CONTRACEPTION AS AN ALTERNATIVE IN DEER MANAGEMENT

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While some deer populations in North America have successfully been kept within the reasonable limits of their habitat through controlled hunting, there are a variety of situations where this is not feasible or wise. National parks, wildlife refuges, and other legally protected areas prohibit the use of hunting as a control method, and small county, state, and city parks in high-density urban areas make hunting an impractical approach. One alternative to deer management in these areas is chemical contraception, an area of research that goes back some 20 years.

As early as 1968, attempts were made to regulate reproduction in Yellowstone National Park's northern elk herd (*Cervus canadensis*). Greer, Hawkins, and Catlin (1968) administered the synthetic estrogen, diethylstilbestrol (DES) to 36 pregnant cow elk between December and March. The elk were live-trapped, placed in a squeeze chute, rectally palpated to determine pregnancy status, and DES was injected intramuscularly in doses of 75, 100, or 200 mg. Two elk were given 16 mg of another steroid, estradiol cyclopentylpropionate (ECP). All drugs were administered between the third and fifth month of pregnancy. Another 33 pregnant and nonpregnant elk were ovariectomized during this same period of time. Only about 30 percent of the pregnancies among elk treated with DES were terminated and both pregnancies for the two elk treated with ECP were terminated. The pregnant elk which were ovariectomized aborted at various times following the surgery.

In the early 1970s, NASA's Plum Brook Research Station near Sandusky, Ohio, had excessive numbers of white-tailed deer (*Odocoileus virginianus*), and an alternative to hunting was sought. Harder (1971) and Harder and Peterle (1974) fed deer DES on corn and apple baits, and administered DES intramuscularly to captured deer, before and during pregnancy. The target oral dosage was 50 to 100 mg per deer per day, and injected deer received 150 mg of DES. Prebaiting trials indicated that commercial pelleted feed was avoided by the deer. Nontarget species feeding on the DES/corn mixture included blue jays, pheasants, red squirrels, voles, mice, and raccoons.

The reduction in fawning resulting from orally delivered DES was statistically significant, but fell short of the goal necessary to stabilize the herd's numbers. On the other hand, the administration of the intramuscular DES reduced pregnancies by about 75 percent.

A year later, Bell and Peterle (1975) implanted both synthetic estrogen and progestin in white-tailed does during pregnancy. The Silastic implants contained 0, 50, 100, or 150 mg of melengestrol acetate (17 alpha-acetoxy-6-methyl-16-methylene-4,6-prenadiene-3,20-dione, or MGA) or 75 mg of DES. These implants were placed subdermally in the right foreleg, and calculated release rates for the steroids ranged from 0.02 to 12.58 mg per day. Only 1 of 10 DES-treated does became pregnant, and among the 39 MGA-treated adult does, 19 were pregnant. In both treated groups, among those deer who were pregnant, there were significantly fewer fetuses per doe.

Matschke (1977a), in an attempt to regulate reproduction in white-tailed deer in Mammoth Cave National Park, Kentucky, administered DES orally to does in an encapsulated form. The steroid was encapsulated in a gelatin coating and mixed with commercial dairy grain. Actual ingested doses ranged from about 500 to 1,000 mg over a two-month period. Pregnancy was interrupted in a high percentage of cases, but aversion to the drugged baits caused a decline in bait consumption and postabortion

pregnancies increased. Matschke (1977b) then tried two synthetic progestins, MGA and DRC 6246 (17 alpha-allyl-17-beta-hydroxy-3-oxoestra-4,9,11-triene). Does were given 50 mg of MGA and 1.0 g of DRC 6246 in daily, oral doses during the breeding season. Does accepted both compounds, mixed in a dairy grain diet, without reservation, but neither one prevented or delayed conception. Matschke (1980) hypothesized that not enough of the steroids accumulated in the deer body fat to bring about prolonged contraceptive action.

Next, Matschke (1977c, 1980) placed subdermal implants containing DES and the progestin DRC-6246 in 23 sexually mature does. Daily release rates averaged 193 micrograms of DES and 93 micrograms of DRC-6246. Nine of the experimental does died from handling-related stress, and none of the remaining experimental does became pregnant. While the experiment proved that fertility could be inhibited pharmacologically, the impracticality of capturing the animals and the resulting stress was a distinct shortcoming to this approach. Matschke (1976) also tried a mechanical birth-control device in deer. The device, designed to prevent intromission by the male, was manufactured from Silastic rubber and anchored in the vagina of the doe. However, the devices failed to prevent pregnancies, and this approach was abandoned. In another experiment, Roughton (1979) fed 0.6 to 1.0 mg of melengestrol acetate daily to captured does in Mammoth Cave National Park. The steroid was administered in a commercial pelleted deer ration between October and March. Pregnancy rates were decreased by 84 percent in treated groups compared to the control group, and total number of fawns decreased by 90 percent. There were no untoward side effects, and in subsequent years, fertility was completely restored. To be effective however, the drug had to be given daily, a requirement that is difficult to meet in wild populations.

In a recent attempt at contraception in deer, the San Francisco SPCA attempted to reduce population growth among black-tailed deer (*Odocoileus hemionus columbianus*), a subspecies of mule deer, on Angel Island, California. Deer were trapped in baited Clover traps, anesthetized with a combination of lidocaine hydrochloride, xylazine hydrochloride (Rompun), atrophine sulfate, and acetylpromazine maleate. Of the estimated 200 or more deer on the island, 67 were captured and Silastic implants containing melengestrol acetate were surgically placed in 30 adult does (Richard Avanzino, personal communication 1987). Of the 205 deer trapped and handled (most of these were recaptures), 3 deer died from handling-related stress (1.5 percent mortality).

During the fawning seasons of 1985 and 1986, the 28 remaining implanted does produced no fawns, corroborating the pharmacological effectiveness of melengestrol acetate. The obvious shortcoming of this study was the inability to trap more than a third of the total herd. While this shortcoming has been the focus of attention for opponents of deer contraception, it is important to note that the low first-time capture rate on Angel Island cannot automatically be extrapolated to other sites. The combination of available food, habitat type, and weather patterns will in large part dictate the success of capture methods.

There are also several recent research projects that, while they did not involve deer, have important applications to deer population control. Ulysses S. Seal (personal communication 1987) placed subdermal implants containing 800 mg of melengestrol acetate in 25 feral goats (*Capra hircus*) on a private ranch in Texas. These feral goats were transplanted from San Clemente Island, off the coast of California, where their numbers had increased dramatically in recent years. The 25 experimental nannies, plus another 25 control females were placed with two billies, and after two years, no kids had been born to the treated goats. As in the case of Roughton's work (1979), it is apparent that melengestrol acetate will successfully suppress fertility in hoofed animals, and deer in particular.

In an entirely different approach to wildlife contraception, Kirkpatrick, Turner, and Perkins (1982) and Turner and Kirkpatrick (1982) reported successfully inhibiting reproduction in feral horses (*Equus caballus*) by administering a microencapsulated form of testosterone propionate (mTP) to feral stallions. This hormone was injected intramuscularly to immobilized animals, by hand, and caused a lowering of sperm count and decreased sperm motility to a point where fertility was decreased by 83 percent. The polymer (DL-lactide) coating developed by

Southern Research Institute in Birmingham, Alabama, permitted the administration of the drug by injection and resulted in a sustained release for up to six months. This particular drug—testosterone—has little value in the potential fertility control of deer, but the microencapsulation process opens new doors for delivery of antifertility drugs to deer. In 1986, Kirkpatrick and Turner (1991) administered both testosterone propionate and the synthetic progestin norethisterone (NET) to feral horses remotely, through the use of a tranquilizer gun and 6.0 cc darts. The remote administration of mTP to stallions decreased fertility by about 45 percent but demonstrated that remote delivery of microencapsulated steroids is possible.

A most promising new approach is immunological in nature. Liu, Bernoco, and Feldman (1989), at the University of California at Davis, have developed a vaccine that causes passive immunization in mares to the zonae pellucidae (a noncellular membrane surrounding the egg) of ova and the early embryo. In an initial test, the vaccine, utilizing porcine zonae emulsified with Freund's adjuvant, caused infertility in 9 of 10 captive feral horses. In four domestic mares given the vaccine, the antibody titers remained high for eight months after inoculation. These mares returned to estrus and became pregnant the following year, demonstrating the reversibility of the approach. A minimum of two injections two weeks apart is necessary for the initial antifertility effect.

In field applications of this contraceptive approach, Kirkpatrick, Liu, and Turner (1990) successfully contracepted 26 feral mares on Assateague Island, Maryland. The vaccine was administered by means of barbless darts, and none of the 26 treated mares produced foals the following year. The following year, 14 of those treated mares were given a single booster inoculation of the vaccine and only a single mare produced a foal the next year (Kirkpatrick et al. 1991). By 1992, a population of the Assateague mares had received 5 annual treatments and only 2 foals had been produced during 70 mare years (Kirkpatrick et al. 1992).

Application of the PZP vaccine was next tested in 7 captive white-tailed deer and proved to be 100 percent successful in preventing pregnancies (Turner, Liu, and Kirkpatrick 1992). The deer were given annual booster inoculations, following a protocol similar to that used with the Assateague horses, and after three years of treatment, not a single fawn has been born. The PZP vaccine has also proved to be an effective contraceptive in captive sika deer (*Cervus nippon taiwanus*), axis deer (*Cervus axis*), sambar deer (*Cervus unicolor*), muntjac deer (*Muntiacus reevesi*), Himalayan tahr (*Hemitragus jemlahicus*), West Caucasian tur (*Capra ibex*), banteng (*Bos javanicus*), and Przewalski's horses (*Equus caballus przewalski*).

What has the history of fertility control in deer and related species taught us about the future? Let us first summarize what we have learned. First, we know that there is a steroid, melengestrol acetate, that will pharmacologically suppress fertility in deer. Second, we have learned that for this drug to be effective it has to be ingested almost daily or administered in subdermal implants. Third, we have learned that there are a variety of baits that will work and some that won't. Fourth, we know that the capture and handling of deer will provide access to only a portion of a given herd and that regardless of the precautions taken, there will be some injury and mortality to a minimum. Fifth, we have learned that microencapsulation can be used to prepare steroids and vaccines alike for remote delivery and sustained release, and, finally, we have learned that vaccines can be made to suppress fertility. It is also very clear at this point that fertility control in deer, in any form, is feasible only in small and relatively confined herds, not in large herds spread out over vast areas of land.

The problem of fertility control in deer then, must focus on two areas. These include pharmacologically successful and acceptable drugs and safe and reliable delivery systems. Unfortunately, not all molecules will be adaptable to all modes of delivery. For example, steroids can be delivered orally, but proteins cannot be without extensive modification. In the event that steroids are acceptable, a successful drug already exists in the form of melengestrol acetate. This drug can be delivered by implants, provided that the cost of capturing animals and some small percentage of mortality is acceptable. We also know that using the techniques of trapping developed on Angel Island, we can treat, at best, only half the herd. Thus, future use of

melengestrol acetate must focus on delivery methods that will replace or augment the use of implants. Obvious alternative approaches include feeding the steroid in grain or apple baits, or in mineral or salt blocks, and delivering the steroid remotely with microencapsulated forms with a tranquilizer gun. Several delivery systems may be necessary to achieve stabilization of a given herd. Of the pharmacological alternatives, melengestrol acetate is the least expensive to use for management, since we already know the pharmacological effectiveness of the drug.

Other progestins have been used for fertility control in humans and in a limited number of animal species. At least five of these progestins have not been tested in deer. These include norethindrone, medroxyprogestone acetate (Provera), progesterone, and norgestimate (Phillips et al. 1987). Also, all of these steroids can be microencapsulated for injection and remote delivery, and they can be delivered orally. Even if these steroids are effective in inhibiting fertility (usually by preventing ovulation), they will probably see little use in deer, since the consumption of meat from treated animals would result in passage of the steroids through the food chain. All of these steroids can be microencapsulated for injection or remote delivery or delivered orally. There would be moderate expense in a research design built around these steroids, since none have been tested for efficacy in deer.

The issue of side effects of most other steroids, both to the recipient wildlife and to humans who might consume these deer, must be addressed. There have been a number of studies involving the administration of melengestrol acetate to both sheep and cattle, and no side effects have been noted for either sex or any age class (Zimbelman et al. 1970). Neither did Roughton (1979) note any side effects on deer. With regard to human consumption, there are three considerations of importance. First, does the drug actually produce harmful side effects? Second, are the drugs likely to be consumed in high enough quantities to cause harm? Third, can hunting seasons in surrounding areas be regulated to prevent any ingestion at all? A number of compounds closely related to melengestrol acetate (megestrol acetate, medroxyprogesterone, mestranol) are available as prescription drugs for a variety of reproductive disorders. Doses recommended for humans range from 20 to 40 mg per day to as high a 600 to 1,000 mg per day (*Physicians' Desk Reference*, 1987). Roughton (1979) was able to suppress fertility in deer with doses of 1.0 mg per day. Assuming that the drug distributes itself evenly through all tissues of the deer—which it does not—the average concentration of melengestrol acetate in a 120-pound deer would be 8.3 micrograms per pound. Allowing for some storage of the drug and assuming even 20 micrograms per pound, an individual would have to eat 1,000 pounds of venison per day to receive even the lowest prescribed doses for humans. Synthetic steroids of the type described here do not distribute themselves evenly throughout the carcass—a large proportion concentrates in reproductive organs and depot fat. Thus, the person consuming 1,000 pounds of venison per day still would not receive doses prescribed for humans. Finally, administration of contraceptive drugs should begin about October, at least at latitudes similar to those in the middle Atlantic states, and end about February or March. It would be a simple matter to restrict hunting in immediately surrounding areas to September, thereby providing a six-month period for drug residues administered during the previous winter to disappear from treated animals.

Where steroids are not an acceptable choice, alternative drugs must be identified and delivery systems found that will permit administration in an effective manner. Currently, the three most promising nonsteroidal approaches are immunological, gonadotropin-releasing-hormone (GnRH) agonists, and the antiprogestins RU-486 and ZK 98.734.

The most highly developed immunological approach currently available is the antizona vaccine described previously. The preparation of this vaccine is a relatively inexpensive process and has already proved effective in captive deer. Currently, this vaccine cannot be delivered orally and must be injected, either by hand or by tranquilizer gun. The need for multiple injections can be overcome by microencapsulation. If the vaccine is administered by hand to captured deer, the animals can be ear tagged to identify them as having received the vaccine, but that might be difficult in the case of remote delivery. It may

be possible to develop a method of marking the deer with a dye at the same time the contraceptive drug is delivered. Oral vaccines are already a reality, and it may also be possible to deliver the antizona vaccine orally once sufficient research has been done. One clear advantage to this approach is that the animal will not possess any harmful residues that can have any effect on someone or some animal who eats the carcass of a treated deer. This approach has been tested in captive deer herds and plans for tests in wild populations are already in the planning stages.

GnRH, a molecule produced in the hypothalamus of the brain, directs the pituitary gland to secrete two important reproductive hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). These two hormones, known as gonadotropins, control the proper functioning of the ovaries in the female and the testes in the male. GnRH agonists are molecules that are similar in structure to GnRH, competing with the natural molecule for tissue receptor sites, but they are physiologically inactive. Thus, reproduction may be inhibited by giving GnRH agonists or by giving vaccines that cause the animals to become immune to their own GnRH. Since both the agonist and the vaccine are protein in nature, they must be delivered by injection, but both can be microencapsulated for prolonged release. As in the case of the antizona vaccine, there should be no harmful residues remaining in the animal. The GnRH agonist buserelin has been implanted in nonhuman primates to suppress ovarian function for up to three to five months (Fraser et al. 1987). One major drawback to the use of GnRH agonists is that this approach also usually causes a decrease or complete inhibition of the animal's normal steroid hormone production. This, in turn, can cause significant and unacceptable changes in the social behavior and/or organization of the animals. Steroids can be administered along with the GnRH agonists to overcome this problem, but the process can become cumbersome. The cost of developing this approach for deer may be great due to the necessity for isolating pure deer GnRH (it differs structurally among different species) and developing the agonists or vaccines and testing them on captive deer.

A relatively new molecule, RU-486, may have important applications in the control of reproduction in deer. This molecule is an antiprogestin, blocking the action of progesterone in the nucleus (Baulieu 1987). Since progesterone is a necessary molecule for many events in pregnancy, administration of RU-486 will interrupt the estrous cycle, whether or not fertilization or implantation have occurred. Like melengestrol acetate, it can be delivered orally as well as by injection in microencapsulated form. In women, a single 600 mg dose interrupts pregnancy in 90 percent of cases, making it an attractive candidate for use in deer. The cost for this approach would be intermediate between melengestrol acetate and the proteins. RU-486 is already available, but it should be tested in captive deer before field tests begin. Another antiprogestin, ZK 98.734 (11 beta-(4-dimethylaminophenyl-17 beta-hydroxyl-17 alpha-(3-hydroxy-prop-1(Z)-enyl-4,9(10)-estradien-3-one) has been shown to be very effective in marmosets (*Callithrix jacchus*) (Puri et al. 1988). The steroid was 100 percent effective in preventing or terminating pregnancy after doses of 5 mg per day.

Another antiprogestin that may be useful in deer is Epostane, a compound that inhibits the synthesis of progesterone by competitive inhibition of an important enzyme (Birgerson et al. 1987). This compound has been tested in women, can be delivered orally, and can be microencapsulated for injection and remote delivery. Since pregnancy is dependent upon adequate progesterone levels, Epostane would prevent implantation and early development of the embryo.

Several areas of research on delivery systems are necessary also. The capture techniques developed in the Angel Island project are good from the standpoint of safety, but only a third of the deer were ultimately captured. Whether this was the result of the trap design or just the nature of the deer is unknown. Perhaps this trapping technique would be more effective in habitats where the winters are more harsh and deer are more hard pressed for adequate nutrition. This hypothesis should be tested.

Another delivery approach that needs research is baiting, with attendant considerations of the most effective and attractive baits and their consumption rates. Harmless chemicals that collect in the bone can be used to determine how much bait was consumed

(Nelson and Linder 1972). Bait testing should examine the possibilities of microencapsulating drugs in order to mask taste. For example, Calanchi (1976) made 5-mg doses of steroid palatable to human patients by microencapsulating them. Previously, the same steroid had been unacceptable in uncoated 200 microgram doses. Thus, the microencapsulation of baits might cure the bait-avoidance problems experienced by Matschke (1977a). This research could proceed without the involvement of contraceptive drugs.

One promising approach to oral delivery of steroids involves the use of mineral or salt blocks. There are no reports in the literature of contraceptive drug delivery to wildlife by means of salt blocks. As in the case of grain and fruit baits, the effectiveness of mineral block delivery could be carried out with nontoxic markers. A very important part of this research should include the identification of nontarget species that consume the baits and the effects of the contraceptive drugs. Thus far, the only study of this nature was reported by Harder and Peterle (1974).

Although preliminary work with remote delivery techniques has been quite promising, further development and refinement are needed. There are currently a variety of tranquilizer guns available, some of which can be used accurately to deliver pressurized autoinjecting darts to target more than 50 yards away. There is also a CO_2-powered gun that shoots small compacted "biological bullets" of drug under the skin. Research on the effectiveness of immobilizing deer without the use of nets or traps should be part of this phase of the research also. At first glance, the idea of treating sufficient numbers of deer with darts may seem unrealistic, but by "spotlighting," or darting deer at night, "ambushing" deer from tree stands at feeding stations, salt blocks, or along heavily used trails, this technique may have more promise than is immediately apparent.

A final consideration is the site of the research. It would be unwise to proceed with fertility control research at any site where the issue of hunting versus fertility control (or any alternative management technique for that matter) has become politicized and volatile. The potential for interference with the research project is too great in these situations. The habitat and the behavior of the deer are considerations in selecting an approach to fertility control. In certain instances, such as an arboretum, where deer are readily approachable, remote delivery via darts would be the method of choice. In other instances, where the habitat is dense and the deer are secretive, combinations of approaches will probably be wise.

Summary

Fertility control in deer has the potential to provide alternatives to traditional approaches to population control, but the concept is largely untested in this species. Previous research indicates there are pharmacologically useful drugs, such as melegenstrol acetate, but delivery systems need refinement, and new drugs need to be tested. Current prospects for delivery include orally, through the use of baits, subdermal implants, or by injection of microencapsulated contraceptive drugs either by hand or by means of a tranquilizer gun. The usefulness of fertility control in deer will be confined to small herds in restricted ranges. It will not provide an alternative to hunting where the herds are large and the ranges are extensive.

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