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THE POTENTIAL VALUE OF GENETICALLY STERILE NORWAY RATS IN REGULATING WILD POPULATIONS

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I appreciate the invitation to address this assembly, and hasten to inform you that I come before you as a Director and representative of the Introgene Foundation of Oklahoma City, not as one who has been actively performing the research of which I shall speak, although I have been following it very closely for approximately five years. I am grateful to the Foundation for sending me to this Conference to present this paper.

The biological control of animal populations took on a new dimension with the development of radiation-induced sterility in the screw-fly some two decades ago, and since that time it has been the dream of population biologists that a similar technique might be developed for controlling populations of vertebrate pests. A means for this may now be at hand for the Norway rat, as a result of the serendipitous occurrence of a remarkable mutation in the rat colony used by Dr. Allan Stanley and Dr. Laurence Gumbreck at the University of Oklahoma School of Medicine. This colony, consisting of animals derived originally from a cross between King and Holtzman rats, was maintained for the study or reproductive endocrinology and related phenomena.

In 1962 a female rat borne in this colony was observed to have an aberrant color pattern, which the investigators perpetuated so that its inheritance might be studied. Without going into the details of the expression of this character in various color patterns of laboratory rats, suffice it to say that in wild-colored animals the gene expresses itself by a white spot or streak on the forehead and a white area of variable extent on the abdomen. In many cases this extends up on the sides as well.

In studying the inheritance of this color pattern it was discovered that males exhibiting the character also were sterile. Successful crosses, therefore, could only be accomplished using normal males, and mutant females. Litters from these matings produced normal and mutant females in equal numbers, as well as equal numbers of normal and sterile males. Anyone with a knowledge of genetics will recognize this as the classic distribution of characters in a heterozygous backcross to a homozygous recessive parent. Since in 18 generations of test crosses, plus many hundreds of additional matings, the color marker and the sterility factor invariably are transmitted together, the conclusion is inescapable that the two expressions are controlled by a single pleiotropic dominant gene (Gumbreck, et al., 1971).

The significant points concerning this mutation are first that it is a dominant gene, second, it produces sterility in the male, and third it also governs a distinctive color pattern whereby sterile males and carrier females may be recognized with 100 percent accuracy from the day of birth.

Further study of these sterile males has elucidated their biology as follows: There is a slight retardation of growth in the sterile males, but at approximately 120 days of age sterile and fertile males are comparable in weight, and in adults sterility does not affect size. Sterile and fertile males appear at least equal in size and behavioral reactions. As will be noted later, the sterile males often appear more competitive than their fertile sibs and even than wild fertile males.

Histological studies of mutant sterile males reveal several interesting points (Gumbreck, et al., 1972). At birth both normal and mutant males have normal-appearing seminiferous tubules with abundant spermatogonia and sertoli cells. At age 20 days normal rats have enlarged germ cells and dividing spermatocytes are frequently observed. In mutant males at 20 days the tubule shows little change from birth. Few spermatogonia are enlarged and there are few spermatocytes. It should be pointed out that this is variable. Some mutants exhibit testes with considerable more activity than is shown on this slide.

At 120 days of age, when the rats are fully adult, normal males exhibit the typical picture of full spermatogenic activity, with abundant sperm production. In mutant males the picture at 120 days is one of regression of activity. Virtually no cellular activity is apparent, and no sperm are to be seen. Often whole sections of the tubules will have

cells that have become vacuolated, and usually the only cells present in quantity are the sertoli cells. Note in this slide, however, the continued abundance of the interstitial cells of Leydig, which produce the male hormone. The next slide is also from a 120 day old mutant. Notice that this individual has some germ cell activity still in progress. It is true that in some individuals some spermatogenesis continues as long as four or even six months before finally ceasing altogether, although in most mutant males sterility is complete by 90 days. Fortunately these protractedly fertile mutants are recognizable without difficulty. Completely sterile mutants have testes approximately one fourth the size of their fertile normal sibs, and the organs are soft and flaccid. In mutants with prolonged fertility the testes, while small, retain firmness and turgidity that make them easily separable from their fully sterile brothers.

Obviously caution requires that in any population studies using sterile males, only selected males over three months of age should be used. Tests made on fully sterile adult mutant rats have shown that they are as large, or larger than wild males of the same age, have high androgen levels, and their adrenal glands are as large or larger than those of wild males. When given the opportunity sterile mutants mate readily and vigorously with wild females and induce in them a state of pseudo-pregnancy lasting approximately 17 days (only a few days less than the duration of a full-term pregnancy) (Stanley, 1970).

Willingness to mate, and the presence of satisfactory androgen levels in the blood suggested the possibility that these sterile males might actually be competitive with normal wild males. It was, therefore, decided to make aggression studies to test the dominance of sterile males in competition with wild and albino normal males, fertile siblings, and sterile cagemates. The results of these aggression studies were expected to indicate whether or not it might be feasible to use sterile males to lower the reproductive rate in wild populations. These confrontation studies, and the population studies that followed, were planned and executed by the late Hobart Landreth until his untimely death by accidental drowning in March, 1973. The techniques of Calhoun (Calhoun, 1963) in his study of the ecology and sociology of natural Norway rat populations were used in this experiment. Briefly, the method consisted of 20 trials, ten minutes each, for each pair of animals, where the animals were introduced into a confrontation chamber and their reactions recorded by direct observation. Seven behaviors used by Calhoun as indicators of dominance were recorded. In the controls, sterile males versus non-cagemate sterile males, aggression of any sort was observed in only 30 percent of the encounters. In all other series, some form of aggression occurred in 90 percent of the trials. Fighting occurred only in encounters of sterile males with wild males and fertile albino males. In these standardized confrontations the sterile males exhibited dominance over wild and albino males in 75 percent of the encounters, and were dominated by their opponents in only ten percent. Fifteen percent of the encounters were neutral or inconclusive. The comparative percentages were 70 percent, ten percent, and 20 percent when sterile males were confronted with their fertile siblings.

These confrontation tests gave sufficient promise of the sterile male being competitive in a social situation that a test was devised in which sterile males would actually compete with wild males socially and sexually (Landreth, 1973).

For this test four large outdoor rat-proof pens 50 x 50 feet were constructed. The walls were of corrugated metal four inches high and were countersunk, trenched, and packed with watered gypsum anhydride so that the perimeter was impervious to digging. Each pen was provided with baled hay in stacks four bales wide, five long, and three high. Spaces between the bales provided hiding places and nesting sites within the stack with free access in all three dimensions. Odd pieces of lumber provided cover outside the haystacks, and lab chow and water were provided ad libitum.

In each such pen twenty males and twenty females all of comparable size were released. Wild rats used in these experiments were held in cages one month before release. All animals were earmarked and weighed before the experiment began. After three months the haystacks and other cover were removed and all animals captured.

The composition of the male test populations were as follows:

Enclosure 1 contained only wild rats, and was used as the control.

Enclosure 2 received 15 wild and five sterile males.

Enclosure 3 received ten wild and ten sterile males.

Enclosure 4 received five wild and 15 sterile males.

Wild females were used in enclosures 1, 3, and 4, but due to a shortage of wild females fertile siblings of sterile males were substituted for wild females in enclosure 2.

Following the 90 day test the following results were tabulated. From the control group 11 females and six males of the original release survived, and there were 140 live offspring. From enclosure 2 eight females, three wild males and one sterile male were recovered, and there were 24 live offspring. From enclosure 3, 16 females, nine wild males, and two sterile males were recovered, and there were 74 live offspring. From enclosure 4, nine females, no wild males, and nine sterile males were recovered and there were 25 live offspring. The reduction in enclosure 4 might have been even greater, as one litter of eight nestlings contained animals bearing the color marker, indicating that at least one of the "sterile males" had not completely ceased sperm production at least two months after being released into the enclosure. A replicate of this test was conducted in 25 x 25 inch indoor enclosures, and the results corresponded to those from the outdoor test.

Expressed as percentages of the progeny produced in the control enclosure, the reductions were 81 percent, 47 percent, and 82 percent in the outdoor tests, as compared to 70 percent, 66 percent, and 91 percent in enclosures 2, 3, and 4 in the replicate indoor test. Both tests failed to show consistent correlation with numbers of sterile males, because of the disproportionately large reduction observed in enclosure 2, where only five sterile males were released with 15 wild males.

The number of progeny in enclosures 3 and 4 in both tests closely fit a linear regression relative to an increasing number of sterile males. One is tempted to explain away the lack of fit for enclosure 2 in the first test on the basis of the females being siblings of the sterile males, and, therefore, more prone to accept them over the wild fertile males. This explanation is purely speculative, as is the conclusion that in the second test the sterile males were for some reason "super competitive."

The tests do provide an initial conclusion that the F_1 sterile male is effective in reducing population recruitment in direct ratio to its numbers, at least in a closed population for a given period of time, the mechanism for the reduction in progeny being the phenomenon of pseudo-pregnancy induced in females who mate with sterile males. The tests also demonstrate satisfactorily that the sterile male is able to compete successfully with the wild Norway rat in mating behavior.

Having demonstrated that using sterile males can reduce population growth in a controlled test situation, the obvious next step was to attempt to apply the method to a wild population. Such a test was initiated on an egg farm near Jones, Oklahoma, a small satellite community east of Oklahoma City. The farm consists of 15 large rectangular buildings on 20 acres of land. These buildings house 185,000 laying hens.

For the experiment the farm was divided into an experimental and a control area. The six buildings on either end served as an experimental and a control area respectively, with the middle row of three serving as a buffer. Sterile males were released periodically in the experimental area. Prior to the beginning of the study a commercial exterminator, using warfarin and cyanide gas, had killed 3,000 rats on the premises (by carcass count).

In August 1972, 1,400 Tomahawk live traps were placed on the premises, 80 traps per building and 200 around the farm perimeter. Each building was subdivided into four divisions and in each division ten traps were placed inside the building and ten outside. By marking and retrapping rats that survived the extermination it was estimated that at the start of the experiment there were 1,000 resident rats occupying the premises.

In September a five-day trapping period in the experimental area yielded 119 male and female rats, which were removed and replaced with 119 sterile males sired by wild-caught males. A short activity study was made immediately following this release. The released animals were observed to huddle together in groups, and movement was minimal. The next day most of them still had not moved away from the release site, and remained huddled together. Within a week many had died, and the rest had moved into sheltered areas where they could not be observed. A prolonged activity study program was devised and put into effect in December. One building was selected for 24 continuous hours of observation.

The building was divided into four quadrats, and each quadrat was watched for 15 minutes out of each hour. Red lights provided illumination during hours of darkness. Instances of chasing, fighting, grooming, and feeding were observed and recorded.

The first 24-hour activity study was conducted December 1 and 2, 1972. Seventeen sterile males sightings were recorded; however, a relatively few recognizable individuals were responsible for most of the sightings. Most sightings were made between 10 p.m. and 3 a.m., and the sterile males seemed to stay to themselves and did not seriously challenge the wild males.

Obviously the introduced sterile males were not faring well. Two possible reasons were proposed, one that the animals, having been fed in cages were unable to adapt to the conditions at the farm in the face of active competition with wild rats, and two that a prolonged season of wet cold weather shortly after the release may have caused deaths from exposure on the part of these naive rats before they recovered from the shock of release and sought adequate shelter.

To counter these factors a pre-release conditioning program was begun, where the males were placed in a large unheated room, provided with hay bales and other harborage, and feed of the type that would be available at the egg farm, mainly chicken chow and dead chickens. This conditioning program, in the jargon of the Foundation, is now referred to as "feralizing." All-male groups, and males in the presence of females have been subjected to this feralizing procedure.

On January 5, 1973, 104 feralized sterile males conditioned for four weeks in an all male group, were released into the experimental area and a 24-hour period of observation was conducted. The rats entered the building without reluctance, and much squealing was heard on the night of the release. Two fights between sterile and wild males were observed. The sterile males began using the usual runways and travel paths without delay, and seemed in all respects to be prepared for the environment into which they were released.

A second 24-hour observation period was conducted on January 16. One hundred nine sightings of sterile males were made, and much movement of the introduced males back and forth was noted, especially along travel routes between burrows and feeding areas.

From September 1972 until February 1973 live-trapping was conducted on both the experimental and the control areas. During the six month period 1,115 individual rats were captured at least once. Five hundred sixty-nine of these were males, 546 were females. Four hundred forty-seven animals came from the experimental side, and 669 from the control side. Population estimates using the Lincoln and Hayne Indices were made in October, December, and February. No significant increases or decreases were noted on the experimental side in the first two estimates when only the unferalized sterile males had been introduced. There was a 16 percent decrease in the February estimate, while in the control area the estimate showed an increase of 11 percent. Examination of females trapped during these estimates revealed that after the sterile males were released a smaller number of pregnant females were found in the experimental area as compared to the control area.

Shortly after this Dr. Landreth met with his fatal accident. It was then discovered that nowhere did he have a written outline of his planned program for the egg farm, and in the emergency the graduate student who had been his helper was left to carry on as best he could. Since the study was to be for 12 months, ending in August 1973, he decided to attempt to learn what the population situation was and began a trap-out of the entire farm, removing the wild animals, releasing the sterile males captured, and making additional releases at intervals. From this point on the program lacked a control area, and the procedures could be considered a program of control more than an experiment.

The trap-out began on April 17 and continued until June 15 when mostly sterile males were being caught. On April 20, 130 feralized sterile males were released, on May 25, 90 more, and on June 28, an additional 84. All were released in the experimental end of the farm. The trap-out resulted in the removal of 662 wild males and 630 wild females. During this trap-out 79 pregnant females carrying 628 embryos were removed from the experimental area and 142 pregnant females carrying 1,492 embryos from the control side. Concurrently there were 727 captures and releases of sterile males, obviously many of them being repeats and since only 527 had been released since the previous September.

Following the April release of 130 sterile males a third 24-hour period of observation was conducted. One hundred eighty sightings of sterile males were made, again mainly between 9 p.m. and 3 a.m., with much interaction observed with wild males, involving fighting, boxing, hip-throwing, and chasing. Large dominant wild males seemed to be able to hold the smaller sterile males at bay, but not to discourage them from repeated attempts to approach choice food sites and occupied burrow systems. During the observation period no more than one large dominant wild male was observed per quadrat. By 3 a.m. of April 26 the sterile males seemingly had secured their positions in the society and were regularly observed feeding, watering, grooming, chasing, and fighting, and the sounds of activity out-of-sight within the building could be heard.

A second trap-out covering the entire premises was initiated on August 15 and concluded on September 1, when no more wild rats were being caught. One hundred thirty-seven females and 108 wild males were trapped and removed from the premises during these two weeks. Forty-six of the females were pregnant, carrying 546 embryos. Forty-seven sterile males caught during this period were removed to the feralizing room and held until November, when they were reintroduced into the premises along with 40 additional recently feralized males. During this August trap-out it was found that by this time sterile males were dispersed evenly throughout the entire farm.

In November 1973 the 47 sterile males trapped in August were combined with 40 newly feralized sterile males and returned to the farm.

On January 26, 1974 trapping was renewed, using a new bait. Trapping has continued to date, and has resulted in the removal of 146 wild males, and 112 females, of which 45 were pregnant. Most of the wild animals caught were extremely large, presumably being old adults who had escaped the previous trap-out and were lured by the new and more attractive bait. The largest of these males are being kept for use as sires for future generations of sterile males.

In summary several points may be made:

1. Removal of females and wild males beginning with the April 1973 trap-out essentially destroyed the operation as a test, as from then on it was impossible to separate the sterile male effect from the effect of removal by trapping. However, it has been demonstrated that genetically sterile male rats can be successfully introduced into a wild population, and that subsequent to such an introduction there is a reduction of the reproductive performance of the wild females. By using the combined methods the level of infestation to the Jones egg farm was kept at a level far below that which prevailed prior to the initial poisoning in the summer of 1972.
2. From the data obtained so far it is not possible to say that the Norway rat can be eradicated by introducing sterile males into the population. The data do suggest that it may be possible, and that in certain circumscribed areas the chance of achieving population control may be quite good.
3. The Jones egg farm, while satisfactory as a test site from the standpoint of its high rat population and its isolation from adjoining areas, was unsatisfactory because of the abundance of food and harborage, and because no attempt has been made to date to exercise environmental control on the premises.
4. The tests to date do not provide an adequate basis for devising a formula for release rates of sterile males. Probably these can be arrived at only by repeated experimentation in a variety of test areas. The numbers must be kept as low as possible because of the cost of rearing sterile males to the age of release. Also, in the short run there would be little to be gained in the eyes of the occupants of the premises merely by substituting equal numbers of sterile males for wild animals.
5. More needs to be learned as to the ways that the sterile males may be exploited to capacity. There are several ways in which their performance may be improved. Sire selection is important. More aggressive sires can be selected, and their behavioral genotype bred into the sterile males. Other heritable characters may be discovered that can be combined with the sterility gene to improve the sterile male's competitive performance. For example, in the Introgene colony

there are now two litters sired by a male rat from North Carolina that is resistant to warfarin. The inheritance of this character will be studied, and if feasible this character will be added to the sterile male's repertoire of useful characteristics. A "killer gene" such as is known in mice would be a useful characteristic to include, and a search for such a character, and for possible sex-linked lethal genes, will be pressed. The list of possibilities is long.

6. More needs to be learned about the process of feralizing, particularly the age at which the process can begin, and the conditions that generate maximum wildness.
7. More attention needs to be paid to the development of a superior trap bait. The one recently under test seems to be much superior to the various types of peanut butter and oats combination used previously. While the Jones egg farm was a poor place to attempt to exercise population control of rats because of the superabundance of available food, it is an unparalleled place to test the luring properties of baits, for the same reason.
8. Better means of monitoring the progress of a control program are needed.
9. Finally, because of the unmet needs outlined in the above summary, it seems that the Introgene program has proceeded as far as it can without massive capitalization. Facilities for rearing and feralizing rats need to be greatly expanded, and above all a staff of population ecologists capable of attacking the problems outlined above must be assembled. Such expertise and support would make it possible to seek answers to the questions raised above, and possibly to devise computer programs to solve the complex problems related to release rates, test monitoring, and the mass of data relating to possible expanded programs of rat control in the future.

Failure to secure capital funding would mean that the thrust of Introgene's efforts would be redirected toward the study of their other extensive repertoire or mutations, many of which now serve as animal models for identical human anomalies, but none of which offer any potential for application to the problem of feral Norway rat control.

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