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REPRODUCTIVE INHIBITORS FOR COYOTE POPULATION CONTROL: DEVELOPMENTS AND CURRENT STATUS

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ABSTRACT: Coyote depredation often causes severe losses of livestock and wildlife in many areas. The use of toxicants is banned for coyote control in the United States necessitating the consideration of alternative methods of control of these predators. This review deals with a class of possible alternatives for population control (reproductive inhibitors) and the conditions associated with selection and application of reproductive inhibitors to the target species.

INTRODUCTION

Reproductive inhibitors may offer a practical approach for population control of a single predator species. The potential for discriminately subjecting a particular species to antifertility compounds is still uncertain but merits further investigation. High coyote population densities often result in undesirable predation losses of various game animals and domestic livestock (Beasom, 1973; Henne, 1975). Theoretically, by controlling reproductive rates, such coyote populations could be reduced. Other prey species would then be an adequate food supply for the coyote.

Considerations pertinent to the application of reproductive inhibitors for controlling coyote populations have been discussed previously (Balser, 1964a). Because many of the assertions are still valid, they will be reviewed here. The following advantages are associated with the use of reproductive inhibitors:

(1) Preventing animals from being born may be more practical than reducing their numbers after they are partly or fully grown and established in a secure environment.

(2) Increasing one or more mortality factors often results in a compensating increase in reproductive rates, or survival or both. This compensating increase reduces the effectiveness of a control program. By suppressing reproduction the compensating increase in reproduction may be overcome, but survival may be increased in the remaining population.

(3) Movement or ingress that occurs when animals are removed from a population may be lessened by occupancy of territories by treated coyotes.

(4) Nontoxic antifertility compounds are safer to use than many toxicants and likely would be more readily accepted by the public. This acceptance could result in more effective population control where the use of lethal techniques is restricted.

The foregoing considerations, on the basis of current knowledge of coyote behavior and reproduction, may be more logical than realistic. We say this because of several critically inherent requirements for chemically induced population control to be effective. These requirements include, but may not be restricted to the following:

(1) The reproductive inhibitor must be effective in a single, oral dose.

(2) The margin of safety between sterilizing and lethal dosage levels must be acceptable.

(3) The antifertility compound must be relatively stable, inexpensive and effective in minute quantities.

(4) It must be odorless and tasteless so as not to cause aversion to treated baits.

(5) The antifertility compound must be relatively host specific in order to minimize the effects from ingestion by non-target species.

(6) It must be effective for relatively long periods during the reproductive cycle.

(7) The practical application of reproductive inhibitors will be dependent upon development of host-specific delivery systems.

In addition to the foregoing criteria for the successful use of reproductive inhibitors, efficacy evaluation in wild coyote populations and development of data for eventual registration by the Environmental Protection Agency are matters of monumental magnitude.

The initial consideration in research on reproductive inhibitors is whether they should be developed to cause chemical castration of the male or those to interrupt pregnancy in the bitch, or a combination that will do both. The monoestrous seasonality of the coyote is an advantage in timing the administration of antifertility compounds for both of these purposes.

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FEMALE ANTIFERTILITY COMPOUNDS

For a female contraceptive to be effective when administered by bait, a single oral dose must be able to either prevent conception or interrupt pregnancy. Thus the choice among known reproductive inhibitors that can be used is limited to estrogenic and androgenic steroids and prostaglandins (PGs). Estrogenic compounds have contraceptive properties if administered within a confined timespan with respect to ovulation and implantation. These compounds inhibit fertility by interfering with oviductal transport of ova either by tubal blocking or by more rapid transport (Greenwald, 1959, 1963; Deanesly, 1963; and Chang and Harper, 1966) or possibly hinder zygote or embryonic survival before implantation (Blye, 1970).

Diethylstilbestrol (DES), a synthetic estrogen, hinders reproduction in penned coyotes (Balsler, 1964). An oral dose of 100 mg caused abortion in six bitches the first 30 days of pregnancy. No toxic symptoms were observed at 20 times the effective abortifacient dose. In field evaluations, results were less conclusive because of the small numbers of animals observed. Four of 20 females from the treated area and 13 of 13 from the reference area whelped, indicating that DES hindered reproductive success. A later field study indicated that DES had an insignificant effect on reproductive success, but the effects of population density and bait delivery probably interfered with the results (Linhart et al., 1968). Another possible limitation may be associated with the short duration of action of DES. Eighteen captive coyotes had ovarian follicular activity distributed over a 2-month period (Stellflug, unpublished data). Thus, a longer acting estrogen or more frequent distribution of short acting estrogens would possibly extend the effectiveness of treatment.

Mibolerone, an anabolic-androgenic steroid, when administered orally on a continuous daily basis, inhibited estrus in over 95% of domestic bitches (Sokolowski and Zimbleman, 1976). By contrast, a single oral dose of 1 mg of mibolerone did not inhibit vulvar swelling or vaginal bleeding in female coyotes when treated before or during proestrus (Gates, unpublished data). Perhaps an oral dose is required on a continuous daily basis for effectiveness which suggests mibolerone would not be useful for coyote population control.

Another class of compounds that has received considerable attention recently in reproductive physiology is the PGs. These compounds exert several physiological effects. Some PGs are potential reproductive inhibitors. In addition to affecting tubal transport (Spilman and Harper, 1973), prostaglandin $F_{2\alpha}$ (PGF $_{2\alpha}$) interrupts pregnancy through lytic action on the corpus luteum (CL) in several species (Inskeep, 1973). The CL of pregnancy is required for progesterone production during early stages of pregnancy and throughout pregnancy in many animals. In the dog, the CL is necessary up to 56 days of pregnancy (Jöchle et al., 1973). During this time, loss of luteal function would result in abortion. Thus, PGF $_{2\alpha}$ may be an efficient abortifacient over an extended period of time and would be effective as an antifertility compound for a considerably longer period of time than estrogenic compounds. In the dog, intravenous administration of 1-4 mg of PGF $_{2\alpha}$ within 2.5-5 minutes resulted in depressed peripheral plasma progesterone but plasma progesterone returned to normal within 24 hr and luteolysis did not occur (Jöchle et al., 1973). A transient decrease in progesterone was also observed in cattle when a sub-luteolytic dose of PGF $_{2\alpha}$ was administered (Stellflug et al., 1977). Recently, 0.5 to 1 mg/kg PGF $_{2\alpha}$ (tham salt, subcutaneously, sc) induced luteolysis in the dog (Sokolowski and Geng, 1977). Even though Lethal Dose $_{50}$ (LD $_{50}$) was 5.13 mg/kg PGF $_{2\alpha}$ there was still significant smooth muscle contraction with the luteolytic dose. Although PGF $_{2\alpha}$ has not been given orally to dogs, PGF $_{2\alpha}$ given orally to dogs caused severe gastrointestinal distress and suggests that PGF analogues given orally may cause a similar reaction (Sokolowski, personal communication). However, the very rapid absorption of PGs may allow oral administration even if the emetic threshold is surpassed. Also various PG analogues may cause fewer undesirable side effects, such as nausea, and still retain properties responsible for increased myometrial and luteolytic activity.

Three PG compounds were recently administered sc to nonpregnant coyotes that were monitored for evidence of luteolysis (Stellflug, unpublished data). Coyotes were observed weekly for time of most extreme vulvar swelling and were laparotomized 3-4 weeks later to confirm the presence of a viable CL. Two of eight animals with CLs were randomly assigned to one of four treatments. The treatments consisted of either 1 cc of carrier vehicle (H $_2$ O : ETOH, 1:1) or 5 mg of PGE $_1$, or 2.5 mg of 15-methyl-PGF $_{2\alpha}$ or 2.5 mg of 16-16-dimethyl-PGF $_{2\alpha}$. Blood samples were collected at 0, 12, 24 and 48 hr after injection and serum progesterone was analyzed by radioimmunoassay (RIA) as described by Louis et al. (1973) to monitor any changes of progesterone in the peripheral blood. Progesterone did not decrease significantly in the females after any of the four treatments. Laparotomies and progesterone analysis of serum samples taken one week after treatments did not reveal a decrease in luteal tissue either. The preliminary indication is that these PGs are not luteolytic in nonpregnant female coyotes between 30-40 days after vulvar swelling. However, this indication does not prove that these PGs or some other may not be effective in causing luteolysis or abortion, or both, in pregnant coyotes. In the cat, PGF $_{2\alpha}$ was not luteolytic but caused abortion (Nachreiner and Marple, 1974), so further research is needed on pregnant coyotes, which were not available at the time of this study. Provided some of the orally active PGs cause abortion in pregnant coyotes, additional research will be needed on the feasibility of an oral route for administration of PGs.

MALE ANTIFERTILITY COMPOUNDS

During the last 10 years interest in reproductive inhibitors for the male has increased. Most of this work has been directed toward rodent population control. The results of this research have provided us with several antifertility compounds that may be worth evaluating for effectiveness in coyotes.

For example, the chemosterilant effect of parenterally administered cadmium (Cd) on the testis has been reported in rats (Parizek and Zahor, 1956; Parizek, 1957; Gunn *et al.*, 1961; Mason *et al.*, 1964), mice (Parizek, 1957; Meek, 1959), rabbits (Cameron and Foster, 1963), guinea pigs and hamsters. (Parizek, 1960), goats (Kar and Das, 1962), monkeys (Kar, 1961; Kar and Das, 1962) and dogs (Sankaranarayana *et al.*, 1973). The coyote testes was insensitive to orally administered Cd at 12 and 24 mg/kg of body weight (Gates *et al.*, 1976). However, the subcutaneous injection of 2.24 mg/kg of body weight (Parizek and Zahor, 1956) is necessary to cause necrosis of the testes in rats. Thus, the oral administration of at least 50 mg/kg would be necessary to cause necrosis in the testes of male coyotes if we assume 5% absorption of Cd, which is the absorption level documented in most species of experimental animals (Friberg *et al.*, 1971). Unfortunately, 24 mg/kg is just below the emetic threshold in coyotes (Gates *et al.*, 1976) so Cd has little, if any, potential as a reproductive inhibitor for controlling coyote populations. Although the gonadotoxic effect of Cd is manifested on the same level as the general toxic effect, the gonadotoxic effect of boron is manifested at a lower level than the general toxic effect (Krasovskii *et al.*, 1976). Thus, boron might be effective as an antifertility compound in male coyotes.

Pipecolinomethylhydroxyindane (PMHI) administered in a single oral dose (150 mg/kg) caused permanent sterility in the male rat (Boris *et al.*, 1974b). PMHI also reduced testicular weight in mice, hamsters, guinea-pigs, rabbits, monkeys and dogs (Boris *et al.*, 1974a). Recent investigations on the effects of PMHI in coyotes indicate that testicular weight was decreased by more than 50% one month after an oral dose of 150 mg/kg and 75 mg/kg and by 45% within 10 days after 37.5 mg/kg (Gates, unpublished data). However, PMHI also caused acute toxicity to the kidneys at these doses. Further studies on smaller doses are in progress. PMHI is extremely emetic in canids, although changes in pharmaceutical formulation or smaller doses may resolve this problem. However, PMHI may impair the ability of the testes to secrete androgens (Boris *et al.*, 1974a). This impaired ability may reduce the chances of a treated male remaining a contender in competing for his domain.

Alpha-chlorohydrin (α -chlorohydrin) and related compounds were discovered as antifertility agents in 1968-70 in several species (Gomes, 1970). A single oral dose of 100 mg of α -chlorohydrin/kg of body weight caused 100% sterility in rats during a 10-week experiment (Cooper *et al.*, 1974). In dogs, chronic subcutaneous administration of α -chlorohydrin (Dixit *et al.*, 1975) caused antifertility effects. After oral administration of 100 mg/kg of body weight, no changes in semen quality were observed; but 500 mg/kg severely depressed semen quality for 1 week in preliminary studies with dogs (Gates, unpublished data). The 500 mg/kg of body weight approached the LD₅₀ for α -chlorohydrin in dogs. The rapidly reversible antifertility properties of α -chlorohydrin in dogs were also reported in male rats, guinea pigs, monkeys and sheep but not in mice and rabbits (Gomes, 1970). Because of the short time that α -chlorohydrin affects fertility and the toxicity observed in dogs, α -chlorohydrin apparently holds little promise as a reproductive inhibitor for coyotes.

Other compounds that affect male fertility and perhaps could be useful in coyote population control are triethylenemelamine (TEM), busulfan and methane sulfonic acid, methyl ester (MMS). TEM arrests spermatogenesis and causes testicular destruction in dogs and rats (Hendry *et al.*, 1951). TEM caused infertility in rats for 90 days after treatment, but beyond 90 days fertility returned suddenly to normal (Steinberger *et al.*, 1959). Seven to 8 weeks after a single dose of busulfan was administered, male rats became infertile (Jackson, 1966). The absence of fertility persisted for 1-4 weeks but could be extended by a larger single dose of busulfan (Jackson, 1966). In conjunction with MMS, a faster acting compound (Gomes, 1970), busulfan might be useful for coyote population control.

CONCLUSION

Research on reproductive inhibitors for coyote control is still in a stage of infancy. Eventual success in developing practical, effective, acceptable methods of coyote population control by anti-fertility methods will require intensive interdisciplinary effort. More basic knowledge of the reproductive physiology of the coyote is most urgent and may lead to valuable insight as to where our major emphasis for control should be placed. Concurrently, more research is required on the most promising compounds. In the female, several prostaglandin analogues and long acting estrogenic compounds should be considered. In the male, boron, low doses of PMHI, TEM and a combination of busulfan and MMS appear most promising to date. The needs and challenges are great.

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