FERTILITY CONTROL AS A TOOL FOR REGULATION OF WILDLIFE POPULATIONS

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FERTILITY CONTROL AS A CONCEPT

Biological control of reproduction and fertility is a normal part of the life history of all organisms. Control mechanisms allow timing of reproduction with respect to age, time of day, season, and other periodic environmental events. Further modulation can occur with variations in temperature, rainfall, nutrition, and health status. Interactions with other members of the species, ranging from pherohormonal stimulation of estrus to social delay of puberty and breeding to infanticide, provide further constraints upon fertility and recruitment. All of these processes ultimately act through molecular neuroendocrine mechanisms that are under genetic control and are subject to natural selection and evolutionary change. The basic neuroendocrine pathways are present in all vertebrates and share common neuroendocrine mechanisms. These pathways are subject to external intervention and interruption in individuals.

Demography

Demographic approaches to fertility control can be formulated in terms of effects on population growth as a function of recruitment and mortality. Fertility interventions might consider any part of the life history from initiation of reproduction to the age of first reproduction. In many cases fertility control intervention in a wildlife population is first considered after the population size is already greater than considered acceptable. This timing usually requires a direct intervention to reduce population numbers to rapidly achieve a population size goal. This harvesting or culling approach has rarely been followed by a long-term management program for population control with a resulting periodic recurrence of the problem.

A demographic model of the population and explicit demographic goals are an essential basis for considering fertility control methodology for population control. If there is concern for maintenance of genetic diversity in the population and retention of reproductive potential, then additional constraints are placed upon the choice of methods for control.

Population growth can be managed through the manipulation of mortality, reproduction, or both. There is a tradition of habitat manipulation for game species to enhance reproduction and thus increase the potential harvest and then to utilize harvesting as a means of reducing the population to prevent habitat damage. Wildlife and fisheries management, with a responsibility and tradition of managing game and food species, have developed culling and harvesting methodologies. The only interest in reduction of fertility has been as a supplement to mortality methods for control of pest species or problem populations. Control of reproduction is generally less efficient than control of mortality since removal of animals immediately decreases the population and the reproductive potential.

Fertility control is being proposed as a potential alternative to mortality methods for humane reasons, genetic management of endangered species, and reversible control of limited populations. Fertility control in the genetic management of captive populations provides control over the selection of breeders, timing of reproduction, and frequency of breeding. This has proven important for increasing the genetically effective population size of captive populations which are limited to populations of a few hundred in total size.

The major elements of population dynamics may be represented by a parabolic curve of recruitment and a hyperbolic curve of the deaths. As population size increases along the population axis, the number of recruits relative to deaths is high. This is because at low density the resources available to the population are high, and most females can be successful in raising young. At the same time, the number of deaths is low because of favorable conditions for life. The point at which the two curves intersect may be defined as K, the carrying capacity.

If one treats a female with fertility control methods, reproduction of that female is removed, but the female continues as a member of the population. However with the mortality of that female, one reduces the population by one and the reproduction of that female is removed as well. Therefore, a unit of mortality intervention automatically carries with it a unit of reproductive intervention, whereas a unit of reproductive intervention does not carry with it a unit of mortality intervention. This means that per animal treated, the efficiency in population control will be double for mortality intervention.

It follows, therefore, that reproductive intervention cannot effectively treat a case where there already are too many animals for the resource base. Reproductive intervention needs to be applied before a population becomes too large, so that treatment achieves population limitation before resources become limiting. This is as opposed to mortality intervention, that can treat either case effectively.

Genetics

Mortality methods have been rejected by zoos as a primary management option because population control can be partially realized by managing reproductive rates. Male sterilization has been used successfully in several species. However, permanent removal of a male from the breeding population has no advantage in a small population. Sexes can be separated when breeding is undesirable, however this increases space requirements, disrupts social relationships, and same sex groups frequently show increased aggression which can result in mortality.

There is a fundamental genetic problem with reducing the number of breeding pairs in a population. Decreasing the number of pairs reduces the genetically effective size of a population, resulting in an increased rate of loss of genetic diversity from one generation to the next. The effective size of a population is maximized by assuring that the maximum number of different breeders reproduce each generation. The offspring will contain a larger fraction of the genetic diversity of the parental generation. Therefore, under the constraint of maintaining zero population growth, the gene pool of the population can be most effectively managed by reducing the reproductive potential of each animal rather than reducing the total number of breeders. These genetic concerns will apply to populations that represent a substantial fraction of the species (or subspecies) genome. Genetic management ordinarily would not be a matter of concern for localized urban white-tailed deer, raccoon, coyote, or beaver populations which are samples of much larger geographic populations.

Captive Population Management

Resource limitations present a constraint to captive carrying capacities. Conway (1986) estimated the total number of spaces available to captive propagation efforts in North American zoos to the 270,000. Captive populations compete for this space and the ceiling of any population size will, in part, be determined by the number of other cooperatively managed populations with similar housing requirements. The process of establishing a workable carrying capacity for a population is therefore a process of compromise between the minimum viable population size requirements dictated by genetic and demographic needs and the realization of limited zoo resources. The success of zoos in adequately managing large numbers of small populations rests in part on how effectively population growth can be managed.

INTERVENTION IN FERTILITY

Points of intervention in fertility range from neonatal survival to initiation of gametogenesis. I will consider primarily methods that affect reproduction prior to conception, but it maybe useful to outline come points of intervention beginning with neonatal survival.

Time of Intervention

Neonatal survival can be reduced by: 1. Specific disease agents in the dam, 2. environmentally acquired diseases, 3. dam nutrition before and during pregnancy, 4. blockage or reduction of lactation, 5. inhibition of maternal response to the neonate, 6. infanticide by predation or conspecifics, 7. timing of parturition relative to season, 8. inbreeding depression, 9. disruption of maternal care, 10. low birth weight.

Pregnancy termination: 1. Abortion, 2. delay in parturition, 3. premature delivery, 4. protein - calory nutritional deficiency, 5. specific nutrient deficiencies or excesses, 6. toxic substances, 7. developmental abnormalities, 8. immunological incompatibilities, 9. drugs and toxic agents, 10. stress - adrenal hormone excess, 11. prostaglandins and corpus luteum failure, 12. placental failure, 13. blockade of progesterone receptors.

Implantation: 1. Timing failure, 2. endometrial preparation, 3. rejection, 4. corpus luteum failure, 5. antibodies to chorionic gonadotropins.

Zygote: 1. Fallopian tube motility failure, 2. zygote degeneration, 3. Tertiary - level of hypothalamus (LHRH).

Fertilization: 1. Ovulation failure, 2. sperm abnormalities, 3. timing, 4. rejection, 5. immunological, 6. ovum maturity.

Folliculogenesis and ovulation: 1. Primary - level of ovary (receptors, hormone synthesis), 2. Secondary - level of pituitary (LH, FSH, Prolactin), 3. Tertiary - level of hypothalamus (LHRH).

Spermatogenesis: 1. Primary - toxins, genetic, antibodies, 2. Secondary - deficient pituitary gonadotropins, 3. Tertiary - hypothalamic failure.

Breeding behavior: 1. Pherohormonal stimulation, 2. stress, 3. isolation, 4. rearing deficits, 5. opportunity, 6. social structure.

Neuroendocrine Mechanisms and Control Loops

The mechanisms by which fertility control may be achieved range from direct removal of the gamete producing organs, to interference with or disruption of the hierarchy of neural and endocrine events leading to gametogenesis and reproduction, to interference by social control. The practice of castration as a method to prevent reproduction and modify behavior is as old as recorded history. Recognition of an endocrine role of gonads in male potency in chickens by Brown-Sequard (and self administration of sheep testes extracts) was the historical beginning of endocrinology. The effort to remedy the loss of human male potency with aging by treatment with ram testes extracts was the beginning of clinical endocrinology. Blockade of reproduction with progesterone was recognized by Pincus (the originator of modern endocrine methods of contraception) as a route to control of human fertility less than 50 years ago.

Endocrine hierarchy of reproduction -- Target tissues and cells - produce gonadal hormones (testosterone, progesterone, estradiol) as essential steps in production of mature gametes, behavioral support of reproduction, fertilization, pregnancy, and parturition. The steroid hormones and other products of the gonads act as feedback signals to the pituitary and hypothalamus affecting the release of their hormones. In sufficiently high doses they can suppress the gonadotropin secretions of the pituitary and result in reproductive failure.

Gonadal hormones - the steroid sex hormones are produced by the testes and ovary as part of the process of gametogenesis and the support of pregnancy in the female. These steroid hormones are also produced in smaller quantities by the adrenals. Analogues and the native hormones are used to suppress the release of gonadotropins by the pituitary and prevent gametogenesis and hence act as contraceptives. Most human female hormonal fertility control agents act to prevent normal gametogenesis as the mechanism of preventing conception. They also affect fallopian tube motility and the state of the uterine lining in a manner that reduces the possibility of implantation. Virtually every cell in the body has receptors for these hormones and is subject to their influence. For this reason, they are a poor subject for immunological control or production.

Pituitary hormones - LH and FSH (gonadotropins) and prolactin (support of lactation and perhaps maternal behavior) act upon cells in the gonads to regulate the production of the gonadal hormones. They are proteins and are particularly inviting targets for immunological methods. However complete blockade results in behavioral effects which may be adverse through reduction or loss of the gonadal hormones.

Hypothalamic hormones - LHRH or GnRH regulates the production and release of the gonadotropic hormones by the pituitary. It is a decapeptide. Synthetic analogs with greatly increased activity (agonists) have been prepared which bind tightly to the pituitary receptors and then block subsequent normal regulation of the pituitary gonadotropins. They can thus block fertility. This approach is attractive since it avoids the potential direct adverse effects of administering steroid hormone analogs and in principle some of the behavioral effects could be mitigated by administration of either estradiol or testosterone.

Neuroendocrine inputs - see modulation systems.

Modulation systems -- Opioid system - the endorphins affect the release of the gonadotropins from the pituitary in many species and may be a part of a stress dependent mechanism for blocking reproduction.

CRF -> ACTH and Endorphins and stress - stress is often suggested as an explanation for disruption of reproduction and depression of the immune system. The corticosteroid inhibitory affects on reproduction have been difficult to document experimentally in wild species and no method has been suggested as a routine for fertility control. It is worth remembering that many of the progestational agents used do have corticosteroid activity and depress the release of ACTH. This activity may be detrimental in some species particularly on removal of the agent.

Pineal and melatonin and photoperiod and season - this system receives input from the retina via a multiple synaptic pathway which provides photoperiod information which serves as the base for circadian and season rhythms. Manipulation of photoperiod or administration of melatonin can be used to alter the timing of reproduction.

METHODS AND PROBLEMS

Problems

Targeting, delivery, and effectiveness are fundamental biological and methodological problems for effective fertility control in wild species. Delivery of the most effective agents has depended upon handling or darting of individual animals. This is true for the surgical, mechanical, hormonal, and endocrine methods. This limits the usefulness of the methods to our ability to treat a particular species and population. Thus it usually is difficult to capture a sufficiently large proportion (79-95% of females) of a deer population to have demographic effectiveness. The handling is labor intensive, and effective trapping of deer is a function of seasonal food availability. Feral horses can be captured more easily, treated, and released. The long duration of the currently studied implants in horses and deer indicates that they may last long enough to be demographically useful. The cost of this technique is probably competitive with the horse capture and adoption program.

Remote delivery to deer, even by dart, would increase the usefulness of any of the proposed methods by eliminating the capture and handling steps. Development of such delivery methods is feasible if funding becomes available to complete the development of prototypes already accomplished.

Remote delivery in baits and feeds has the major problems of control of target animals, selection of target species, and the lack of any single dose ingestion methods. Immunological methods using recombinant vaccines, similar to those being developed for rabies, may offer such an approach in the future.

Delivery: Injection of suspensions or oil-based preparations are usually short term; a season or less. Hormones in microencapsulated pellets offer the possibility of 2 season effectiveness in some species. It is also possible that suitable antigens or vaccines could be delivered in pulsed release pellets to provide the multiple injections necessary for suitable antibody reasons. Long-term effectiveness might be dependent upon booster injections.

Oral methods are only useful in highly controlled environments which allow effective daily treatment.

Silastic Implants - have been used in more than 40 species in captive environment and in 6 free-ranging species. They have proven 90% or more effective in terms of individuals treated. Population effectiveness appears to have been achieved in horses and goats over the limited time period of the studies. Of course, they do not immediately reduce population size.

Morbidity: anemia, delay in parturition, endometrial disease, carcinogenesis, appetite depression, weight gain, delayed infections, acute infections, depression, lactation.

Behavior: aggression, depression, rejection of cubs, maternal behavior, dominance relationships and social structure, and territory defense.

Effectiveness: species differences in response, mechanical failures, proportion of population treatable, proportion of effectively treated, loss of devices.

Costs: number of individuals to treat, number of treatments (single - implants, multiple - injections, oral, immunological), costs of treatment materials, costs of application, costs of monitoring, costs of failure, comparisons with other methods of population control.

<u>Methods</u>

Surgical: castration, ligation, injections of sclerosing agents.

Mechanical: intrauterine devices, vaginal devices, vas deferens plugs, injections, suspensions, oil-based preparations, pellets, pulsed release microcapsules.

Implants: slow release devices - diffusion from silastic tubes and rods; osmotic pumps - short-term experiments.

Oral: Baits - distribution, access, and specificity.

Behavioral: separation (captive animals), territorial protection (wolf study).

Seasonal: light pulses, melatonin.

<u>Agent</u>

Chemical: male gametogenesis, sterilants, toxicants.

Endocrine: steroids and analogues - basis of most widely used methods in all mammalian species. LHRH agonists and antagonists - demonstrated effective.

Immunological (Hunter and Byers): the basic concept of immunocontraception is to inhibit fertility by means of antibodies combining with and inactivating a reproductive-tract protein or hormone necessary for successful reproduction (Talwar, 1986). There are several potential methods of immunocontraception being investigated which include the development of vaccines to gamete antigens and reproductive hormone antigens.

Neutralization of integrative hormones can interfere with gamete production in both sexes or can interfere with pregnancy. A major problem with such immunization is that the effects of hormones are widespread and diverse in the body. Hence, the risk of unwanted adverse side effects from immunization is high.

<u>Pituitary Hormones</u>

The pituitary gonadotropins, LH and FSH, stimulate the production of sex steroid hormones and gametogenesis. As such, they are essential for reproduction. Active and passive immunologic approaches have been proposed for control of fertility by antibodies intercepting the action of one or both gonadotropins.

<u>Hypothalamic Hormones</u>

Antibodies produced against LHRH block ovulation and cause ovarian regression in rats and testicular regression and arrested spermatogenesis in rabbits. The severe reduction in gonadal steroid production after immunization, the variability in the response of individuals to the treatment, and the lack of a suitable adjuvant made immunization against LHRH for contraceptive purposes appear impractical.

<u>Zona Pellucida Proteins</u>

The zona pellucida is an acellular glycoprotein layer surrounding the mammalian oocyte, which the sperm must attach to and penetrate for fertilization to occur. Antibodies to it can totally inhibit fertility <u>in vitro</u> and <u>in vivo</u>. Antisera raised against the zonae of several species are tissue specific by have varying degrees of crossreactivity between species.

<u>Sperm Antibodies</u>

The presence of antisperm antibodies is a major cause of immunoinfertility in both men (autoimmunity) and women (isoimmunity). Normally, the male's blood-testis barrier prevents sperm antigens, synthesized for the first time at puberty, from being detected by the body's immune surveillance system. If this barrier is broken, autoantibodies against testicular specific glycoproteins are generated which result in destruction of spermatocytes, spermatid, and spermatozoa. The animal's libido is not affected, but is sterile.

<u>Placental Components and Products</u>

Immunization against placental hormones produced during pregnancy have been used to control fertility. It should be noted that pregnancy-specific proteins are usually species specific. With the exception of pregnant mares serum (PMS), little is known about pregnancy specific proteins or even if they are present in non-domestic species.

EXAMPLES

<u>Golden Lion Tamarins (Ballou, AAZPA/SSP Program)</u>:

The issues facing the management of the captive population is rapid population growth and genetically effective population size management. Golden lion tamarins are best kept in captivity as monogamous pairs and have tremendous reproductive potential. They reach sexual maturity at 18 months of age, can live 20 years, and can reproduce twice a year. Gestation is 125 days. Litters average 2 offspring with a maximum of 4. The regulated use of contraceptives could allow reproduction once every 2 years rather than twice a year while maintaining stable family groups in normal behavioral conditions.

During phase 1 of the project only one possible pregnancy among 34 breeding seasons was observed, $p < 0.0001$ so the implants were successful at preventing pregnancy. Mortality rates were not affected, and there were no major behavioral problems or significantly disruptive social disturbances in any of the groups.

The impact upon long-term retention of genic diversity by controlling population growth without contraceptives by establishing a limited number of permanent breeding pairs was compared with controlling population growth by breeding all individuals in a limited number of specified, pre-determined age classes while using implants to prevent all other reproduction. Assuming no difference between the sexes, the effective size of the population using the strategy of limiting the number of breeding pairs was 76, or 15% of the actual population size. Over the next 200 years, or 33 tamarin generations, 20% of the genetic variation will be lost.

Prevention of reproduction with implants during age classes 5 through 8 and within each breeding age class once one litter is produced. This strategy markedly increases the effective size of the population not only by increasing the total number of different breeders in the population (from 90 to 120), but also by decreasing the variation in the number of young produced by each individual (from 37.8 to 7.7). The effective population size is now 274, or 55% of the actual population size. After 200 years, 94% of the original genetic variation will be retained in the population.

Mountain Goats (Hoffman and Moorhead in Olympia National Park):

One technique each for females and males was selected for extended field testing. The effectiveness of each treatment was assessed on an individual and population level. Reproductive success in treated and untreated (control) females was determined annually through a combination of aerial and ground observation. Treatment effectiveness on an individual basis was tested by comparing the proportion of treated to untreated females with young.

Subdermal implants of melengestrol acetate (MGA), a steroid ovulation inhibitor, were tested in females. A solid, silastic cylinder (diameter 13 mm, length 40-50 mm, weight 4-6 g) containing MGA was implanted subcutaneously in the dorso-lateral region of the neck in each female. Twelve female goats were captured, treated with the MGA implants, and released. Treated animals were fitted with radio transmitter collars to aid in relocation and monitoring of reproductive success. The use of MGA implants appeared to be effective in reducing reproductive performance in female mountain goats for 3 to 5 years, with approximately 90% effectiveness in curtailing reproduction.

Chemical vasectomy, or epididymectomy, was selected as a suitable method for testing. In this procedure a sclerosing agent is injected into the testes, epididymis, or vas deferens, resulting in permanent sterilization in males of various species. Hemorrhage is minor, infection unlikely, and behavior is largely unaffected by the technique. Chemical epididymectomy has been used recently with apparent success on feral dogs the Galapagos Islands. Little training and no surgical equipment is needed to carry out the procedure.

Five male goats were captured, treated, and released in 1985. Radio-collars on animals aided in relocation and monitoring. Animals were injected in the caudal epididymis of each testis with .75 cc of a liquid sclerosing agent (Chem-cast; Bio-Ceutic Laboratories, Inc., St. Joseph, MO). Treatment of male goats did not affect reproduction or population size in the Mt. Carrie subpopulation during the one-year period of study (1985-1986). Reproductive organs of treated vs. untreated males did suggest that chemo-vasectomy had caused sterility. Behavior of the treated individuals was apparently unchanged.

Lions (Berry and Orford in Etosha National Park, Nambia):

Thirteen lionesses in 4 prides, comprising 6% of the adult female population, were used. Contraception was administered in 2 forms to 13 lionesses: 5 received an injection of medroxyprogesterone acetate; 8 received an intramuscular implant of melengestrol acetate (MGA) prepared and supplied by Seal, pers. comm. (1982); 2 of these 13 lionesses received both forms of contraception, viz. initially Depo-Provera, followed by an MGA implant. Activity patterns, behavior and social cohesion in the experimental prides did not alter significantly, but a drought resulted in prides changing their territories. The lionesses treated with contraceptives remained anoestrus, but could be returned to fertility by removing implants. Three MGA implants were removed from lionesses after 22 months. These animals ovulated and became pregnant within 36 days during which time focal animal studies were carried out.

Based on this experience, Berry recommended the use of hormonal contraceptive implants for controlling overabundant lions in ecologically disturbed conservation areas in preference to culling, for several reasons.

His reasons, presented in part here, summarize the thinking of a manager trying to develop a management strategy for a small population in a bounded reserve:

1. Contraception is reversible and can be terminated at will if errors in its application become apparent. Culling in contrast, is final and errors committed are irrevocable.
2. Contraception can be rotated through the breeding stock of lionesses, allowing the gene pool to be tapped. Culling, on the other hand, destroys genes, lessening the genetic reserve.
3. Contraception does not significantly alter behavior, activity, or social cohesion in free-living lion prides. Culling of lions may cause marked social disturbances, disrupting the processes of natural selection.
4. Intensive culling of lions for a period of 4 years in Kruger Park (335 lions representing 63% of the number in a selected area were culled) met with limited success since they regained 90% of their pre-cull numbers only 17 months after cessation of culling.
5. Unpredictable and undesirable side effects may occur when animals such as carnivores, which occupy a tertiary trophic level in the nutrient and energy flow through a system, are injudiciously removed.
6. On aesthetic grounds the intensive, long-term culling of lions in a national park like Etosha will not meet with approval of the public, including the lay press. Lions are one of the main attractions for tourists visiting Etosha and popular opinion is a major factor to take into account when creating a favorable image of nature conservation.

SUMMARY

A program to utilize contraception for population control should have explicitly formulated genetic and demographic population goals. The program will require a long-term commitment to management with treatments of animals added to the population on a periodic basis (every 2 - 7 years depending upon the species and intensity of treatment) since fertility control will ordinarily not be used to manage a population to extinction. This also implies a suitable marking of treated animals to minimize the costs of repeated treatments.

The species suitable for fertility control are primarily long lived with relatively low rates of reproduction - perhaps 1 to 6 young per year. These are K-selected species as contrasted to r-selected species with high rates of reproduction (boom and bust) and high rates of mortality which are not easily modified.

Given the current delivery technology, populations of 100 to 200 animals are most easily treated for difficult to capture species, although individual populations up to 1000 could be handled in species like feral horses.

Species with limited populations subject to the vagaries of environmental stochasticity might best be treated with reversible agents to allow survivors of a catastrophe to reproduce to replenish a population. Also animals that have not reproduced should become breeders at least once in their lifetime to maximize the effective population size and minimize the rate of loss of genetic diversity.

Delivery methodology remains the limiting factor in successful and practical application of fertility control to free ranging wild populations. Possible developments range from remote delivery with dart systems, oral treatments with highly species specific recombinant vaccines, microencapsulated treatments that allow controlled and pulsed delivery, and the use of new agents that can be delivered in smaller volumes by available methods.

Much of the materials presented here are drawn from chapters by the authors noted in a book "Fertility Control of Wildlife Populations" based upon a symposium held in Philadelphia and edited by myself.