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Immunocontraception as a wildlife management tool: some perspectives

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Conflicts between humans and wild animals are not a new or an unusual phenomenon. Agricultural production may be limited because of crop damage by rodents or birds; exotic species may destroy or threaten to destroy native wildlife populations; diseases may be spread to domestic animals or humans by wildlife vectors. An extensive list can be comprised of such examples. Dealing with such conflicts is one of the greater challenges in wildlife management. One of the newest concepts to be applied to this challenge is immunocontraception.

A historical perspective

After 4 decades of research, contraceptive programs for effective wildlife damage control have not been developed and implemented (Kennelly and Converse 1997). Chemical contraception through the use of synthetic steroids, estrogens, and progestins (i.e., chemosterilants) was investigated during the 1960s and 1970s in coyotes (*Canis latrans*; Balser 1964; Brusman et al. 1968), pigeons (*Columba livia*; Woulfe 1970, Sturtevant 1971), red-winged blackbirds (*Agelaius phoeniceus*; Guarino and Schafer 1974), rats (*Rattus norvegicus*; Garrison and Johns 1975), coturnix quail (*Coturnix coturnix*; Schafer et al. 1977), and white-tailed deer (*Odocoileus virginianus*; Matschke 1976, 1977*a*, *b*, *c*, 1980; Roughton 1979). However, none of these efforts have led to development of a practical wildlife management tool for various reasons, including the need for repetitive applications, which makes chemosterilents impractical in most field situations. Steroids also tend to persist in tissue, and this raises environmental concerns. However, recent advances in reproductive physiology, immunology, and molecular biology have provided new methods of contraception. As a result of these innovations, some of the difficulties that have made chemosterilants impractical as a wildlife management tool may be overcome. Much of the recent interest in immunocontraceptives has been applied to white-tailed deer (Garrott 1995); however, this technology is also applicable to other wildlife species such as rodents, birds, and coyotes.

A review of the technology

Immunocontraception vaccines control fertility by stimulating the production of antibodies against gamete proteins, reproductive hormones, and other proteins essential to reproduction. The antibodies interfere with the normal physiological activity of these reproductive agents (Talwar and Gaur 1987). This approach is a natural process in that antibodies induced in the target animal inhibit reproduction and do not require constant or repetitive treatment of the animal with synthetic compounds; initial treatments are effective for 1-3 years (Turner and Kirkpatrick 1991).

Reproduction can be blocked at many sites in the reproductive process (Griffin 1992, Jones 1983). For example, an immunocontraceptive vaccine can shut down the reproductive activity of both sexes by developing gonadotropin-releasing hormone (GnRH) antibodies, which block GnRH and prevent the release of other essential reproductive hormones (Miller et al. 1997). Reproduction in females can be prevented by antibodies that bar sperm penetration of an ovulated egg by binding to the zona pellucida or to the sperm (Dunbar and Schwoebel 1988). Egg and embryo development can be hindered by (1) preventing implantation and development or gestation of the fertilized egg by producing antibodies to chorionic gonadotropin hormone (GC) or a similar hormones in different species responsible for the maintenance of pregnancy (Talwar et al. 1994), or (2) blocking riboflavin transport to the developing em-

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bryo. This process of causing infertility by interfering with gestation in called contragestion. It may be possible to design immunocontraceptive antigens that stimulate production of antibodies that are genus- or species-specific; however, at this time the technology is not available.

Gonadotropin-releasing hormone

GnRH is produced in the brain by the hypothalamus. It controls the release of the pituitary reproductive hormones, follicle-stimulating hormone, and luteinizing hormone. These hormones, 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 reproductive hormones leads to atrophy of the gonads and concomitant infertility of both sexes. Both avian and mammalian forms of GnRH have been identified (Sad et al. 1993, Melon et al. 1994). GnRH has be demonstrated to be an effective immunocontraceptive in several mammalian species (Robertson 1982, Ladd 1989, Adams and Adams 1992, and Awoniyi et al. 1993). Miller et al. (1997) demonstrated the immunocontraceptive effect of GnRH on the male and female Norway rat. GnRH also has been used as a contraceptive for domestic pets (Ladd 1994).

We have ongoing research on the use of GnRH to control the fertility of white-tailed deer. We have found that the GnRH vaccine acts as a contraceptive or as a contragestive depending on the immune response and the timing of the vaccine (Miller et al. In Press).

Melatonin

In fall-and-winter seasonal breeders, GnRH is activated by the release of melatonin from the pineal gland. Short days and long nights increase melatonin secretion. It is hypothesized that the change from long days to short days following the summer solstice increases the nocturnal levels of melatonin secretion. This increased melatonin level induces an increase in GnRH secretion, which, in turn, activates reproductive activity. Antibodies to melatonin could inhibit this reproductive "wake-up call" of the seasonal breeder (Lincoln 1992). Although there is no active research on the use of melatonin as a contraceptive agent new insight into the many rolls of melatonin in regulating our diurnal pattern may increase the interest in this compound as a contraceptive agent

Zona pellucida

The zona pellucida (ZP) is an acellular, glycoprotein layer located between the oocyte and the granulosa cells on the outer surface of the egg. In order 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 interfering with oocyte maturation, which leads to the death of the developing oocyte (Dunbar and Schwoebel 1988). Several authors have published on the use of procine zona pellucida (PZP) as a contraceptive agent in wildlife (Kirkpatrick et al. 1990, Turner and Kirkpatrick 1991, Turner et al. 1992, Turner et al. 1996, Turner et al. 1997). We have a multi-year study using PZP to contracept white-tailed deer in which we report the relationship between infertility, antibody titer, and hormone levels (L. A. Miller, B. E. Johns, and G. Killian, unpubl. data).

Sperm antibodies

Antibodies to sperm-head proteins can be produced. These antibodies are produced in the female and are available to bind to sperm present in the oviduct. Sperm-protein immunocontraception is being investigated for contraception in the red fox (*Vulpes vulpes*) and the rabbit (*Mus* spp.) in Australia (Tyndal-Biscoe 1991, Morell 1993).

Chorionic gonadotropin hormone

Chorionic gonadotropin (CG) hormone, which is produced by the implanted embryo in some species, induces the corpus luteum on the ovary to continue production of the progesterone required for the maintenance of pregnancy. Antibodies to CG reduce the blood levels of this hormone and thereby preclude successful implantation of the fertilized egg. This method of inducing infertility is called contragestion. Clinical trials are under way at the National Institute of New Delhi to test a human CG vaccine for contraception in fertile women (Talwar et al. 1994). Many species use other hormones to maintain the implanted embryo. Antibodies against these hormones have the potential to reduce fertility by inhibiting development of the implanted egg; the egg simply sloughs off and is reabsorbed.

Riboflavin carrier protein

The riboflavin requirements of the developing embryo are satisfied by the active transport of this water-soluble vitamin across the placenta. This transport is facilitated by a gestational-specific carrier protein called the riboflavin carrier protein (RCP). RCP plays a pivotal role in embryo development in both avian and mammalian species (Natraj et al. 1987, 1988).

Antibodies to RCP may prove to be a valuable immunocontraceptive. They have been shown to inhibit embryo development in mammals and may have the same effect in avian species when tested.

As interest grows in immunocontraceptive research, new methods of reproductive inhibition will appear that may supersede the approaches we are investigating today.

The immune self

The neonate vertebrate immune system develops a recognition of "self" proteins and hormones and does not produce antibodies against them. This self recognition is essential for survival because the production of antibodies against pathogenic bacteria and viruses is also essential for survival. However, self-fighting antibodies do sometimes form, resulting in abnormal, destructive processes, as demonstrated in diseases like multiple sclerosis and some forms of arthritis.

The entire immune system is in constant surveillance to determine what is "self" verses what is "foreign." If the immune system detects a foreign substance, it attacks that substance with antibodies already present or forms new antibodies to fight the foreign invaders. However, if the foreign material is recognized as familiar but harmless, the immune system may be unresponsive because a tolerance to the material was developed in a previous exposure (Ernst et al. 1988). Tolerance of harmless, foreign material may develop when repetitive, minute quantities are encountered or when exposure to large amounts occurs. Development of tolerance to food proteins is a normal process in the digestive tract, where particles and organisms are examined and either tolerated or attacked by antibodies. For example, in the small intestine, groups of lymphoid cells known as Peyer's patches (PP) sample food proteins and microorganisms as they pass through the intestine. Attracting the attention of these intestinal immune cells and similar immune cells in the pharynx region of the throat will be a key to the success of an orally delivered immunocontraceptive vaccine.

Antifertility vaccines are directed against self reproductive antigens (hormones or proteins) to which the recipient normally is immunologically tolerant. These antigens are made "non-self," or "foreign," by being coupled with a protein that is foreign to the animal. As the animal samples the conjugated "self-foreign" or "non-self" protein, its immune system produces antibodies to its own proteins or hormones (those essential for reproduction). This induced immune response against self is the key to immunocontraception. The infertility lasts as long as there are sufficient antibodies to interfere with the biological activity of the targeted reproductive protein or hormone. The duration is usually 1-2 years.

In a recent review article on current immunology research, Pennisi (1996) points out that scientists are discovering that "foreignness" may not be sufficient to invoke an immune response. A "danger" signal from stressed or damaged cells, in addition to the foreign antigen, may be needed to activate the immune system. This alarm signal may be a group of molecules on the surface of both bacterial and mammalian cells, called heat-shock proteins, which are gene-regulated and are produced and released from the cells when they are stressed by heat or other environmental factors. This additional information may be important in the preparation of effective immunocontraceptive vaccines.

Vaccine delivery

Subcutaneous or intramuscular injections are the traditional forms of vaccine delivery. To accomplish this in free-roaming animals, the vaccine must be delivered by a dart or a biobullet (Kirkpatrick et al. 1990, Garrott et al. 1992, Turner et al. 1992). Although this method may be effective in some confined locations, it is impractical for dealing with wildlife populations in large open areas.

Oral vaccination, with the exception of the oral polio vaccine, has received relatively little attention for humans and even less for animals; it requires larger quantities of vaccine and is less predictable than the injections. In mammals, oral immunization takes place via the mucosal immune system, which includes the pharyngeal immune follicles (e.g., tonsils and other similar tissues) and the immune follicles of the small intestine (e.g., PP; Mestecky and McGhee 1989). Because vaccines are proteins, they are rapidly digested in the stomach when administered orally. Hence, immunization must occur in the pharyngeal area; otherwise, the vaccine will need protection to pass through the stomach for release in the small intestine (McGhee et al. 1992, Miller et al. 1997).

The most effective way to deliver an antigen orally is to protect it until it is taken up by the PP. A combination of 2 approaches could lead to effective antigen uptake and potentiation of the mucosal immune response: (1) using an enteric coating on the delivery vehicle to slow the gastral degradation of the antigen until it is released in the small intestine, and (2) designing the vaccine to have enhanced attraction and attachment properties to the immune follicles in the small intestine (O'Hagan 1994, Walker 1994).

Recent advances in understanding the mechanisms by which pathogenic viruses and bacteria colonize and infect the intestinal tract have given us new information to use in developing successful and safe oral vaccines (killed or attenuated live). For example, if a vaccine bacteria is to be effective, it must be able to survive the stomach's acid and proteolytic enzymes so that it can attach and be taken in by the immune cells of the small intestine. For attachment to occur, it must have surface adhesive properties allowing it to adhere to the intestinal wall. Bacteria without adhesive properties are carried out of the gut with the waste material. Therefore, a vaccine consisting of a harmless bacteria with an inserted immunocontraceptive antigen and properties that allow it to be readily taken into the intestinal wall can be an effective oral immunocontraceptive. Bacteria used for this type of vaccine would be similar to the many kinds of bacteria that are normal flora in human and animal digestive tracts. We conducted a feasibility study in which we demonstrated that a harmless, live, genetically engineered tuberculin bacillus (BCG) could be safely administered to white-tailed deer; a substantial antibody response was created without transmitting the live bacillus to control deer in adjacent pens (Miller et al. 1998).

Liposomes are spherical, artificial, biological membranes (made up of phospholipids and cholesterol) that can be used to protect oral vaccines from stomach acids. Cholesterol and other lipids in the liposome membrane protect it from gastrointestinal degradation and make the liposome attractive to macrophages in the PP, where it is avidly taken up because of the membrane's lipophilic nature. This characteristic of the membrane causes the liposome to mimic a pathogenic bacteria cell when presented to the immune system. The liposome therefore acts as an antigen microcarrier capable of directing the antigen directly to the PP. Although the liposome is attractive to the macrophages, before it can reach them it must bind to the mucosal surface of the intestine. Increasing the mucosal-adhesive property of a liposome increases the mucosal-uptake efficiency, thus requiring smaller doses of oral vaccine. The most common liposome adhesive is a bacterial lectin, the nontoxic B subunit of cholera toxin. It is derived from a family of enterotoxins produced by several strains of enteropathogenic bacteria (Holmgren et al. 1992*a*). Lectins have multiple binding sites and can bind to receptors on the liposome as well as to intestinal receptors.

Recent advances in molecular biology and immunology have provided us with new tools, such as live vectors that can be used as delivery vehicles. A well-known application of this technology in wildlife management is the use of the live vaccinia virus to deliver oral rabies vaccines to raccoons (*Procyon lotor*) and red foxes (USDA/APHIS, Biotechn., Biologics, and Environ. Protection 1991). The attenuated vaccinia virus, a member of the pox viruses (*Poxviridae vaccinia*), was used as a vaccine against small pox for >20 years. Using recombinant genetic engineering, researchers at the Wistar institute inserted the gene responsible for the encoding of the glycoprotein rabies virus into the vaccinia virus. This recombinant pox virus, when administered orally, vaccinates the target animal against rabies. The tonsil lymphoid tissue is thought to initiate the immune response in these target animals. This pox virus might be a vector for an immunocontraceptive vaccine.

Immunocontraceptive studies at DWRC/NWRC

In 1991 we initiated research at the Denver Wildlife Research Center (DWRC), Denver, Colorado and the National Wildlife Research Center (NWRC), Fort Collins, Colorado to develop immunocontraceptive vaccines to address problems of wildlife damage control. The focus has been on synthetic vaccines for oral immunization of white-tailed deer, rodents, starlings (*Sturnus vulgaris*), and brown-headed cowbirds (*Molothrus alter*). In the fall of 1995, work began on the contraception of coyotes using both GnRH and PZP vaccines. Other species will be added as funding allows.

We injected vaccines in captive animals with various vaccine preparations. Rats sterilized with GnRH vaccine remained sterile for >1 year (Miller et al. 1997). White-tailed deer vaccinated with ZP of porcine origin remained sterile for 1–3 years as also observed by Turner et al. (1996) and Miller et al. (In press). We have reduced the production of testosterone to nonbreeding levels in male brown-headed cowbirds and starlings with avian-specific GnRH vaccine.

Our initial work centered on development of the vaccines and measurement of the immune responses and hormonal levels following systemic vaccination. Our goal was to deliver the vaccines orally. We successfully sterilized Norway rats via oral vaccination with GnRH encapsulated in an adhesive liposome that was designed by our group.

Effectiveness of the contraceptive vaccine

In addition to breeding trials, the effectiveness of immunocontraceptive vaccines is assessed by mea-

suring serum progesterone, testosterone, and antibody titers. A reduction in hormone levels as well as elevated antibody levels should correlate with the sterility of the animal. All immunocontraception vaccines presently being studied result in some behavioral changes, as suggested by Garrott (1995). These behavioral responses vary from total reduction of sexual function in both males and females to multiple estrus in the females immunized with ZP.

Because of concern that immunocontraception might selectively affect strong and healthy animals, we began a study to investigate the relationship between successful contraception and the health of test animals. Our hypothesis is that an animal accelerates breakdown of muscle to amino acids and ceases growth as part of an integrated physiological response to fever, stress, and infection. In this response, newly available amino acids are sent to the liver to provide protein material essential to stop bleeding, to stop infections by producing antibodies, and to provide an extra supply of glucose for energy. In other words, growth is secondary to survival. Therefore, the production of antibodies, whether to a disease organism or to an immunocontraceptive vaccine, occurs as a priority response in both healthy and unhealthy animals. Our study addresses the question of whether or not immunocontraception selectively allows the weak to multiply and the strong to become immunosterile.

The potential of immunocontraception in wildlife management

Immunocontraception as a technology is available today, but only in laboratory settings, pen studies, and limited field situations with small numbers of animals. Immunocontraceptive vaccines are being produced in limited quantities. Animals injected with these vaccines become infertile for 1-3 years. However, for effectively controlling free-ranging animal populations, these vaccines will have to be administered orally. The technology for developing oral vaccines is in its infancy, but rapid progress is likely because of a worldwide demand for oral vaccines against diseases such as cholera (Holmgren et al. 1992*b*) and the acquired immune deficiency syndrome (AIDS) virus.

To address public concerns (Bomford 1990) about the administration of a contraceptive vaccine we are continually consulting with the Food and Drug Administration (FDA). Immunocontraception may bring a greater safety to consumptive use of wildlife by humans and other animals. An animal that has been immunocontracepted contains antibodies that prevent reproduction, in addition to millions of other antibodies, all of which just like any other proteinaceous food consisting of amino acids, are harmless to the organism that digests them.

Warren (1995) discussed a number of the factors relevant to the practical and logistical implementation of contraceptives for controlling wildlife. He correctly pointed out that it will take a team approach involving the laboratory scientists (e.g., immunologists, molecular biologists, reproductive physiologists) who develop the contraceptive vaccines and associated technologies and the wildlife biologists who must fine tune the development of the delivery systems and field measures of efficacy and safety. This is a promising technology to be integrated with traditional methods of wildlife population management. Continued research is the key to developing the full potential of this technology.

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Brad Johns has been a research physiologist at the NWRC since 1967. He has conducted research with a variety of vertebrate pest species including coyote and rodent reproduction. He received a B.S. in biology from Colorado State University. At present, he is part of the biotechnology research team developing immunocontraceptives. ***Donald Elias*** holds undergraduate and graduate degress in forestry, wildlife biology, and natural resources management from the College of Natural Resources, Colorado State University, and a Paralegal Diploma from the School of Paralegal Studies, Professional Career Development Institute. He is a certified wildlife biologist and is a research wildlife biologist at the NWRC in Fort Collins, Colorado.