REPRODUCTIVE CONTROL METHODS

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INTRODUCTION

In the United States, conflicts between humans and animals continue to increase. Overpopulation of white-tailed deer is an increasing problem in some sections of the United States. Rats cause major damage worldwide, yet attempts to control them by contemporary means (e.g., poisons or traps) are often less than satisfactory. Avian species, such as blackbirds, cause economic damage to sunflower growers; and starlings, pigeons, and Canada geese are becoming an increasing problem in cities. A growing interest in nonlethal methods for population control of nuisance or damaging species of wildlife has fostered research in reducing fertility of these overabundant wildlife species. Fertility may be reduced by interfering with the fertilization of the egg (contraception) or interfering with the implantation or development of the fertilized egg (contragestion).

The most important fundamentals for success in inducing infertility in a particular species are an understanding of the reproductive behavior and physiology of that species and selecting the most suitable infertility agent. Examples of reproductive behaviors that need to be considered are seasonal versus year-round breeding, monogamous or polygamous mating, multiestrus or monestrus; and does the species need a specific vegetation, temperature, or landscape to be successful in reproduction. If one could change a critical factor needed for successful reproduction, one could effectively reduce the reproductive rate of the target species. A common reason some species are overabundant is that they are adaptable to multiple or changing environments, thus their populations increase in spite of a rapidly changing landscape. Less adaptive species many times become extinct.

Recent infertility research has centered around immunocontraceptive vaccines, which control fertility by stimulating the production of antibodies against gamete proteins, reproductive hormones, or other proteins essential for reproduction. These antibodies interfere with the normal physiological activity of the reproductive system. Two common targets for immunocontraception are gonadotropin releasing hormone (GnRH) and zona pellucida (ZP).

GONADOTROPIN RELEASING HORMONE

The use of gonadotropin releasing hormone (GnRH) immunocontraceptive vaccine can shut down the reproductive activity of both sexes by causing development of antibodies blocking GnRH thus preventing the release of other essential reproductive hormones.

GnRH is produced in the brain by the hypothalamus. It controls the release of the pituitary reproductive hormones, follicle stimulating hormone, and luteinizing hormone, which in turn control the functions of the ovaries and testes. Antibodies to the hypothalamic hormone will reduce the circulating level of biologically active GnRH, thereby reducing the subsequent release of reproductive hormones. The reduction or absence of these hormones leads to atrophy of the gonads and concomitant infertility of both sexes.

GnRH contraceptive vaccines have been evaluated as immunocastration agents in pets, cattle, horses, sheep, and swine for more than 10 years, but little research has been done in wildlife species. Recently, in studies with Norway rats it was found that both males and females immunized with a GnRH vaccine were 100% infertile. The National Wildlife Research Center (NWRC) just finished a long-term study on the effect of GnRH on white-tailed deer in which we achieved an 86% reduction in fawning during active immunization and a 74% reduction over 5 years (Table 1).

ZONA PELLUCIDA

Zona pellucida (ZP) immunocontraceptives were the first to receive widespread publicity as contraceptives in deer and feral horses. ZP is an acellular glycoprotein layer located between the oocyte and the granulosa cells on the outer surface of the egg. For a sperm to fertilize the egg, it must first bind to a receptor on the ZP. An enzyme in the sperm then breaks down the ZP, allowing the sperm passage into the ovum. Antibodies to this glycoprotein layer result in infertility either by blocking the sperm from binding to and penetrating the ZP layer or by interference with oocyte maturation, leading to the death of the deve-

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Table 1 Summary of fawns born during 5-year GnRH vaccine study

Year	Treatment	Fawns/does
1994–95	Primed and boosted	3/4
1995–96	Primed and boosted	0/6
1996–97	Boosted	1/8
1997–98	No boost	3/8
1998–99	No boost	9/9
Breeding herd		156/90 (x = 1.7)
Sham controls		35/19 (x = 1.8)
GnRH treated		16/35 (x = .46)
= 74% reduction in fawns in GnRH group		

x = Average number of fawns/does.

loping oocyte. The ZP vaccine in use today comes from the pig ovary and is called porcine zona pellucida (PZP). PZP vaccine has been used to produce immunosterilization in dogs, baboons, horses, burros, coyotes, and white-tailed deer. In a white-tailed deer study at Pennsylvania State University, we achieved 89% reduction in fawning during the 2 years of active immunization. A 76% reduction in fawning was observed over the entire 7-year study (Table 2).

STATUS OF ORAL IMMUNOCONTRACEPTION

Fertility control as a technology is available today, but only in laboratory studies, pen studies, and in limited field situations with small numbers of animals. Immunocontraceptive and contragestive vaccines are being produced in limited quantities and animals injected with these vaccines become infertile for 1–3 years. However, to be practical for controlling free-ranging animal populations, these agents will have to be given orally. The technology for developing oral vaccines is in its infancy. Oral delivery is a very difficult technology to develop and may increase USDA and FDA regulatory involvement because it is a new and unproven technology.

Warren discussed a number of the factors relevant to the practical and logistical implementation of contraceptives for controlling wildlife. He correctly pointed out that development will take a team approach involving the laboratory scientists (e.g., immunologists, molecular biologists, and reproductive physiologists) who develop the contraceptive vaccines and associated technologies, and the wildlife biologists who will need to contribute to the development of delivery systems and the means to measure field efficacy and safety.

INDUCED INFERTILITY AS A MANAGEMENT TOOL IN AVIAN SPECIES

Interfering with egg laying or the hatchability of the egg appears to be the best approach to reducing the reproductive capacity in birds. Egg addling, including shaking,

Table 2 White-tailed deer PZP immunocontraception

Year	Treatment	Fawns/does	Yearly average	Cumulative average
1992–93	Primed and boosted	4/11	.36	.36
1993–94	Boosted	1/11	.09	.23
1994–95	4/9 boosted	1/9	.11	.19
1995–96	None boosted	3/9	.33	.23
1996–97	None boosted	7/9	.78	.33
1997–98	None boosted	9/8	1.13	.44
1998–99	None boosted	8/7	1.14	.52
Breeding herd		156/90		1.73
Sham controls		35/19		1.84
PZP treated		33/64		.52
		0.72% reduction in fawns in PZP group		

freezing, or oiling eggs in a nest effectively reduces egg hatchability. However, this method is labor intensive and may be useful only in small-scale operations. We are currently studying Nicarbazin (NCZ), a compound that interferes with egg laying and egg hatchability. Research is being conducted in collaboration with Koffolk Inc., the manufacturer of NCZ. Koffolk has an FDA-approved use of NCZ in broiler chickens for control of coccidiosis caused by *Eimeria* (protozoan parasites that are passed from chicken to chicken in the feces). Large-scale broiler chicken production is not possible without effective control of this parasite.

One of NCZ's side effects is that if fed to breeder or layer chickens, their eggs, although fertilized, often do not hatch. NCZ causes bleaching of the brown color in the eggshell and yolk-mottling (white spots occurring on the yolk) due to fluid transfer from the albumin into the yolk via increased yolk membrane permeability. Severe yolk membrane breakdown causes the yolk and the albumin (white) to blend together, destroying the conditions necessary for viable development of the embryo. When NCZ is withdrawn from the diet, egg production resumes within a few days. Koffolk, Inc. is interested in development of NCZ as an oral goose fertility control agent (Fig. 1).

Another oral contraceptive being studied is 20,25-diazacholesterol, an extremely potent inhibitor of cholesterol synthesis in laboratory animals. The 20,25-diazacholesterol is structurally identical to cholesterol except for the replacement of the carbons with nitrogens at positions 20 and 25. 20,25-diazacholesterol (which we call DiazaCon) acts to reduce the production of reproductive hormones in two ways: by reducing the cholesterol in the endocrine cell and reducing the cholesterol side chain cleavage needed for the production of the reproductive hormones. Conjugated linoleic acid (CLA) might have potential as an oral contraceptive in avian species. Linoleic acid is a 18 carbon fatty acid found in many plant seed oils with double bonds in the 9, 12 position. CLA has double bonds in either the 9, 11 or the 10, 12 positions. This change in the double bond position makes the molecule ineffective as a linoleic acid molecule. When CLA is added to the chicken feed at 0.5% by weight concentration and fed to laying chickens, their egg yolks will solidify when chilled in the refrigerator. When the clutch is being laid, the bird does not sit on the

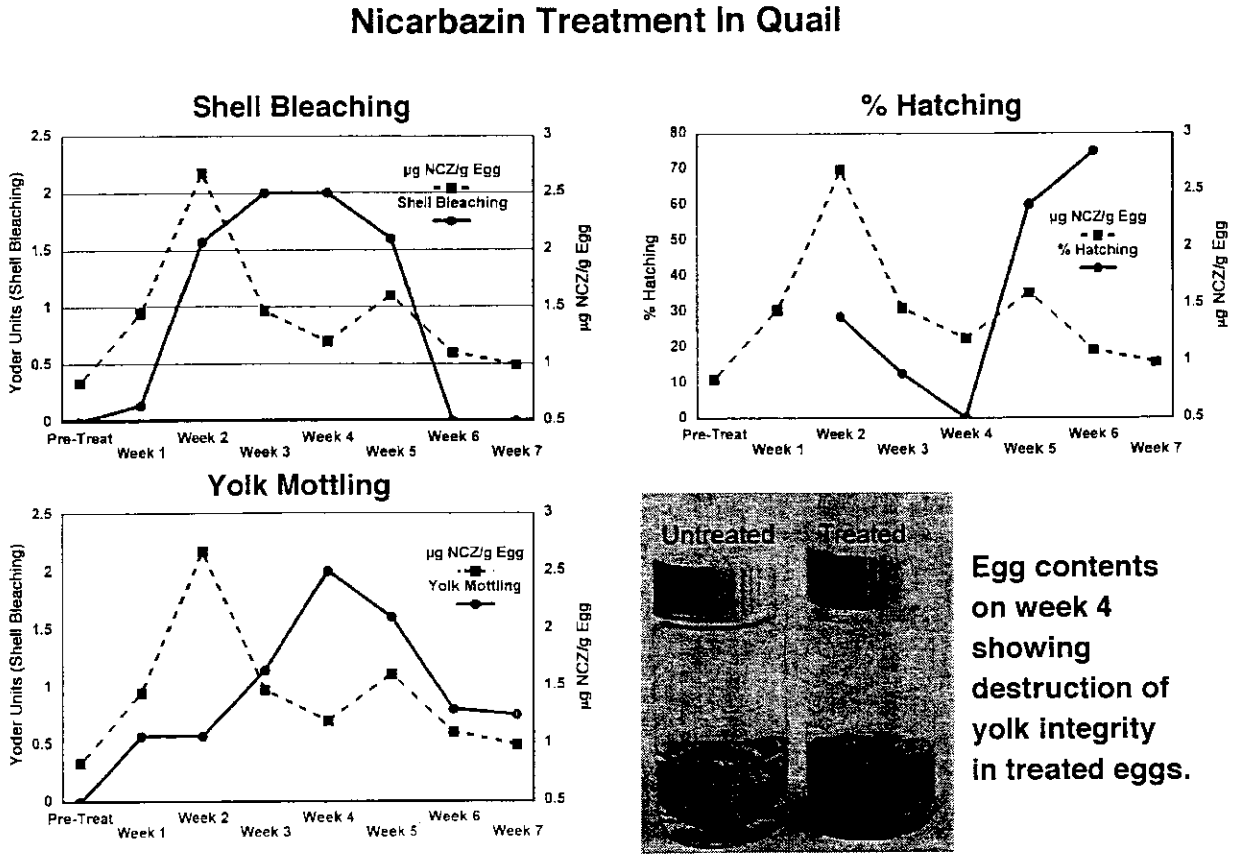

Fig. 1 Nicarbazin treatment in quail.

nest until the clutch is complete. As the temperature drops in the night, the unprotected yolks of CLA-fed birds will solidify. This change in density apparently is not completely reversible and interferes with the hatchability of the eggs.

NEED FOR MORE RESEARCH IN INDUCED INFERTILITY

As human and animal populations increase and as public opinion against hunting and lethal control increases, the need for fertility control becomes extremely important. Wildlife contraceptive technologies are potentially valuable as a new tool to be integrated with more traditional methods of wildlife population management: however, there is relatively little funding for this type of research. Because of the variety of animals that have become overabundant there is a large variation in their reproductive physiology that needs to be understood before their reproductive capacity can be curtailed effectively.

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