhage and hematoma. Misplaced shots can break bones or even kill the animal (Thomas and Marburger 1964).

Report—Muzzle report can cause problems in darting either captive or free-ranging animals. In captive situations, the noise can be more disturbing to animals than getting struck with a dart. Disturbed animals are then more difficult to approach, or the entire group of animals may run away.

Maintenance—Some systems need to be cleaned frequently in order to remain operable.

Performance Reliability—Systems are classified regarding consistency of shot-to-shot performance.

Ease of Use—Systems are classified relative to their simplicity of operation or ease of use under field conditions.

Overall Versatility—The above categories are evaluated to arrive at a subjective opinion on the overall versatility of the propulsion system.

Table 2. Comparison of muzzle velocity and kinetic energy of 2-mL darts representing three different brands

Brand	Weight	Muzzle velocity	Kinetic energy
	(g)	(ft/sec)	(ft-lb)
Pneu Dart®	9.8	284.2	27.7
Aeroject®	13.3	256.9	30.1
Cap-Chur®	17.3	249.7	37.1

Data represent the mean value of three firings. All darts were fired from a CO_2-powered gun using fresh charges between dart types. Muzzle velocities were measured by chronograph 0.5 m from the muzzle. Muzzle energy was calculated by standard formula. Nonmetric values are reported in order to compare with other ballistic data. All darts contained 2 mL (2 g) saline.

Darts

Most projectile RDS use a dart to deliver liquid or viscous products. Darts can be thought of as "flying syringes" consisting essentially of a needle, body, plunger, and tailpiece. They differ in the manner in which the plunger is pushed forward to inject the dart's contents and in the materials of construction. Darts have also been used to implant small, solid devices, such as electronic transponders (Kreeger, unpubl. data). Theoretically, darts equipped with large-bore needles could also deliver semisolid or solid implants required for controlled drug release (see In Vivo Drug Delivery Systems).

Darts discharge their contents either by expanding gas from an explosive powder charge, compressed air, vaporized gas (butane), chemical reaction (acid–base), or compressed spring (fig. 1). The mechanisms that enable the dart to discharge its contents upon impact range from moderately simple systems having few parts to complex systems of intricate design and operation.

Dart bodies can be made of aluminum or synthetic polymer (polypropylene, polycarbonate, etc.). Dart tail designs range from elaborate fins molded from synthetic polymers to simple strands of yarn stuffed into the back of the dart (Corson et al. 1984).

Dart needles can be as large as 75 mm long and 2.16 mm in inside diameter. Darts using explosive

charges expel their contents in <0.001 second and thus require large-bore needles to allow the rapid expulsion of liquid. Needles are designed to either expel contents from the standard front opening (end port) or through a side port with the front opening occluded. End-port needles expel their contents more rapidly than do side-port needles, but large-bore needles can become plugged with a core of tissue when they penetrate hide and muscle (Henwood and Keep 1989).

Needle shafts can be smooth, or they can be equipped with a variety of barbs or collars to retain the dart in the animal. Smooth-shafted needles are used to deliver the drug and then fall out on their own, eliminating the need to capture the animal to remove the dart. If the dart contents are under high pressure, however, smooth-shafted needles can "rocket" back out of the animal due to the expulsion of the liquid and therefore not fully inject the substance.

Some needles are equipped with small collars that barely secure the dart in the animal but eventually fall out on their own. One company (Pneu-Dart) manufactures a gelatin collar that is rigid when dry but dissolves when it comes into contact with tissue fluids. These collared darts stay in the animal long enough to ensure complete expulsion of the contents but still fall out on their own later.
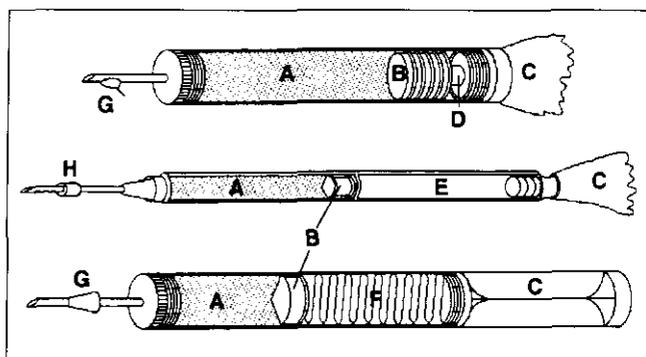

Figure 1. Schematic drawing of typical construction used in darts. (A) drug chamber, (B) movable plunger, (C) tail piece, (D) explosive charge, (E) compressed air chamber, (F) spring, (G) barb, (H) needle collar (slides back to discharge drug after dart penetrates skin).

To retain the dart in the animal securely, either spring barbs or metal collars are used. These darts require manual removal from the animal. Experiments with retractable barbs have been successful, but these are not commercially available (Van Rooyen and De Beer 1973, Smuts 1973). Barbed darts usually create a greater wound upon removal than do collared or barbless darts. Some barbs are so tenacious that they can be removed only with a scalpel.

Darts can be modified to mark as well as treat the animals that they hit. Darts can be equipped with dye-filled bladders fixed to the base of the needle that burst upon impact to mark the treated animal (Bush 1992). These bladders also serve as cushions to decrease the impact trauma of the dart. Another dart (Pneu-Dart) utilizes a "piggy-back" tailpiece containing the dye or paint that breaks loose from the dart body upon impact to spray the area.

Darts can also be equipped with small radio transmitters enabling location of animals that have run off after being darted with immobilizing drugs (Nielsen 1982, Lawson and Melton 1989). The effective transmitter range of these darts is usually <300 m, but the technology of small transmitters that can withstand impact energy holds promise of extended ranges. The price for such darts complete with reusable transmitter is $100 to $150.

The advantages and disadvantages of each dart injection system are listed in table 3. The following criteria were analyzed.

Injection Speed—If injection speed is rapid (e.g., <0.001 second), tissue can be injured and absorption slowed. However, if injection speed is slow, the animal (e.g., carnivores) may have time to remove the dart before all the contents have injected.

Weight—Lightweight darts may cause less impact when they strike the animal (table 2), but lightweight darts traveling at high speeds may be more subject to wind drift and prop wash.

Volume—This category lists the volumes capable of being delivered by each system.

Table 3. Characteristics of dart types

Category	Powder	Com-pressed air	Gas[1]	Spring
Injection speed	Rapid	Slow	Moderate	Moderate
Weight	Light–Heavy	Light	Light	Medium
Volume (mL)	1–25	1–10	1–6	2–3
Reliability	High	Medium	Medium	High
Contents under pressure	No	Yes	Yes/No	Yes

[1] Gas can be from either butane or acid–base mixture. Gas darts may be pressurized prior to firing or develop gas pressure after striking the target.

Reliability—Dart systems are rated based on consistency of injecting the entire dart contents.

Contents Under Pressure—This is a Yes/No rating only. The contents of some dart systems are pressurized when they are initially loaded. This type of dart is more prone to leaking or spraying contents than are darts that do not develop any expulsion pressure until they strike the animal.

Biobullets

A .25-caliber, biodegradable implant (biobullet) was developed to remotely administer biologics and pharmaceuticals to domestic and wild animals. Biobullets have been used successfully to treat elk *(Cervus elaphus)*, bighorn sheep *(Ovis canadensis,)* bison *(Bison bison)*, gray wolves *(Canis lupus)*, fallow deer *(Dama dama)*, roan antelope *(Hippotragus equinus)*, impala *(Aepyceros melampus)*, waterbuck *(Kobus lece)*, greater kudu *(Tragelaphus strepsiceros)*, wildebeest *(Connachaetes gnou)*, zebra *(Equus burchelli)*, and eland *(Taurotragus oryx)* (Jessup 1993, Kreeger unpubl. data).

There has been increasing interest in the potential of biobullets to deliver contraceptive products. Immunocontraceptives have been administered to white-tailed deer *(Odocoileus virginianus)* and feral horses *(Equus caballus)* using biobullets (Warren et al., this volume).

A biobullet is comprised of an outer, biodegradable casing and either a solid, semisolid, or liquid payload (fig. 2). Hydroxypropylcellulose (a food additive) and calcium carbonate are the primary components of the casing, which when injection-molded under high temperature and pressure, becomes a hard, plastic-like material. Upon entry into the animal and contact with tissue fluids, the casing immediately begins to dissolve and is entirely liquefied within 24 hours. The 10-sided bullet mates with a decagon-rifled barrel. This construction prevents the barrel fouling encountered with conventional land-and-groove rifling and allows for hundreds of rounds to be fired without cleaning.

The desired drug is inserted into the hollow base of the casing and can dissolve immediately upon contact with tissue fluids, if so designed. Freeze-dried vaccine pellets, for instance, dissolve completely within 3 hours, and concentrations of pharmaceuticals are detectable in the blood 30 minutes after administration (Kreeger, unpubl. data). Because the casing dissolves upon contact with a solvent, liquid formulations need to be first placed into a gelatin capsule then the capsule inserted into the casing. Semisolid formulations, such as silicone rubber, can be dispensed directly into the casing.

Currently, the casing is manufactured to deliver a 125- to 300-mg payload. The exact specifications of each casing are presented in table 4. Both casings

Figure 2. Biodegradable, 0.25-caliber biobullet showing position of payload and decagon rifling.

Table 4. Specifications of biobullet casing

Casing	Weight empty	External length	External width	depth	Cavity width	volume
	(mg)	(mm)	(mm)	(mm)	(mm)	(µL)
"Short"	481.0	14.66	6.43	6.60	4.06	85.44
"Long"	556.0	20.95	6.43	14.22	4.85	262.68

are .25 caliber (6.43 mm diameter), but .20-caliber (5.08-mm) biobullets have been developed and used successfully.

The maximum effective range is approximately 25 m. Longer ranges can be achieved by increasing the velocity and/or by formulating a heavier casing. Faster or heavier biobullets, though, would then have a *minimum safe* range because such projectiles could penetrate thin-skinned or small animals too deeply if shot at close distances. The average penetration distance in the hindquarter muscle mass of cattle is from 5 to 7.5 cm. Small-caliber or lighter weight bullets could be developed to decrease penetration, if necessary.

Biobullets are currently delivered by a clip-fed, pump-operated, compressed air-powered rifle. The compressed air is delivered by either a 1.44- or 2.78-L air tank. The larger tank can fire 300–350 biobullets before refilling. The biobullet is propelled at approximately 900 ft/sec. A single-shot, compressed-air rifle has also been developed that eliminates the need for an external air tank (Kreeger, unpubl. data).

The multiple shot capacity of the biobullet remote delivery system provides significant advantages over dart RDS for treating herds of animals. The preloaded biobullets eliminate loading time, spills, and accidental human exposure while ensuring complete dosage delivery. Another benefit of biobullets over darts is that if the animal is missed, the biobullet will completely degrade within a few days, reducing the possibility of human exposure.

The disadvantages of the biobullet RDS are the limited payload (300 mg), limited range (25 m), possible difficulty in refilling the air tank, and cumbersome system of air tank, regulator, hose and gun.
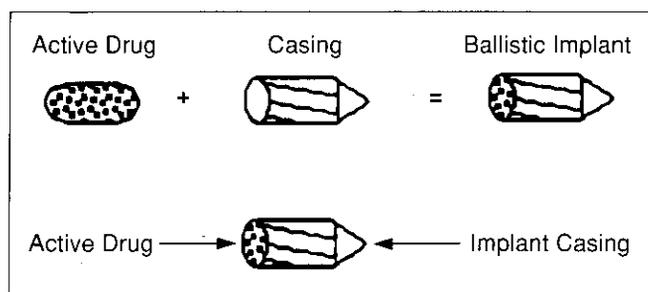
Biobullets have been used to administer electronic identification transponders (Trovan®) to cattle; but the operation of the transponder after delivery was variable, and this technique requires further development (Kreeger, unpubl. data). If transponders could be developed to withstand the impact of ballistic delivery, both a contraceptive and a transponder could be administered simultaneously. Thus, treated animals would be permanently marked which could aid field data collection and efficacy testing.

Theoretically, a polymeric (see below) biobullet could be manufactured so that the entire biobullet becomes a controlled drug delivery device. This technique could provide even greater flexibility in payload and dissolution rates.

Other Drug Delivery Systems

Although probably not a true remote delivery system in the context of this discussion, the remote capture collar (RCC) is a device that could aid researchers in the field evaluation of contraceptive safety and efficacy. The RCC is essentially a radiotelemetry collar that not only provides a location signal from the animal but also allows the researcher to remotely inject either an immobilization drug or a contraceptive product at the push of a button. The RCC allows multiple recaptures of the same animal providing long-term opportunities for pregnancy diagnosis, blood and urine sampling, contraceptive readministration, physical evaluation, and the collection of other data that require animal sampling.

The RCC consists of a transceiver that emits a location signal and also signals animal activity, battery life, ambient temperature, and dart status. The general sequence of its use is as follows: an animal must be initially captured by some means and the RCC fitted and the darts loaded with an anesthetic or other product. Currently, the darts can deliver 1.5 mL of a liquid product per dart. Usually, a single anesthetic dose is concentrated in each dart, allowing a backup dart should the first one fail to completely anesthetize the animal. However, a dart could also contain a liquid contraceptive which could be adminis-

tered sometime after the animal was initially captured and treated. This feature may be useful for immunocontraceptives requiring repeated doses. At some later date, the researcher relocates the animal via the radio signal and moves to within 3.2 km (2 miles) and transmits a signal to fire one of the darts. The RCC then signals back if the dart successfully fired. The researcher can then monitor the animal's activity via the activity signal; when that signal indicates no activity, the animal is assumed to be immobilized and the researcher can close in on it using the radio signal.

Once the anesthetized animal has been located, new darts and batteries can be attached to the collar, samples taken, and data collected. If the batteries fall below a certain voltage, or both darts are triggered without the animal becoming immobilized, or simply at the command of the researcher, the RCC will disengage from the animal and emit a low-level signal allowing recovery by the researcher without the need to recapture the animal. Again, this feature could allow revaccination or a second (or third) contraceptive treatment with recovery of the collar without the necessity of handling the animal.

The RCC has been successfully used on gray wolves, white-tailed deer, and black bear (Ursus americanus) (Mech et al. 1990). The collar sells for $1,495 and the triggering transmitter for $2,395.

Implant Guns

Implant guns are devices that insert implants either intramuscularly or subcutaneously and require capture and restraint (either chemical or physical) of the animal. Implant guns use belts or clips capable of holding up to 20 doses that are inserted via a large-bore needle. Implant guns are being used to administer progesterone, testosterone, etsradiol, norgestomet, or other substances. Drug substances can be in the form of pellets or polymers. One product combines an injectable solution with a controlled-release hydrophilic polymer to provide an immediate as well as a delayed effect with a single administration. Most products are intended as growth promotants for production animals, but some are used to synchronize estrus in cattle.

Implant guns thus provide a means of inserting a variety of formulations without the need for a surgical incision and implantation. Animals can be treated quite rapidly and released immediately after treatment if manually restrained. Nonbiodegradable implants can be inserted into the ear, a desirable site because it will not be eaten if the animals are intended for human consumption. It may be possible to obtain implant guns and empty clips for those wishing to manufacture their own formulations for experimental use in wild animals.

In Vivo Delivery Systems

Very few drugs provide effective contraception after only a single administration. Immunocontraceptives, such as zona pellucida (ZP) vaccines, invariably require multiple administrations to create an anamestic response to develop and maintain effective titers. Steroid contraceptives and gonadotropin-releasing hormone (GnRH) agonists must be continually administered in order to remain effective over time. I have previously discussed how to get contraceptives *to* the animal, but it is equally important to review technologies that provide controlled release of the contraceptive *within* the animal.

Controlled-release systems (CRS) deliver a drug at a predetermined rate for a given period. The active ingredient in CRS differs from those in sustained-release preparations, which do not dissolve in the stomach yet do dissolve in the intestine. Generally, sustained-release systems release drugs in less than a day and are characterized by a drug concentration peak followed by a decline (Langer 1990). Multiple administrations of sustained-release preparations result in oscillations between these peaks and valleys. Sustained-release preparation are thus not uniform or "controlled." Controlled-release preparations are designed to reach and then maintain the drug within a desired therapeutic range following a single administration. The release rate of CRS should ideally be "zero order" in which the amount of drug released to the absorption site remains constant over time. Controlled-release preparations can also be designed

to preserve drugs that normally would be rapidly metabolized and destroyed.

Although the bulk of the following discussion will emphasize CRS that can be delivered remotely, it should not be forgotten that such systems can be administered to captured animals by a variety of means. Surgical implants, transdermal patches, and vaginal rings are all viable delivery systems that can be employed as determined by efficacy, economic, and animal safety considerations.

Classes of Controlled Release Systems

There are five general classes of CRS appropriate for wildlife contraception: mechanical pumps, osmotic pumps, chemically controlled systems, diffusional systems, and liposomes.

Mechanical Pumps—Implantable mechanical pumps have been tested and proven in human medicine for the delivery of insulin, heparin, and other agents. Some mechanical pumps are powered by hermetically sealed, compressible fluorocarbon pushing against a septum that separates the gas from the drug compartment. The vapor pressure exerted by the propellant forces the drug solution through a filter and flow regulator at a constant rate. Mechanical pumps have to be surgically implanted and are relatively expensive, but they can be refilled and are capable of precise drug control. Their use for wildlife contraceptives is probably limited to research applications.

Osmotic Pumps—Osmotic pumps are devices consisting essentially of a liquid drug reservoir surrounded by an osmotically active polymer ("energy source") which, in turn, is surrounded by a water-permeable membrane (fig. 3). The osmotically active polymer maintains a constant water gradient across the rate-controlling membrane. The polymer acts as an energy source to create hydrostatic pressure on the reservoir. The reservoir consists of a soft, low modulus drug-impermeable elastomer that releases a water-soluble drug through a small opening to the body when "squeezed" by hydrostatic pressure. At steady-state, these pumps follow zero-order kinetics (Eckenhoff and Yum 1981). More simply, an osmotic pump or "osmotic tablet" can consist of a drug sub-
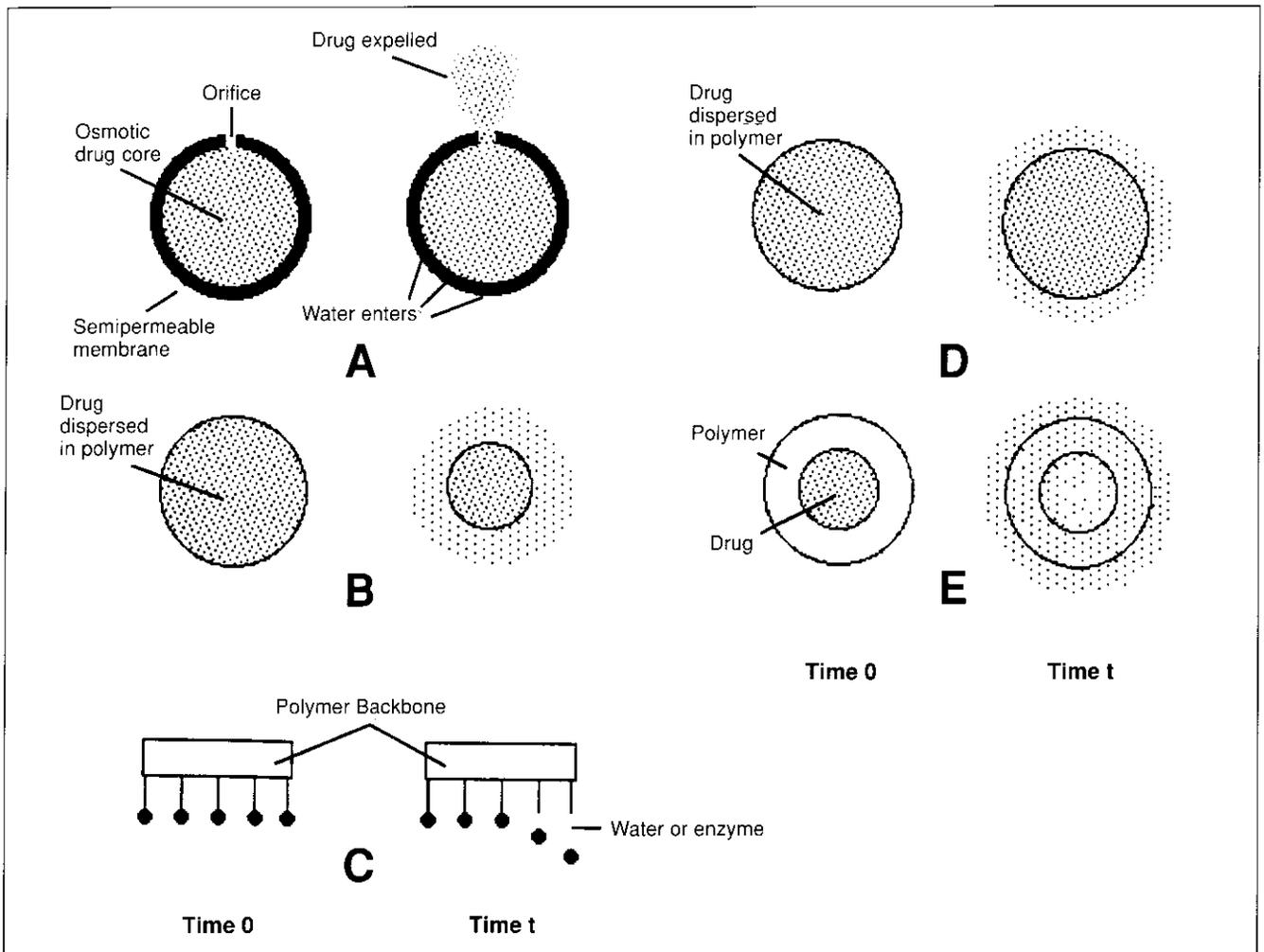
Figure 3. Polymer release mechanisms: (A) osmotic pump, (B) polymer degradation, (C) backbone cleavage, (D) diffusional matrix, (E) diffusional reservoir (after Langer 1990).

stance and an osmotic polymer or simple salt all surrounded by a semipermeable membrane. Osmotic hydration drives the drug out of a laser-drilled orifice (Squire and Lees 1992). Osmotic pumps need not be expensive, but they require animal capture and surgical implantation unless delivered by biobullet. However, depending on the potency of the drug substance, micro-osmotic pumps or osmotic tablets theoretically could be designed and delivered remotely.

Chemically Controlled Systems—The advantage of chemically controlled drug delivery systems over mechanical or osmotic pumps is that they need not be surgically implanted and they are biodegradable. Thus, no residues are left in the animal, which is not an unimportant concern in food-producing species. Release of the drug takes place by the following mechanisms:

1. Gradual biodegradation of a drug-containing polymer matrix. The drug substance can either by dispersed in the polymer matrix or encapsulated in it. The drug is released into the tissues at controlled

rates; the particular kinetics depend on the chemical composition of the polymer, the solubility of the drug in the polymer, and how the polymer matrix was prepared (fig. 3).

2. Cleavage of unstable bonds coupling a drug to a polymer backbone (fig. 3).

Diffusional Systems—Like chemically controlled systems, diffusional systems need not be surgically implanted nor removed if they are biodegradable. Drugs diffuse through polymers, leaving the polymer intact, or the polymer may biodegrade after the drug has been exhausted. There are two types of diffusional systems: reservoirs and matrices (fig. 3). Reservoirs can be surrounded by either a porous or nonporous membrane. In porous membrane reservoirs, the drug passes through liquid-filled pores of the polymer membrane rather than through the polymer itself. Thus, drug solubility within the liquid medium of the pores is more important than drug solubility in the polymer.

In matrix systems, the drug is distributed throughout the polymeric system. Such systems normally do not provide zero-order release because the drug is initially released from the outer layers and then released from sequentially deeper layers of the matrix.

Liposomes—Liposomes are vesicular structures built of one or more lipid bilayers surrounding an aqueous core. The backbone of the bilayer consists of phospholipids. Size, number of bilayers, bilayer charge, and bilayer rigidity determine in vivo performance. Liposomes deliver their contents through macrophage phagocytosis, membrane fusion, surface adsorption, or lipid exchange (Nässander et al. 1990).

Probably the earliest and certainly the most widely used controlled-release system for the delivery of contraceptives to wildlife employed silicone rubber (polydimethylsiloxane) implants (i.e., a diffusional system). In 1964, Folkman and Long determined that Silastic™ implants could deliver drugs for an extended period in dogs. Subsequently, silicone implants were devised to deliver steroid contraceptives to white-tailed deer and other species (Bell and Peterle 1975,

Seal et al. 1976, Matschke 1977, 1980). Silicone implants containing melengesterol acetate have been used to control fertility in dozens of species representing hundreds of individuals held in zoos. Silicone implants are not biodegradable and generally require surgical administration. More potent agents, however, may be delivered remotely via biobullets containing small, silicone implants (see Kesler, this volume).

In the 1980's and 1990's, research on the use of polymers as excipients for controlled drug release has virtually exploded. Polymers can be used to form microspheres, microcapsules, implants, coatings, and fibers. Polymeric CRS are biodegradable and offer versatility in terms of release rates and duration. Although research on the use of polymeric CRS for wildlife contraception is in its infancy, this technology probably offers the most promise to the wildlife biologist in the future.

Polymers

Polymers are high molecular weight substances, made up of a chain of identical, repeated base units. Many polymers used in CRS are polyesters, an ester being an organic compound formed by the elimination of H_2O between the -OH of an acid group and the -OH of an alcohol group. Thus when implanted in vivo, polyesters are usually biodegraded by simple hydrolysis as opposed to requiring enzymatic action.

It is possible to design polymeric implants or microspheres that could be remotely delivered by a dart or biobullet. Once implanted, the polymer would consistently release a contraceptive drug or vaccine over an extended period of time (Aguado 1993, Morris et al. 1994). For substances such as zona pellucida vaccines, polymers could be used to coat pellets or form microspheres of a lyophilized vaccine which would degrade at specific intervals to provide one or more boosters. Additionally, polymers have been developed that not only provide for the controlled release of antigen but do so from a biodegradable antigen delivery device which degrades into material with adjuvant properties (Kohn et al. 1986, Morris et al. 1994).

There are virtually hundreds of candidate polymers being studied for controlled release (Chasin and Langer 1990), and a discussion of their specifics is beyond the scope of this chapter. Three principal biodegradable polymers developed for controlled contraceptive steroid release are copolymers of lactic and glycolic acid (Beck and Tice 1983), poly–ε–caprolactone (Ory et al. 1983), and poly(ortho esters) (Heller et al. 1984). A brief discussion of these and other polymers is included below to familiarize the reader with this subject.

Lactide/Glycolide Polymers—Lactide/glycolide polymers are some of the most widely investigated biodegradable excipients for controlled drug delivery. Their advantage is versatility in polymer properties and performance characteristics. For wide applications in controlled drug delivery, it is imperative that a range of rates and duration of drug release be achievable (Lewis 1990).

Homopolymers and copolymers of lactic and glycolic acids are synthesized by ring-opening and melt condensation of the cyclic dimers, lactide and glycolide (Kulkarni et al. 1971). Additionally, lactic acid exists as either D or L stereoisomers; thus, D, L, or racemic DL polymers can be synthesized. Performance versatility is achieved through the various combinations of the stereoisomers of lactic acid and/or glycolic acid. Because biodegradation is achieved through hydrolysis of ester linkages, crystallinity and water uptake are key factors in determining the rates of in vivo degradation (Lewis 1990). For example, water uptake increases as the glycolide ratio in the copolymer increases (Gildling and Reed 1979, Rosen et al. 1988) so that copolymers having a high glycolide component degrade sooner than do lactide polymers (table 5).

Lactide/glycolide polymers also provide fabrication versatility. At least three types of CRS based on these polymers have been investigated: microcapsules or microspheres, implants, and fibers. Microspheres have been used to deliver a variety of steroids and steroid contraceptives, such as norethisterone, levonorgesterel, testosterone, testosterone propionate, progesterone, norgestimate, and

Table 5. Biodegredation of lactide/glycolide polymers (after Lewis 1990)

Polymer	Approximate biodegredation time
	(Months)
Poly(L-lactide)	18–24
Poly(D,L-lactide)	12–16
Poly(glycolide)	2–4
85:15 (D,L-lactide-co-glycolide)	5
50:50 (D,L-lactide-co-glycolide)	2
90:10 (D,L-lactide-co-caprolactone)	2

estradiol benzoate (Beck et al. 1979, 1980, 1981, 1983, 1985). A virtually infinite variety of lactide/glycolide polymer implants can be made by injection molding, compression molding, or screw extrusion. Rods comprised of 50:50 molar poly(D,L–lactide–co–glycolide) were successful in the extended, controlled release of a potent GnRH agonist in rats (Furr and Hutchinson 1992). Hollow fibers spun from poly(L–lactide) have been used for delivery of levonorgesterel (Eenink et al. 1987).

The rate and duration of steroid release is affected by (1) polymer composition, (2) drug:polymer ratio, (3) microsphere size distribution, and (4) microsphere quality (Lewis and Tice 1984). The smaller the microsphere, the higher the drug concentration and the shorter the duration of release due to the relatively greater surface area (Lewis 1990).

Lactide/glycolide polymers have also been used for controlled release of vaccines to provide initial and repeated antigen exposure in order to stimulate the desired anamestic response. Such technology could be useful for one-time administration of zona pellucida vaccines. A human contraceptive vaccine based on lactide/glycolide polymers is in development using a 37-amino acid peptide of beta–human chorionic gonadotropin (β–HCG as the antigen conjugated to diphtheria toxoid. The antigen is administered with microencapsulated muramyl dipeptide as an adjuvant

to provide 9–12 months of elevated antibody titers in rabbits after a single injection (Lewis 1990).

Over the last 2 decades, lactide/glycolide polymers as excipients for the controlled release of bioactive agents have proven to be both safe and efficacious in animal and human trials. The ready availability of these polymers from reputable firms, plus their versatility offer promise to biologists developing contraceptive delivery systems for wildlife.

Poly–ε–caprolactone—Poly–ε–caprolactone (PCL) was initially evaluated as a biodegradable packaging material to reduce environmental pollution due to its degradation by micro-organisms (Potts et al. 1973). The success of other polyesters such as poly(lactide) and poly(glycolide) as drug delivery systems led to the evaluation of the degradability of PCL in vivo (Schindler et al. 1977). The PCL homopolymer degrades very slowly compared to poly(glycolide) and appears to be quite suitable for long-term drug delivery, including contraceptives (Pitt and Schindler 1984). If desired, biodegradation of PCL can be enhanced by copolymerization with poly(DL–lactide) (table 5), and PCL has shown an exceptional ability to form compatible blends with a variety of other polymers as well (Koleske 1978, Pitt 1990).

PCL and its copolymers are highly permeable to low-molecular- weight (<400 daltons) drugs (Pitt et al. 1979a). As a comparison, the diffusion coefficient of PCL for several steroids is two orders of magnitude less than that of silicone rubber, but drug solubility is greater in PCL. Thus, the permeabilities (the product of the diffusion coefficient and solubility) of PCL and of silicone rubber are not greatly different (0.6×10^{-10} v. 2.2×10^{-10} g/cm·sec, respectively) (Pitt 1990). This high permeability of PCL and its copolymers coupled with controlled biodegradation lends PCL to the development of delivery devices that are based on diffusion-controlled drug delivery during an induction period prior to weight loss of the matrix. Subsequent biodegradation of the polymer eliminates the need for removal of the spent device (Pitt 1990).

Biodegradation of PCL begins with random hydrolytic chain scission of the ester linkages, manifested by a reduction in the viscosity and molecular weight of the polymer. This rate does not change despite 10-fold changes in the surface-to-volume ratio, indicative of a bulk process. Implant weight loss is not observed until polymer molecular weight has decreased to approximately 5,000 daltons, at which time there is a decrease in the rate of chain scission. Weight loss is then attributed to an increased probability the production of excised fragments that are small enough to diffuse out of the polymer bulk and to the breakup of the polymer mass to produce particles small enough to be phagocytized (Pitt 1990).

PCL can be formed into films, rods, microcapsules, or reservoir devices. Reservoir devices for the delivery of steroid contraceptives have been developed where drugs are surrounded by a PCL capsule that biodegrades after the drug is exhausted. Improved zero-order kinetics could be obtained by suspending the drug (levonorgestrel) in an oil within the PCL capsule (Pitt et al. 1979b). Increased permeability of reservoir devices can be obtained through copolymerization of PCL (Pitt et al. 1980).

Poly(ortho esters)—Although polymer diffusion systems have been developed to deliver contraceptive steroids, there is a need to develop systems where drug release is predominately controlled by polymer hydrolysis. Such polymers could be an important means of polypeptide delivery for those polypeptides that do not diffuse from polymers at useful rates, particularly as molecular weight increases (Heller et al. 1990).

Poly(ortho esters) are polymers containing acid-labile linkages in their backbones. Hydrolysis rates of poly(ortho esters) can be manipulated by incorporation of acidic or basic excipients into the matrix. Under certain conditions, the hydrolysis of such polymers could also be confined predominantly to the outer surface so that the resultant surface erosion allows excellent control of the release kinetics of incorporated therapeutic agents (Heller et al. 1990).

Two methods of controlling erosion rates of poly(ortho esters) are (1) using an acidic excipient to accelerate the rate of hydrolysis and (2) using a basic excipient to stabilize the interior of the device. When a hydrophilic polymer with a physically dispersed

acidic excipient is placed into an aqueous environ-
ment, water will diffuse into the polymer, dissolving the
acidic excipient. That dissolution lowers the pH to
accelerate hydrolysis of the ortho ester bonds (Heller
1985). Conversely, when long-term surface erosion is
desired, the addition of a basic excipient, such as
$Mg(OH)_2$, stabilizes the interior of the device so that
water penetration into the matrix does not lead to
hydrolysis. Theoretically, erosion can only then occur
at the surface where the base has been eluted or
neutralized. This is thought to occur by water intrusion
into—and diffusion of the slightly water-soluble basic
excipient out of—the matrix. Polymer erosion then
occurs in the base-depleted layer (Heller et al. 1990).

The use of basic excipients to control and
prolong release of contraceptive steroids was demon-
strated by Heller (1985 and 1986) and Heller et al.
1990. Polymer rods containing 30 percent
levonorgestrel by weight and 7.1 percent $Mg(OH)_2$ by
molecular weight were implanted subcutaneously in
rabbits. Polymer erosion and drug release appeared
to occur concomitantly, and bulk erosion was not
evident, indicating surface erosion. Blood concentra-
tions of levonorgestrel were reasonably constant once
the initial burst subsided.

Polyanhydrides—Aromatic polyanhydrides were first
synthesized in 1909 but did not receive much attention
until they were investigated as replacements for
polyester fiber. The major deficiency of polyan-
hydrides in this role was their hydrolytic instability;
however, this same instability rendered polyan-
hydrides attractive as biodegradable drug-carrier
matrices (Rosen et al. 1988). Generally, it is desirable
to have a polymeric system that degrades only from
the surface. To achieve such heterogeneous degrada-
tion, the rate of hydrolytic degradation at the surface
must be faster than the rate of water penetration into
the bulk of the matrix. This characteristic would also
aid in the delivery of water-labile drugs by making it
more difficult for water to interact with these sub-
stances until they are released (Chasin et al. 1990).

Polyanhyride homopolymer implants generally
erode completely, leaving no insoluble residue.
Throughout erosion, implants decrease in size while
retaining physical integrity, suggesting surface erosion
(Rosen et al. 1988). Erosion and drug release profiles
are approximately zero order, and complete release of
drug substance correlates with complete matrix
erosion. Copolymers of bis (p–carboxyphenoxy)
propane (PCCP) and sebacic acid (SA) can be
formulated to achieve degradation rates between 1 day
and 3 years depending on the PCCP–SA ratio; the
erosion rate increasing with an increasing proportion
of the hydrophilic SA (Leong et al. 1985).

Polyanhydride microspheres have been devel-
oped for the controlled release of proteins. In a recent
study, when trypsin was placed inside polyanhyride
microspheres, the activity loss was <10 percent at
37 °C for 12 hours compared to an 80-percent activity
loss for unprotected trypsin. The protein-loaded
microspheres displayed near zero-order erosion
kinetics without any large initial burst (Tabata et al.
1993).

Polyphosphazenes—Polyphosphazenes are a class
of polymers that can serve two quite different func-
tions: they can form inert, long-term structural compo-
nents, or they can be made hydrolytically unstable so
as to function as bioerodible materials. The hydrolytic
stability or instability is determined not by changes in
the backbone structure but by changes in the side
groups attached to a long-chain backbone of alternat-
ing phosphorus and nitrogen atoms. Side groups
attach to each phosphorus molecule, and these
groups can range from hydrophobic groups that confer
water insolubility that protect the backbone against
hydrolysis through groups that generate water solubil-
ity together with hydrolytic stability, to side groups that
provide a facile pathway for hydrolytic breakdown of
the polymer to innocuous, excretable, or metaboliz-
able molecules (Allcock 1990).

Poly- and Pseudopoly(amino acids)—Although
many biodegradable polymers have provided signifi-
cant treatment advantages, there is a continual
concern about potential toxicity associated with a
polymer that degrades in vivo. To alleviate this
problem, polymers have been derived using naturally
occurring nutrients or metabolites. The development
of poly(lactide) and poly(glycolide) polymers is a good

example of this approach. Poly(amino acids) have been extensively investigated as candidates for a material that does not give rise to toxic degradation products because these acids are derived from natural molecules. However, the number of promising materials has turned out to be quite limited. One of the major limitations of synthetic poly(amino acids) is the pronounced antigenicity of those poly(amino acids) containing three or more different amino acids. Another limitation is that synthetic poly(amino acids) may have undesirable material properties. For example, most synthetic poly(amino acids) derived from a single amino acid are insoluble, high-melting materials that cannot be processed into shaped objects by conventional fabrication techniques. Many poly(amino acids) also absorb a significant amount of water when in an aqueous environment (Kohn 1990). Nonetheless, natural poly(amino acids) have been developed that are nontoxic and biodegradable. Poly(g–glutamic acid) polymers, synthesized by *Bacillus lichenformi,* have successfully delivered porcine growth hormone over an extended period (Fan and Sevoian, unpubl. data).

To overcome these difficulties of synthetic poly(amino acids), pseudopoly(amino acids) have been developed. Pseudopoly(amino acids) replace the peptide bonds in the backbone of synthetic poly(amino acids) with a variety of nonamide linkages. In peptide chemistry, the term "pseudopeptide" often denotes a peptide in which some or all of the amino acids are linked by bonds other than peptide linkages. Thus far, few pseudopoly(amino acids) have been developed, but initial investigations support the theory that they tend to retain nontoxicity and good biocompatability often associated with conventional poly(amino acids) while at the same time exhibiting significantly improved material properties (Kohn 1990).

Conclusion

Whether contraceptives useful for wildlife population management will ever be developed, let alone employed, is currently unknown. Whatever technologies are ultimately devised, however, it will never be an easy task to administer contraceptives to wildlife. In the above discussion, readers have merely viewed the contraceptive iceberg from the surface. Because there are tremendous financial rewards in the field of delivery systems, an immense amount of research goes on unseen and unannounced by both public and private investigators.

Nonetheless, the future development of contraceptive delivery systems by both the human and veterinary medical communities will work in favor of the wildlife biologist. Many potential technologies were not even discussed in this review as they were deemed premature for wildlife applications. For example, it is possible that isolated cells, such as luteal cells, could be encapsulated and protected so as to continually elaborate progesterone to prevent estrus cycling (Sefton et al. 1992). Even viruses and bacteria could be drafted as contraceptive delivery systems to produce sperm or ZP antigens via recombinant DNA technology (Morell 1993).

Ultimately, methods of delivering contraceptives to wildlife may be as varied as the species targeted. No one technology is likely to satisfy all the concerns on efficacy, efficiency, and animal and human safety. Also, the exigencies of wildlife overpopulation occurring in so many locations and circumstances will require the efficient and selfless collaboration of all concerned scientists. Thus, technologies from many disciplines will have to be combined to provide biologists with the extensive and sophisticated armamentarium required to confront the task of wildlife population control.

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List of Manufacturers

Advanced Telemetry Systems
470 First Ave. N.
Isanti, MN 55040
(Wildlink™ Data Acquisition and Recapture System)

Palmer Chemical & Equipment Co., Inc.
P.O. Box 867
Palmer Village
Douglasville, GA 30133 USA
(Cap-Chur® RDS)

Paxarms Limited
P.O. Box 317
Tomaru, New Zealand
(Paxarms RDS)

Peter Ott AG
Vet. Med. Gerate und Pharmazeutica
Postfach, CH 4007
Basel, Switzerland
(Dist-Inject® RDS)

Pitman–Moore Inc.
421 East Hawley Street
Mundelein, IL 60060
(Ralgro® implants)

Pneu Dart, Inc.
P.O. Box 1415
Williamsport, PA 17703
(Pneu-Dart® RDS)

Sanofi Animal Health, Inc.
7101 College Blvd.
Overland Park, KS 66210
(Syncro-Mate–B® implants)

Syntex Animal Health
Division of Syntex Agribusiness, Inc.
4800 Westown Parkway
Suite 200
West Des Moines, IA 50266
(Synovex® implants)

Telinject USA, Inc.
9316 Soledad Canyon Road
Saugus, CA 91350 USA
(Vario® RDS)

The Upjohn Company
Animal Health Division
7000 Portage Road
Kalamazoo, MI 49001
(Implus™ implants)

Wildlife Pharmaceuticals, Inc.
1401 Duff Drive
Suite 600
Fort Collins, CO 80524
(Dan-inject® RDS)

Wildlife Technologies, Inc.
429 So. Montana Ave.
New Richmond, WI 54017
(RDS, Biobullets)

Zoolu Arms of Omaha
10315 Wright Street
Omaha, NE 68124 USA
(Zoolu Arms RDS)