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Remotely Delivered Contraception With Needle-less Norgestomet Implants

Darrel J. Kesler

Abstract: A remotely delivered contraceptive was developed that suppressed estrus and prevented pregnancy in deer with 100-percent efficacy. This contraceptive utilized norgestomet, a potent progestin that is approved by the Food and Drug Administration (FDA) for use in cattle. Although the needle-less norgestomet implant is not FDA approved for use in deer, it is safe for treated animals, humans, and the environment. The remote delivery of this implant can be accomplished up to 40 m away and causes minimal tissue damage and stress if administered properly. Because of its ease, its simplicity of delivery, and the control it provides for proper drug handling, the needle-less norgestomet implant holds much promise for control of the overpopulation of deer in the United States. Further, no part of this product will remain to pollute the environment. Although this contraceptive was developed for female deer, preliminary studies suggest that the needle-less norgestomet implant may be effective in males. Widespread use of the needle-less norgestomet implant in deer requires further extensive (and costly) establishment of safety and efficacy as well as FDA approval.

Keywords: Remote delivery, needle-less implants, norgestomet, norethindrone acetate, wildlife contraception, black-tailed deer, white-tailed deer, controlled release, silicone, Food and Drug Administration

Introduction

Deer overpopulation has become a major problem in many areas of the United States. Warren (1991) has presented a detailed review of the historical causes of this problem, the ecological effects of deer overpopulation, and the need for controlling deer populations. Overpopulated deer herds are causing significant economic losses in the form of crop damage, damage to landscape plantings, transmission of diseases to livestock such as cattle (Forbes and Tessaro 1993), and damage to vehicles and humans (injury or death) in deer–vehicle collisions. In many areas, regulated public hunting has been proven to be an effective means of controlling deer populations (Behrend et al. 1970); however, this procedure has become very controversial and political. Contraception of deer may, therefore, be a logical alternative to control deer population.

The purpose of this article is not to provide an extensive review of the literature but rather to review a specific contraceptive (and its development) developed for deer. Because this contraceptive utilizes a steroidal compound, I will refer to other steroids that have been tested for deer contraception, but I will not attempt to provide an extensive review of other contraceptive compounds or procedures.

The selection of a deer contraceptive involves several criteria. The following is a selected list of essential criteria:

- Safety. This involves not only the animals being treated but also the human population and the environment.
- Cost. The product has to be cost effective relative to other methods of population control.
- Efficacy. The product has to be highly effective. Although 100-percent efficacy is not essential, like an equivalent product for humans, it still must be highly effective in preventing unwanted pregnancies.
- Ease of delivery. The product must be uncomplicated and easy to deliver. Even if a product meets the previous three criteria with 100-percent efficacy, it will not be routinely used unless it can be delivered with simplicity and ease.

Several contraceptive systems have been tested in deer and are reported in the literature. None of the developed contraceptives, however, have been accepted with enthusiasm either because of efficacy or because of the difficulty in their delivery. The contraceptive most widely tested is the steroidal compound melengestrol acetate (MGA®; 17α–hydroxy–6–methyl–16–methylenepregna–4,6–diene–3,20–dione; fig. 1) (Budavari 1989, Bell and Peterle 1975, Matschke 1980, Plotka and Seal 1989). MGA is approved by FDA for use in cattle (0.5 mg is orally administered daily; Zimbelman and Smith [1966]) for the suppression of estrus, increased rate of weight gain, improved feed efficiency (Bennett 1993), and, more recently, estrus synchronization in the United States. Another steroid tested is levenorgesterel (also referred to as norgestrel; 13β–ethyl–17α–ethynyl–17β–hydroxygon–4–en–3–one; fig. 1) (Budavari 1989, Plotka and Seal 1989, White et al. 1994). Levenorgesterel is

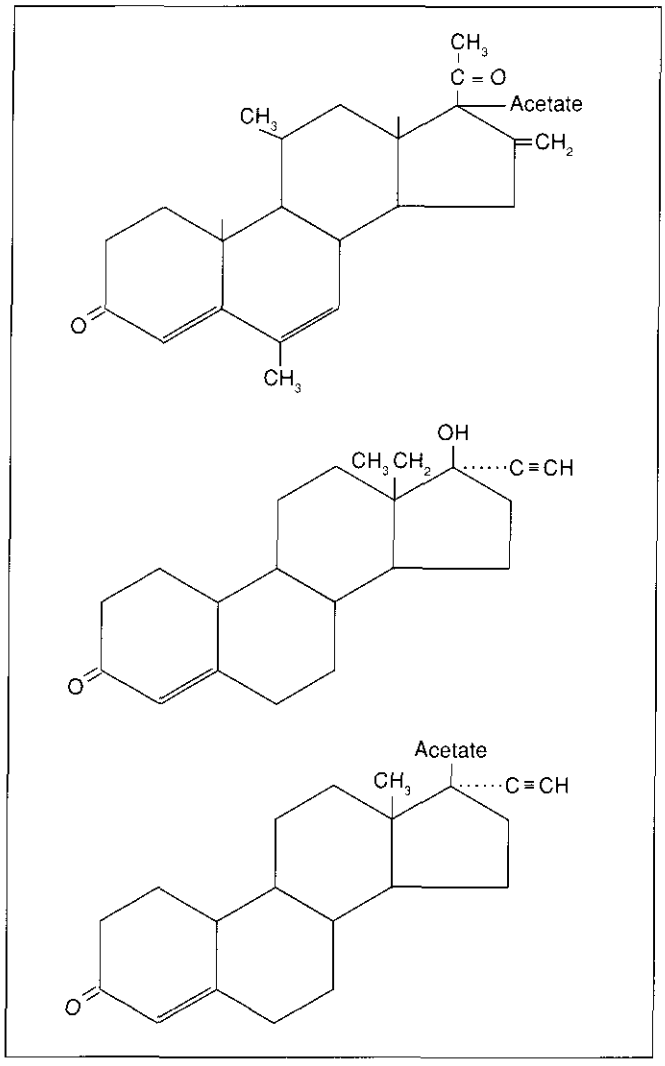

Figure 1. Chemical structures of melengestrol acetate (top), levenorgesterel (middle), and norethindrone acetate (bottom).

the active component of the Norplant® implant approved for human use as a contraceptive implant by FDA in the United States (McCauley and Geller 1992).

Although effective, MGA requires the implantation of a relatively large implant. These implants necessitate capturing the target animal and performing minor surgery for implantation (Plotka and Seal 1989). The implants have been demonstrated to be efficacious for several breeding seasons (Matschke 1980). Levenorgesterel also requires animal restraint for implant placement; however, the implants are smaller than the MGA implants. Unexpectedly, both studies that used levenorgesterel in deer reported that—administered at dosages similar to those used efficaciously in humans—levenorgesterel was not an effective contraceptive in deer (Plotka and Seal 1989, White et. al. 1994).

Both MGA and levenorgesterel were delivered via silicone (polydimethylsiloxane) (Roseman 1972). Because controlled chronic release of steroids in vivo (which is necessary for steroidal contraception) is obtained with silicone implants, and because they are biocompatable in mammals (Dziuk and Cook 1966), silicone proves to be an efficacious delivery system suitable for steroidal compounds in deer (Kesler 1989).

Norethindrone Acetate (NA)

The first compound selected for efficacy evaluation was norethindrone acetate (19–nor–17β–ethynyl–17ß–ol–3–one acetate; fig. 1) (Budavari 1989). Its chemical structure is very similar to that of levenorgesterel. NA is used in combination with ethynylestradiol in the United States (with FDA approval) as an oral contraceptive in humans. A human contraceptive was selected because investigators originally assumed that it would be reasonable to obtain FDA approval (for use in deer) for a compound already approved for a human use. NA was also selected because (1) the acetate provides longer in vivo half-life (Sinkula 1978), and (2) esterification enhances steroid secretion from silicone implants (Christensen and Kesler 1984 and 1986, Kesler et al. 1996). NA implants have been used efficaciously (as a contraceptive) in humans (McCauley and Geller 1992). The first, and last, study (as reported below) was in beef heifers; the compound norgestomet was then selected for evaluation as a deer contraceptive.

Fourteen beef heifers were selected for the study. Heifers were divided into two groups. All heifers had been previously synchronized with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$; Kesler 1985a and b, Kesler and Favero 1989a) and observed for estrus. Twelve days after detected estrus, all heifers were bled, and

plasma was assayed by a validated enzyme-linked immunosorbent assay (ELISA) (Kesler et al. 1990) for progesterone concentrations. All 14 heifers had progesterone concentrations greater than 1.5 ng/mL, which suggests that they had corpora lutea that developed subsequent to the previously detected estrus (Kesler et al. 1981). Half (7) of the heifers were subcutaneously implanted with an NA matrix silicone implant. The cylindrical implants, each 3.5 mm in diameter and 2.5 cm in length, were implanted subdermally on the convex surface of the ear. Each treated heifer received one implant that contained 11.5 mg of NA (equivalent to 8.35 mg of norethindrone). At the time of implant insertion, all heifers were administered a luteolytic dose of $PGF_{2\alpha}$. Implants were left in situ for 4 days; after removal, total remaining NA was determined (Kesler et al. 1995 and 1989c). In vitro implant secretion over 4 days was also determined and corrected for in vivo secretion by the procedure reported by Machado (1994).

NA was released from the silicone implants in a typical linearly declining fashion ($r = -0.997$; $y = x(-0.21) + 1.15$) (Ferguson et al. 1988, Kesler and Favero 1989c, Kesler et al. 1995). Over the 4-day period, a total of 2.53 mg (22 percent of the total) was delivered in vivo. Three of the four control heifers (43 percent) were detected in estrus whereas all seven (100 percent) of the treated heifers were detected in estrus (table 1).

Estrus was detected at similar times after $PGF_{2\alpha}$ treatment for both groups. To verify $PGF_{2\alpha}$-induced luteolysis, all heifers were bled 2 days after $PGF_{2\alpha}$ treatment, and plasma was assayed for progesterone concentrations (Kesler et al. 1990). The progesterone concentrations in all heifers suggested that luteolysis was ensuing or had ensued.

In summary, NA did not suppress estrus. In fact, during a period of high NA secretion (2.53 mg over the 4-day period), there was a tendency for more ($P = 0.02$) NA-treated heifers than control heifers to display estrus. Therefore, NA was not considered further.

Table 1. Norethindrone acetate implant secretion and estrus suppression efficacy in beef heifers

Item	Control	Treated
Number	7	7
Number in estrus	3 (43%)	7 (100%)[1]
Mean interval to estrus	61 hours	59 hours
Norethindrone acetate secreted		
Day 1	0	947 µg
Day 2	0	738 µg
Day 3	0	501 µg
Day 4	0	341 µg

[1] Differed from the control group at the 0.02 level of significance.

Norgestomet Chemistry and Physiology

Chemistry

Norgestomet is approved by FDA for use in cattle for estrus synchronization (Darling 1993). The procedure, designated Syncro-Mate B®, includes a 9-day implant containing 6 mg of norgestomet and an intramuscular injection that consists of 3 mg of norgestomet and 5 mg of estradiol valerate that is administered at the time of implant insertion (Chien 1978, Kesler et al. 1995). The purpose of the implant is to suppress estrus. When it is used for estrus synchronization in cattle, subsequent timed breeding (cattle are bred 48–52 hours after implant removal) pregnancy rates range from 40 percent to 60 percent (Odde 1990, Kesler and Favero 1996). Norgestomet has also been successfully used for resynchronization in cattle (Favero et al. 1993 and 1995, Machado 1994, Kesler et al. 1994) and for estrus suppression and synchronization in sheep (Kesler and Favero 1989b and 1997).

Chemically, norgestomet (17α–acetoxy–11β–methyl–19–norpreg–4–ene–20,dione; SC 21009) is a modified 19–norprogesterone (fig. 2). Norprogesterone is identical to progesterone except that the methyl group at the 19 position is absent. Norgestomet has two other modifications: the presence of a methyl group at the 11 position and an acetate at the 17 position. Acetate has been added to provide longer half life in situ (Sinkula 1978). Norgestomet is me-

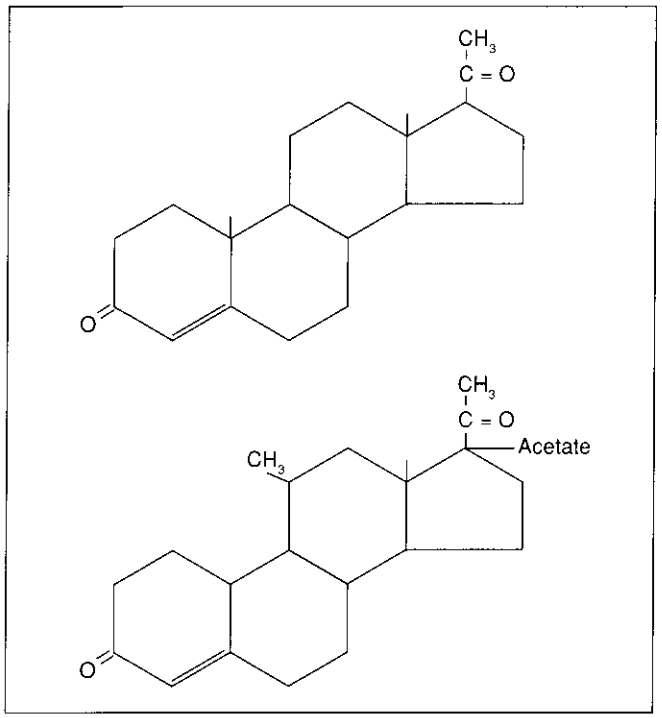

Figure 2. Chemical structures of progesterone (top) and norgestomet (bottom). Norgestomet is a norprogesterone (exactly like progesterone except the methyl group at the 19 position is absent). Two other differences from progesterone are that norgestomet has an acetate at the 17 position (in order to increase half-life in vivo), and a methyl group is included at the 11 position.

tabolized quickly (Moffatt et al. 1993) and is excreted in the urine and feces (Searle 1982). In both urine and bile, most of the excreted metabolites are highly polar materials demonstrated to have only about 4 percent of the progestational activity of norgestomet in the Clauberg assay (Searle 1982).

Norgestomet is a highly biologically active progestin. Gilbert et al. (1974) demonstrated that norgestomet is 15 times more biologically active than progesterone when orally administered to rabbits and 216 times more biologically active than progesterone when subcutaneously administered to estradiol–17β-treated mice. Wishart (1972) demonstrated that 140 µg of norgestomet and 45 mg of progesterone were required to suppress estrus in all treated heifers (which means that norgestomet is 321 times more potent than progesterone in this model). These data, combined with the data of Zimbelman and Smith (1966), would suggest that MGA is 90 times more potent than progesterone. This minimal dose of norgestomet required to suppress estrus in cattle was confirmed with silicone implant delivery of norgestomet by Machado (1994) and Machado and Kesler (1996). In their studies, 6-mg and 8-mg silicone implants were administered to cows for 16 days. None of the cows with 8-mg implants were detected in estrus with implants in situ. The smallest daily dose of norgestomet released by these implants was 136 µg, which occurred on day 16. However, in three cows with 6-mg implants, estrus was detected the first day after implant secretion dropped below 136 µg/day. Although this represents only 16 percent of the treated cows, 100-percent efficacy of estrus suppression was lost.

Norgestomet's principal mode of action for estrus synchronization is by suppressing estrus. Further, norgestomet has the progesterone biological activity to maintain pregnancy in ovariectomized heifers (Favero et al. 1990; Kesler, in press). Favero and coworkers demonstrated that norgestomet would maintain pregnancy from day 10 through parturition. Upon removal of the norgestomet implants, parturition (if the implants were removed at term) or abortion (if the implants were removed at midgestation or earlier) occurred within 52 hours. Therefore, norgestomet is as effective as progesterone (but at a substantially reduced dosage) for two of progesterone's main biological actions: estrus suppression and pregnancy maintenance.

Progesterone also has a role in regulating luteinizing hormone (LH) and subsequent follicular growth and maturation. Experiments utilizing the commercial hydron (polyethylene glycomethacrylate; Short 1975) norgestomet implant (6 mg) have demonstrated that, when it was implanted during pro-estrus, the dominant follicle present was maintained for the duration of the treatment, and there was no growth of medium or small follicles (Rajamahendran and Taylor 1991). Systemic estradiol concentrations were also elevated, and there was insufficient progestin activity to maintain a strong negative feedback on LH pulse frequency in a manner comparable to that of the luteal phase of a normal estrous cycle (Savio et al. 1993).

Rajamahendran and Taylor (1991) suggested that this implied that the norgestomet treatment given during pro-estrus mimics the actions of low concentrations of progesterone. This time period is, in fact, a time of low norgestomet secretion by the hydron implant (Kesler et al. 1995), and, therefore, obtaining a low progestin effect would be expected. In fact, when implants were changed during the persistence of the dominant follicle, LH pulse frequency decreased, estradiol concentrations decreased, and follicular atresia occurred (Savio et al. 1993). Therefore, when given in appropriate amounts, norgestomet was effective in provoking the progestinlike negative feedback on LH pulse frequency and on follicular atresia.

These conclusions were supported by Butcher et al. (1992), who reported that daily injections of 100 mg were was required to elevate systemic progesterone concentrations to levels of the luteal phase (5 to 7 ng/mL). In contrast, daily injections of only 45 mg were required to suppress estrus in all treated animals (Wishart 1972). The dosage selected for the norgestomet implant was based on the minimal quantity required to suppress estrus.

Administration of norgestomet on days 5–21 of the estrous cycle had no effect on progesterone secretion by corpora lutea (Domatob et al. 1994) and no negative effects on the establishment of pregnancy (Favero et al. 1993 and 1995, Machado 1994, Kesler et al. 1994). In order to assess the effect of norgestomet on early corpora lutea function and development in bovines, norgestomet was administered on days 1, 2, 3, and 4 after estrus (2 cows/day). The implants were left in situ for 12 days. In all eight cows, development of the corpora lutea, secretion of progesterone, and length of the estrous cycle were unaffected by norgestomet treatment. Therefore, negative feedback of norgestomet during met-estrus and di-estrus did not disrupt corpora lutea development or function (Kesler, unpubl. data).

It has been reported that norgestomet has a higher binding affinity to bovine uterine receptors than progesterone (Moffatt et al. 1993). Interestingly, however, although norgestomet has a higher binding affinity to bovine receptors, it did not bind (less than 0.1-percent cross-reactivity) to highly specific anti-progesterone immunoglobulin G developed in rabbits (Kesler et al. 1990). Norgestomet exhibits only a weak ability to competitively bind bovine endometrial glucocorticoid receptors (Moffatt et al. 1993). Although norgestomet does not interact with endometrial estrogen receptors, it exhibits weak estrogenic activity when tested in an estrogen-dependent stimulation of human breast cell test. However, to provoke estrogen stimulation, a dose of at least 100 mg of norgestomet given at one time would be required (Moffatt et al. 1993).

Norgestomet Safety

To obtain FDA approval for its use in cattle, investigators conducted numerous studies to establish norgestomet's safety in both the treated animals (cattle) and humans (Searle 1982). For cattle, studies were conducted with doses up to 60-fold excess to the recommended dose (6 mg implants). Daily observation of animals indicated no adverse reactions. Further, postmortem evaluation of the thoracic and abdominal viscera indicated that norgestomet caused no adverse effects.

To evaluate human safety, researchers conducted several studies in both monkeys and rats (Searle 1982). The study conducted in monkeys was designed to evaluate the human oral contraceptive effect of norgestomet. Oral treatment of 30 and 100 μg/kg (but not 0 and 10 μg/kg) per day increased the length of menstrual cycles, decreased the ovulation rate, and decreased the number of cycles during the 84-day treatment period. Throughout the treatment period, the only remarkable effect was amenorrhea, which was observed in five of six and three of six monkeys orally administered daily doses of 30 or 100 μg/kg, respectively. Further, when norgestomet was administered at these doses, the conception rate was depressed to zero. The 10 μg/kg of norgestomet per day had no significant effects on menstrual cycle length, ovulation rate, amenorrhea, or conception rate (Searle 1982).

For the rat studies, norgestomet was administered orally by gavage to two generations of rats at daily doses of 0, 0.0001, 0.001, 0.01, 0.1, or 1.0 mg/kg (Searle 1982). Administration of all doses produced no clinical signs indicative of toxicity. Weight gain was affected slightly only in the second-generation rats treated at the 1.0 mg/kg daily dosage. Also, in these same second-generation rats, fertility was slightly lower when compared to that of controls. There were no gross or histologic (adrenals, pituitary, and sex organs) changes that could be attributed to treatment with norgestomet. Absolute and relative organ weights from the treated groups were not different from the controls, although there was a slight decrease in liver weights in all treated animals.

In published resynchronization studies where norgestomet was administered during pregnancy, 158 pregnancies have resulted (Favero et al. 1993 and 1995, Machado 1994, Kesler et al. 1994, Domatob et al. 1997). No adverse effect of any kind has been observed. Therefore, the administration of norgestomet does not appear to affect embryonic or fetal development. However, as previously noted, norgestomet will inhibit parturition and therefore should not be inadvertently administered to pregnant animals where the implant is not going to be removed before parturition (Favero et al. 1990; Kesler, in press).

Contraceptive Efficacy

One study of norgestomet's contraceptive efficacy in deer was completed in 1995 (Jacobsen et al. 1995), and another was more recently published (DeNicola et al. 1997). Jacobsen's study was conducted in confined black-tailed deer. This study included 10 deer of which 7 were treated with 42-mg norgestomet implants approximately 1 month before the breeding season. In addition to the 10 female deer, 2 fertile males were included in the same confined area. Observations were collected over a 2-year period after treatment.

Subsequent to treatment, all of the treated female deer failed to exhibit estrous behavior. Further, males exhibited neither intentional pursuit, courting, nor tending bond behaviors toward treated females. After the first breeding season, all three control deer fawned, producing two sets of twins and one set of triplets. None of the seven treated deer fawned. All of the 10 female deer exhibited estrous behavior the next breeding season, and all 10 conceived.

Although this study utilized a small sample, additional studies with white-tailed deer (DeNicola et al. 1997) confirm the contraceptive effect of the 42-mg norgestomet implant. In addition, a contraceptive effect with similar efficacy to that of the 42-mg implant has been demonstrated with a 21-mg norgestomet implant (DeNicola et al. 1997).

The desired duration of contraception is controversial. Some groups encourage lifetime sterilization; others suggest that contraceptives should be reversible. The needle-less norgestomet implant was designed, as data confirmed, to be a 1-year contraceptive. Therefore, after 1 year of reducing the deer population, a decision can be made regarding how to control it in subsequent years.

Release from the 42-mg implant has been evaluated. This was accomplished by utilizing a validated in vitro system that mimics in vivo secretion (Kesler et al. 1995). Implants were evaluated daily over a 4-month period. The release of norgestomet from the implants was in a typical linear declining fashion (see figs. 3 and 4; Kesler et al. 1995). The best fit line was determined by correlating daily norgestomet released *v.* the log of day in vitro. This produced a correlation coefficient of –0.996. The maximal release of 638 µg was on the first day. During the first 3 months, more than 136 µg of norgestomet was released daily. This is a quantity that, as described earlier, suppresses estrus in cattle. The amount of norgestomet released daily thereafter decreased linearly. Based on the best fit release, norgestomet was released from the implant for 252 days.

For practical reasons, emphasis was placed on developing a contraceptive for the female deer. However, the contraceptive effects of progestins in males have been known for some time (Liskin and Quillin 1983). To assess the usefulness of norgestomet in male animals, researchers conducted a preliminary study to evaluate its effects on fertility-related factors in male rats.

This study included six males rats that were 12 weeks old at the onset of the experiment. Three rats served as controls and received no treatment. The other three rats were each administered one 6-mg silicone implant. At the end of 9 days, the implants were removed and replaced with new 6-mg silicone implants. This cycle continued for 63 days (7 implants/rat—9 days/implant). On day 63, all six rats were killed and trunk blood was collected. The plasma was analyzed for testosterone concentrations via a validated ELISA (Kesler et al. 1990). In addition, testes were collected and weighed. Mean individual testis weight of the norgestomet-treated rats was reduced ($P < 0.01$) and was only 37 percent of the control rats' mean testis weight (table 2). Mean testosterone concentrations in the plasma of norgestomet-treated rats were only 15 percent of the control rats' testosterone concentration. Although not highly significant ($P = 0.19$), norgestomet clearly had a biological effect on testosterone concentrations. A high level of significance ($P < 0.05$) was not achieved because the untreated rats demonstrated significant variability in their testosterone concentration and because so few animals were included in this prelimi-

Table 2. Mean testosterone concentrations and testes weights of rats treated with norgestomet.

Item	Control	Treated
Number	3	3
Mean individual testis weight	2.08 g	0.76 g[1]
Mean testosterone concentrations	4.54 ng/mL	0.66 ng/mL[2]

[1] Differs from the control group at the 0.01 level of significance.

[2] Differs from the control group at the 0.19 level of significance.

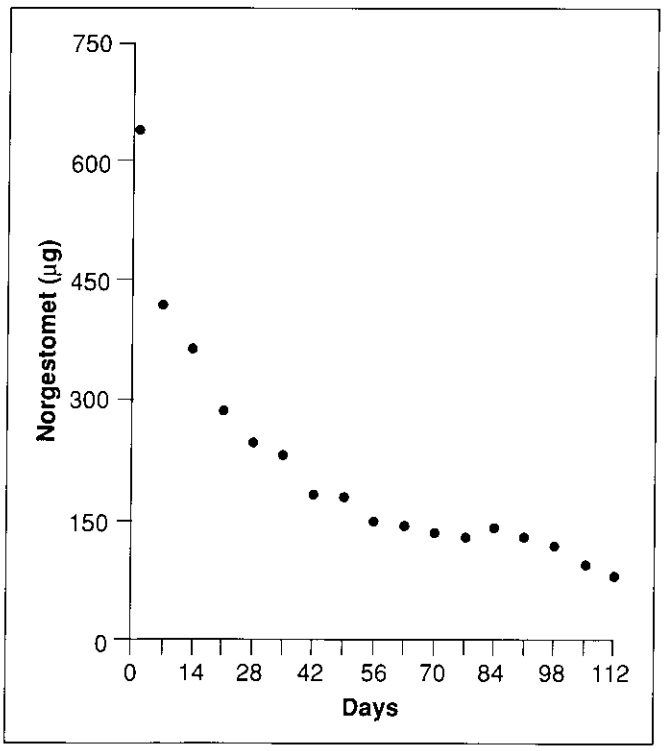

Figure 3. Actual daily in vitro release of norgestomet. Daily observations were collected; however, only weekly observations are illustrated.

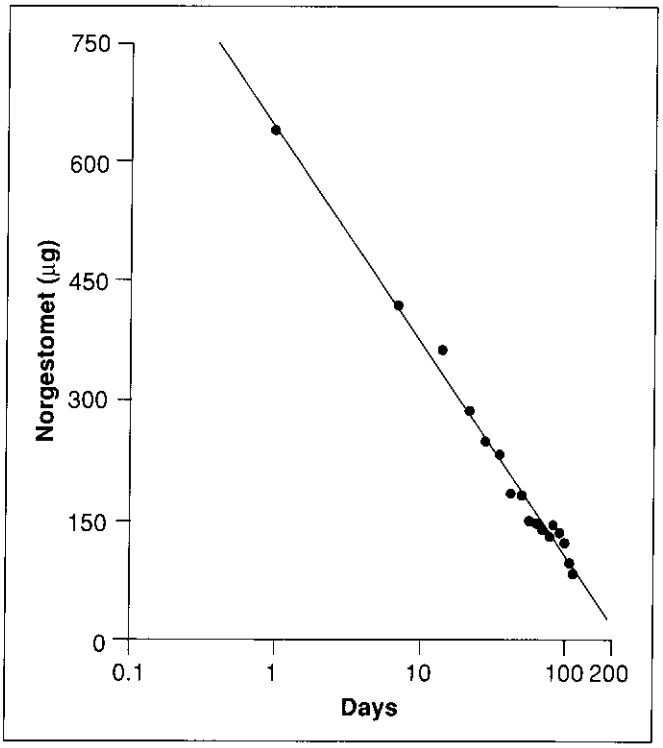

Figure 4. Daily release (with days converted to log of days) in vitro of norgestomet. Daily observations were collected; however, only weekly observations are illustrated. The regression equation is Y = X (−265.26) + 637.23 with Y = norgestomet concentration [µg] and X = log of days (r = −0.996; $P < 0.01$).

nary study. However, the three norgestomet-treated rats had the three lowest concentrations of testosterone in their plasma.

Collectively, these data suggest that norgestomet may have a contraceptive effect in males. However, these studies were conducted with high concentrations of norgestomet and not in deer. Further investigations evaluating sperm concentrations in the epididymis of male deer or in their ejaculate are needed.

Remote Needle-Less Delivery

Delivery of contraceptives to free-roaming animals is critical to successfully suppressing reproduction. The idea contraceptive should (1) be capable of being delivered remotely, (2) not pollute the environment, and (3) allow control such that only animals intended to be treated are treated and that the drug is handled and dispensed properly.

The norgestomet implants used in the deer efficacy studies were needle-less implants (fig. 5) that could be delivered at distances up to 40 m from the target animal (DeNicola et al. 1996). The needle-less implants have two major components. Their outer shell is manufactured from food-grade biodegradable and biocompatable chemicals. The components are already approved as food additives; even if all of the implant remained in place at the time of slaughter and was eaten by humans, that would not pose a hazard (U.S. Government 1993). The outer biodegradable shell is 0.635 cm in diameter and 2 cm long. The second component is the norgestomet manufactured in a matrix silicone implant. The silicone matrix is 0.42 cm in diameter and 1.4 cm long. It weighs 215 mg, of which 42 mg (19.5 percent) is norgestomet. The outer shell combined with the silicone/norgestomet weighs about 880 mg.

The needle-less implants are propelled via a compressed-air delivery system. For the 1995 study (Jacobsen et al. 1995), the needle-less implants were delivered at 26,152 cm/second (858 feet/second) producing 3.07×10^5 g-cm (22.15 foot-pounds) of kinetic energy. This system was designed for use in cattle, whose skin is far thicker than that of deer (Kesler and Favero 1997). Propelling the implants with that much kinetic energy caused trauma in deer (Jacobsen et al. 1995).

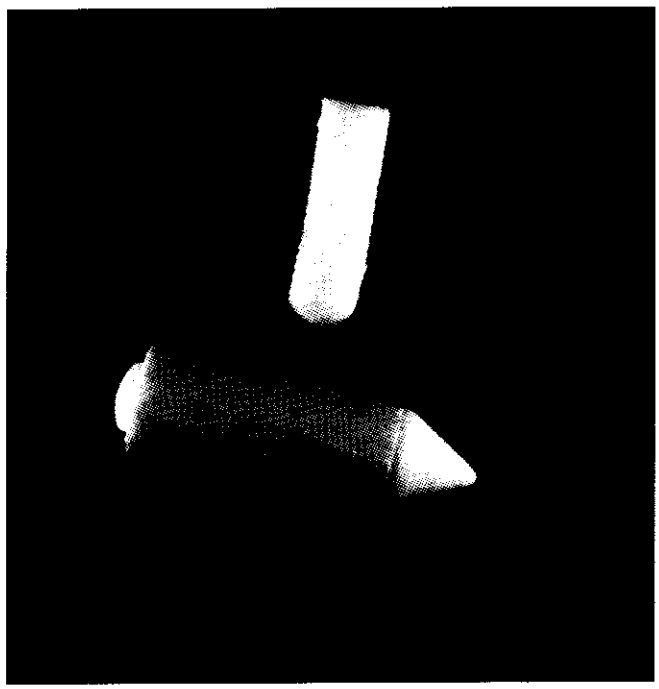

Figure 5. The needle-less norgestomet implant used in the deer studies. The photo shows the outer biodegradable shell (0.635 cm in diameter and 2 cm long) and the inner silicone matrix norgestomet implant (0.42 cm in diameter and 1.4 cm long).

Jacobsen's coworkers administered the needle-less implants in biceps femoris or semitendinosus or semimembranosus muscular at a distance of 3–30 m. Upon contact, deer exhibited one of two reactions: fleeing response without any apparent change in gait, followed by standing and grooming of the administration site, or immediate carriage of the hindlimb and lack of attempted weight bearing for variable durations.

In subsequent studies, the needle-less implant has been delivered with far less kinetic energy. Using less kinetic energy does not compromise the accuracy but significantly reduces the trauma in deer (DeNicola et al. 1997). In fact, when needle-less implants can be delivered silently, deer have minimal reaction to

their delivery. In one study where cortisol concentrations were monitored to evaluate stress caused by the needle-less implant, they were not increased (Kesler, unpubl. data).

Upon contact with the skin, the needle-less implant first causes it to stretch (Gould 1984). After stretching, the implant penetrates the skin by producing a slit in it. After penetration has occurred, the skin then contracts back to almost its original form, with only a small slit left behind. The entry slit is shorter than the diameter of the projectile. Minimal, if any, bleeding occurs after penetration. Scab formation follows (Willis et al. 1994, DeNicola et al. 1996). The projectile does not carry a portion of the animal's hide into the wound but leaves behind only a small, raised welt on the skin at the point of projectile entry (Drake and Paul 1976, Kesler et al. 1989a).

Upon entry into living tissue, the outer shell dissolves in vivo in approximately 6 hours. I conducted both in vitro and in vivo studies to determine dissolution of the outer shell (table 3). The matrix silicone implant, although biocompatable and nonirritating, remains and delivers norgestomet by Fick's first law of diffusion as long as there is norgestomet contained within the silicone. By design, two deer that have been remotely treated with needle-less norgestomet implants were killed (about 2 months after treatment), and investigators examined the administration sites and musculature. In both cases, the norgestomet–silicone implant was recovered. Surrounding tissue was normal (DeNicola et al. 1996).

This remote delivery system is unique and has many advantages over all other delivery formats. Another remote delivery system utilizes syringe darts. Although syringe darts provide remote delivery, a nondegradable syringe and needle remain in the environment. Another remote delivery system being proposed utilizes genetically engineered viruses which provides no or very minimal control on its spread (Morell 1993, Wagner et al. 1994).

Table 3. In vitro and in vivo dissolution of the biodegradable shell of the needle-less norgestomet implant

Hour	Percent of implant dissolved	
	In vitro[1]	*In vivo*[2]
0	0	0
1	40	—[3]
2	70	—
3	90	—
4	95	—
5	98	[4]98.25
[5]6.39	100	—
24	—	[6]100

[1] In vitro conditions consisted of suspending the implant shell in 100 mL of phosphate buffered saline (pH 7.0) at 37 °C.

[2] In vivo conditions consisted of subcutaneously implanting the implant shell in rabbits. At 5 and 24 hours after implantation, eight rabbits (four each time) were killed to determine the amount of implant shell remaining.

[3] No observations were collected for times marked —.

[4] At 5 hours after implantation, approximately 2 percent, 0 percent, 3 percent, and 2 percent of the implant was remaining.

[5] The implant shell had completely dissolved at 6.08, 6.42, and 6.67 hours after placing the implants in solution.

[6] At 24 hours after implantation, no intact implants were present in any of the four treated rabbits.

Government Regulations

It is not the purpose of this article to review government regulations; however, it is important to make a few important comments. First and foremost, the norgestomet–silicone contraceptive reported herein is not approved for use by FDA. An Investigational New Animal Drug (INAD) authorization has to be granted to conduct the experiments reported. FDA has required that these studies be conducted only on confined animals and that they do not escape in such a way that they could enter the human food chain. Although approved in cattle, norgestomet is not approved for widespread use in deer. Before that approval is possible, a sponsor much accomplish numerous tasks (table 4) to ensure that the product is efficacious and safe not only to the treated animals but also to the humans that may consume treated animals. It is my opinion that this product can be approved by FDA.

Table 4. Information required to be submitted to the FDA's Center for Veterinary Medicine when requesting approval for the marketing of a new animal drug product (Center for Veterinary Medicine 1994)

1.	Identification
2.	Table of Contents and Summary
	i. Chemistry
	ii. Scientific rationale and purpose
3.	Labeling
	i. Label identification
	ii. Nonprescription labeling
	iii. Prescription labeling
	iv. Use restrictions
	v. Medicated feed labeling
	vi. Draft labeling
4.	Components and Composition
	i. Components
	ii. Composition
	iii. Fermentation of drug substance
5.	Manufacturing Methods, Facilities, and Controls
	i. Manufacturer
	ii. Personnel
	iii. Facilities/equipment
	iv. New drug substance synthesis
	v. Raw material control
	vi. Manufacturing instructions
	vii. Analytical controls
	viii. Lot control number
	xi. Container
	x. Stability
	xi. Additional procedures
	xii. GMP (good manufacturing practice) compliance
6.	Samples
7.	Analytical Methods for Residues
8.	Evidence to establish safety and effectiveness
9.	Good Laboratory Practice Compliance
10.	Environmental Assessment
11.	Freedom of Information Summary
12.	Confidentiality of Data and Information in a New Animal Drug Application

However, requirements for distribution have yet to be accomplished.

Since animals treated with norgestomet would have their implant in situ during the hunting season, a legitimate concern is finding the answer to the question, what will happen to the people who consume such an implant in a treated animal? First, tissue studies demonstrate that minimal norgestomet residue exists in all treated cattle tissues except liver and kidney (Searle 1982). Second, in regard to consumption of an implant, the silicone is exceptionally durable. When placed in vitro in concentrated hydrochloric acid over a 3-day period, the polymer is unaffected. Therefore, complete breakdown and absorption of all remaining norgestomet (like the effect on compressed pellets) is extremely unlikely (or impossible). Further, implants incubated in 250 mL of 1 N hydrochloric acid (at 37 °C), to mimic the acidic conditions of the stomach, released the same amount of norgestomet as in plasma in vitro conditions. New implants incubated for 24 hours in plasma and 1 N hydrochloric acid released 638 µg and 648 µg, respectively (within 1.5 percent of each other). Therefore, consumption of an implant a few weeks after implantation would release less than the safe 10 µg/kg daily dose previously discussed in monkeys.

Summary

Progesterone, produced by the corpus luteum, suppresses estrus in deer and cattle. Synthetic progestins (melengestrol acetate and norgestomet) that suppress estrus in cattle are also effective in deer. Synthetic progestins that are effective contraceptives in humans, however, do not suppress estrus and are not effective contraceptives in deer or cattle. Steroidal compounds are often viewed negatively because of the diethylstilbestrol (DES) scenario, even though they are widely used by humans. DES became implicated as a carcinogen because large doses (50 mg/day) of DES given to pregnant women caused an increased incidence of cervical cancer in their daughters (0.14 to 1.4 cases per thousand exposures [Cheeke 1993]). Norgestomet evokes all progesteronelike actions but at a much reduced dosage. Further, there are no data available to indicate that this steroid poses a risk. In addition to the data reported herein, norgestomet has been used for over a decade in cattle without any reported problems to either the cattle or to the human consumption of meat from treated animals. The only known progestin potent enough to be manufactured in a remotely delivered needle-less implant and still be efficacious as a contraceptive is norgestomet. This

contraceptive system was evaluated by a scientific committee for use in wild goats (Warren 1992). That committee gave the needle-less norgestomet the highest possible ratings for delivery, safety, and efficacy. All data support their conclusions. In fact, the committee rated the needle-less norgestomet implant as the best contraceptive for wild goats (Warren 1992). Based on all data available, the same conclusion can be reached for deer. I encourage further evaluation and support of the development of this contraceptive for use in deer.

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