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SHOULD WE KILL THE RATS OR IS BIOLOGICAL CONTROL PREFERABLE?

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These questions are becoming more controversial in recent debates which have emerged from new realizations of rodent impact on health, conservation, and economy. The controversy, coupled with widespread evidence of genetic resistance, bait aversion, and other modes of adaptive behavior and physiology displayed by rodent pests, represents a new appreciation for one of man's most persistent problems. Old World rodents live in commensal association with man and his domestic animals. These rodents include black rats (sometimes called roof rats), Norway rats (sometimes called brown rats, sewer rats, wharf rats), and Old World (house) mice. Of the three types of Old World rodents, the most feared and successful are Norway rats, which are eminently bound by the habits of man and which have been well provided for by man. An interesting and readable account of rat association with man (Zinsser's *Rats' Life and History*) relates the episode of disease and destruction which began when these pests adopted their commensal association with man and moved from Central Asia to all regions of the earth, except the Arctic, sub-Arctic, and Antarctic zones. Since about the time of the Crusades, man has made a considered effort to wage war against house mice, roof rats, and alley rats. Still, these species maintain healthy populations throughout the world, despite human efforts to eradicate them by trapping, release of predators, shooting, poison baiting, bacteriological warfare, and the use of poison gas. Thus far, only destruction of the harborage that provides housing for rats and the storing of food supplies in rat-proof containers have denied rats their cohabitation with man. Unfortunately, total elimination of rat harborage is rarely possible so that there are always large reservoir populations of the pests nearby. They invade and infest wide areas whenever conditions become favorable. Better sanitation, food and debris storage, and disposal and clean-up campaigns are essential to rat control. Yet, some situations cannot be corrected for economic reasons. Even in the United States we have the persistent problem of broken storm and sanitary sewers and a lack of rat-proof grain storage in many areas. In the United States there is probably at least one rat for every human being; in other parts of the world where grain storage and sanitation are not as sophisticated as ours, there may be 25 to 50 rats for every human being. Portions of Asia and Africa undoubtedly have huge reservoirs of rats; the most troublesome of these is the Norway rat because of his aggressive and adaptive behavior.

Let us examine for a moment some of the public health problems that we face as a result of rat infestation. In the United States, about 14,000 rat bites per year are reported. Usually, such bites are inflicted in slum areas and afflict the young and the elderly, those who are helpless. Many more rat bites undoubtedly go unreported to Public Health authorities. Rats do not bite because they are enraged, but, rather, to consume. Although the case is cruel, it needs to be pointed out as a potential health hazard directly inflicted by these pests. In addition, rats are potential carriers of diseases; some diseases are borne by the ectoparasites carried on the animal's body. One such parasite—the Egyptian rat flea—spreads "pasteurella" organisms that cause bubonic plague. More common diseases borne by rats include leptospirosis, salmonellosis, typhus, hepatitis, tulleremia, hemorrhagic jaundice, poliomyelitis, trichinosis, and Lassa fever. The latter, appearing in African countries, is a particular variation of a lethal virus infection. Since rats can transmit these diseases via their urine and feces in food stores in which they have been feeding, huge stores of grain are destroyed on evidence of rat feces or fur in the grain. The economic cost of rat-borne disease in terms of medical attention required, drugs administered, and work lost is most difficult to estimate.

On the world scale, another public health problem results from grain and food consumption by rodent pests. There is an ever-growing awareness that the world grain used is presently at the limits of production so that because of political, logistical, and supply problems, much of the world's population has already begun to starve. It is noteworthy that in some portions of the world more than 50% of the grain crop (stored or planted) is consumed by rodent pests. Ten percent of the grain crop in the United States is presently lost to rats. Of the grain shipped and grown in other parts of the world, 40 to 90% goes to rats. The worst ravages are in countries like India, Bengladash, and certain portions of Africa. Before one examines the present world food supplies, he must note that in our present situation much of the world population is below the 2000 calorie level on a per capita base. If we examine the impact of population in terms of tons of grain presently utilized and projected for 1985, we will note that there will be some increase in food production, but it will barely keep pace, if not fall behind, the human reproductive rate. The present human cereal requirements (based on the World Health Organization estimate of 311 kg./capita base) is in the order of 1.38 billion tons. In 1985 we will require 1.63 billion tons. Conservative estimates of rodent waste (40%) are presently in the order of 0.5 billion tons of grain consumed or destroyed by rodents. By 1985, at the present rate of rodent destruction, we anticipate that 0.7 billion tons of grain will be wasted by rodent contamination and feeding. If we were to provide rodent control at 2% of the present world numbers, we would have a deficiency today, but by 1985 (with increased productivity brought about by new strains of grain and projected new land brought into production), we would be slightly above the world demand. In the United States alone, in the order of 25 million dollars worth of grain is eaten by rats; rat associated destruction is estimated to be in the order of 1 to 3 billion dollars a year. This economic impact is added to by loss of productivity and energy waste which result from a lack of conservation in food production as well as from the impact of chronic enteric disease on human populations and animal production.

In view of the drastic impact and a potential disaster which might be inflicted by rodent plagues, why is it that man has not been able to reduce rodent numbers below 35 billion? Rats are extremely intelligent and display unusual modes of physiological and behavioral adaptation. Interestingly enough, rat populations grow into just the carrying capacity of space and food available; approximately the animal's body weight in food is eaten on a weekly basis. This means that about 250-400 gms. of grain and of water per week are required to maintain an adult rat; the food requirements for these animals increase as pregnancy and lactation are added to female metabolic costs. Limitations in space or food tend to limit population. These limitations are probably brought on by density effects and intraspecific strife. A high degree of social order in rat colonies speaks to a regulation of reproductive rate under saturated density conditions which just meets the mortality losses. When animals are in saturated density conditions, two critical events tend to occur. The breeding members of the population are primarily restricted to a few dominant males and high-ranking females. This mode of behavioral regulation in breeding extends even to the physiology of the species in that juvenile emergence and high-density, stress-induced effects not only increase the mortality rate of the population, but actually interfere with reproductive development and cause regression of rat sex organs and accessories. At the same time, high densities affect reproduction and the ravages of disease are more pronounced so that a substantial attrition takes place in natural rat population during the year. This attrition varies from a mortality rate of 10 to 20% per month. Interestingly enough, when predators are introduced to rat populations, the effects of predation are not to control numbers but to reduce the number of diseased and socially subordinate animals. The ravages of extreme climate, too, affect mortality rates so that mortalities are higher in the winter than in the summer in our region of the hemisphere.

The following illustrates some of our observations with reference to rat population growth in this region. Rat growth rate and rat food consumption rates are nearly equivalent. An expansion into the space provided occurs when food is provided in abundance; when a maximal population level is reached, it is maintained at essentially stable numerical levels. There is seasonal breeding in this portion of the hemisphere where winter cold and short photoperiod affect reproduction. A seasonal success rate with reference to colonization occurs; that is, new colonies can readily be formed in the wild during the spring and summer, but not so readily in the winter. There is a seasonal incidence of high fertility even in dense populations; a spring surge in reproduction is followed by a reproductive slump in the summer as the juveniles begin to assume adult pelage and to compete as mature, aggressive adults. There is a seasonal variation in endocrine function, particularly evidenced by adrenal secretion, sex hormone secretion, and reproductive tissue response. Moreover, as illustrated by renal pathologies, a seasonal variation in the severity and frequency of pathology occurs. With reference to daily activities, cold temperature modulates activity downward, but even in warmer times, there appears to be a distribution of forage habits so that preferred times of day are taken by the dominant animals, and less preferred times of day by subordinate animals. Reducing the population number by poisoning, trapping, shooting, or natural disaster tends to initiate the recruitment of breeders in the population so that reproductive rebound is a common phenomenon contributing to population recovery. This release of inhibition when densities are lowered may be effective in new colonization patterns as well.

In addition to the aforementioned behavioral and physiological capacity, some additional traits are noteworthy among rodents, particularly among Norway rats. These animals show additional kinds of adaptation; genetic adaptations have appeared with reference to resistance to the lethal effects of an anticoagulant (Warfarin). The development of Warfarin resistance in Europe has been known for some time, and Warfarin-resistant colonies of rats have been discovered by Jackson in various parts of the United States as well. Such Warfarin resistance results from genetic selection and could be overcome by using analogs of the dicumarol drugs. Owing largely to the delayed effects of the drug, Warfarin has been one of the more successful verminicides. The relative safety of Warfarin is attributed to its favorable toxic ratio, that is, rats generally are more susceptible to Warfarin poison than other species. A more immediate problem for rat control is the behavioral adaptation of rodents. The extreme intelligence of these animals speaks to an association of illness with the ingestion of foods that bear poison. It is believed that rats can associate illness with a poison bait and will not take that bait again. Although the evidence is somewhat controversial, generally speaking, in experimental trials where rats have associated illness with a particular bait, they will not take that bait even though the toxicant is not mixed with the bait carrier. Some toxicants, on the other hand, have taste in themselves so that rats will not only avoid the bait which originally brought on illness, but will associate the flavor of the toxicant with illness, so that alternate bait forms cannot be used. If the toxicant and its flavor can be masked in baits, then bait substitution (as suggested by Chitty) is a workable device for getting a second take. Whether rats can be induced to retake baits by retraining toward a particular bait which is not carrying the toxicant is an open question. Certainly, there have been evidences that following sub-lethal poisonings with red squill, baits containing red squill would not be taken even a year later. This visceral learning of food preference with reference to bait toxicity is a poorly understood phenomenon. Wild rats do display a general level of central nervous system excitement and wariness not prominent among their domestic cousins so that such behavioral tests conducted in the laboratory may not be altogether representative of the sharpened sensory abilities of wild rats. In addition to the animals' intelligence which modifies their learning capabilities so that toxic circumstances are avoided, they must in some way also impart information to their cohorts. Aversions to toxic baits taken by the mother are also shown by offspring as well as by some other cohorts. Whether such aversions are learned via scent markings or result from changes in the mother's milk and behavior remain open questions.

Let us turn now to the chemical warfare which has been waged against rats. If we are to use toxicants to kill the rat, then we should be able to accomplish the kill with a single dose. While single-dose toxicants are effective in rat control, their action should be delayed somewhat so that association with toxicity is not as likely to be made when rats do not take the killing dose. The oldest of the toxicants used is arsenic. This substance is single-dose effective, is accepted fairly well but reaccepted very poorly. Like all of the inorganic toxicants, arsenic is a broad spectrum toxicant which has no target specificity. Arsenic can only be used in specialized situations which require special handling and special knowledge. Because arsenic does provide some taste, rats develop tolerance both on a physiological and on a behavioral level. Extremely toxic fluoracetates which are very effective in single doses are so toxic that only minute quantities need be taken. Of the organic toxicants, strychnine, red squill, chlorolose, and Warfarin have all been used. The mechanisms of action of these drugs are all quite different. The safest of these is Warfarin. Norbormide is also a relatively safe drug. Bait acceptance is best with Warfarin, re-acceptance is good, and there is a very good target specificity for rodents. The animals do, however, as we pointed out earlier, develop genetic resistance to this anticoagulant drug. Because of the extreme toxicity of some of these compounds, a series of risks needs to be tabulated. There is a very high risk with the use of arsenic (for example) in that the effective dose in rats (1 mg./kg.) is much higher than the lethal dose for humans. On the other hand, if we compare Warfarin, the effective dose for rats is several orders of magnitude lower than the lethal dose for humans. There is a moderate risk to desirable wildlife and humans with the use of Warfarin in that accidental consumption only of large doses of this anticoagulant could cause death. Norbormide also seems to be moderately safe to use. The way in which red squill is made safe is to mix it with an emetic so that if pets or humans take the drug accidentally, they will vomit; rats do not have the vomiting reflex.

Biological warfare, too, has been tried by man as a rodent control measure. Of the early biologicals used, infections were most often introduced in the rat colonies. Rats now are reasonably resistant to typhus and carry the disease long enough to transmit it to man. Leptospirosis and salmonellosis also have been introduced in rat populations and have had immediate but transient effects on reducing rat numbers. Rats now chronically carry these diseases. Efforts to control rats by imposing bounties and by using weapons are very similar to efforts at introducing predators. The difference between bounty methods, shooting or trapping, and the predator method is that the predator which is introduced may opt for other prey. All these methods have a tendency to maintain low populations once the population has been brought down, but usually clean up only those members of the population disadvantaged by reason of age or social status or disease.

Several new approaches to rat control have recently been tried. Some of these approaches involve the design of new toxicants which rats are not genetically resistant to and which are single-dose effective. Microencapsulation of the drugs can prolong organ action until long after the meal is taken. Examples of such toxicants include new anticoagulants which are analogs of Warfarin and vitamins involved in the metabolism of vital organs. Vacore, a recently announced product, is an example of these. In addition, genetic sterilization by the introduction of lethal genes into the population appears to be a promising mode of control. Nonetheless, the social life of rats is such that foreign animals introduced into a population are very likely not to survive. An experiment done in Baltimore by Christian, Davis, Calhoun and Richter did involve introducing manually sterilized, vasectomized and ovariectomized rats into resident populations. Nonresidents were either driven off or killed. Therefore, the introduction of aggressive, sterile, lethal-gene-carrying rodents into populations has some major obstacles to overcome.

The promise of utilizing chemosterilant or birth control methods for controlling rodent populations remains. Human birth control agents (provera, mestranol) have been tried, but since these agents required constant doses to suppress estrus, and since they carry some undesirable taste, they have not been thought to be commercially feasible. Depoprovera, a broad spectrum reproductive suppressant which acts on females, may eventually be developed to some level of efficacy. The advantage in reproductive control stems from two features of rat populations: (1) The high mortality rate seen in natural populations would eliminate the population were reproduction not maintained at a fairly high level; (2) Toxicants and killing methods, while they will reduce rat numbers, will release an inhibition caused by density factors and promote reproduction and recovery of the population if all animals are not killed.

Chemosterilant methods, similar to those used for control of insect populations, were suggested sometime back by Knippling and by Davis. Knippling's calculations represented on a theoretical basis the time it would require for a rebound to take place if a 70% kill were managed; recovery would occur within three generations. The same calculations indicated that sterilization of both sexes would reduce the number of the same population for twelve generations. Certainly, if there were any nonsterile members of the population present, we would anticipate some gradual recovery after reproductive inhibition. However, if killing *and* reproductive inhibition could be accomplished, the rebound effect would not be possible. Our own calculations based upon effective sterilization of various portions of the population are presented in the following illustration. Within the breeding periods evident in this portion of the United States, we can expect up to a 300% increase of population numbers within a six-month period. Where the breeding season is longer, we would anticipate an even greater increase as theoretically possible if space and food were not limiting factors. The growth rate of partially sterilized populations is much lower. On the basis of these calculations and on some preliminary trials in Calhoun pens, we began to implement field studies which tested a new chemosterilant, U-5897. This drug is simple chlorhydrin and had been used as an antihypertensive agent. Ericcson discovered, serendipitously, its sterilant effect on the Norway rat. The drug does show transient antifertility effects in several species but shows permanent sterilization effects in the Norway rat. These effects are accomplished by caput epididymal lesions and are specific to the Norway rat. The drug is effective in a single oral dose and has a permanent lesioning capability. It does not, however, interfere with androgen production, so important to a social status integration of dominant male rats in natural populations. With a single oral dose, the population in an isolated quarry was reduced first by the toxic effects of the drug; the rats took more of the drug than we had anticipated. Second, the drug prevented reproductive rebound. Repeated trapping yielded no pregnant females, no juveniles, but lesioned males. About 90% of the population was rendered sterile with the initial dose.

Several of the other dump trials provided similar successes, but because immigration was possible, these dump settings require a second dose of drug to be given at least once a year (preferably twice a year) during the breeding spurts that we mentioned earlier. We attempted the use of this drug in the sewer system in Ralston, Nebraska. Cooperation of the City Council and citizens of the City of Ralston made these trials possible. The Ralston community had a dramatic rat episode during the summer of 1973. In 1974, after we had reduced the neighborhood hazard by major clean-up campaigns and some poison, we began to treat the sewer system in the older portion of this city. These sewers have breaks in them which provide ideal harborage for reservoir populations of the rats. Our census indicated that approximately 700 rats were in the system. Following a treatment with U-5897, we again had both lethal and antifertility effects. The rate of reinfestation of the city (by the pattern of census) was confined to the immigrants from the outside, rather than as the result of population increase from reproduction. Several field trials have consistently lowered and maintained low populations of the rats for more than six months. Such an effect dramatically illustrates that reproductive rebound was overcome with the use of this particular drug.

While U-5897 is only a beginning to antifertility control of problem rat infestation, and while antifertility methods have to be applied on an area-wide basis to be effective, we believe that our field trials show that use of such methods is a practicable matter. We are hoping that with the cooperation of the Upjohn Company and the World Health Organization these trials can be implemented on a wider scale throughout the world. U-5897 represents one additional approach to rat control. It complements a limited arsenal of methods which employ chemical and biological techniques for rat eradication. Since the rat is such a wily and intelligent creature, it is unlikely that populations will be totally eradicated. Nonetheless, if rats could be managed at 2% of the present level, enough food conservation could be achieved to feed the increasing hungry mouths of humans in the world.

We believe that careful attention to sanitation, to food storage, and to general neighborhood and yard cleanliness is the best answer to rat control. In situations where pests crop out and emerge in plague proportions, in situations where it is economically difficult to achieve ideal storage and sanitation conditions, we believe the methods we have begun to develop will be helpful. At a time when conservation of resources is not just a matter of aesthetic desirability but of essential survival, we believe that better, more diversified and efficacious methods of rodent control need to be sought. These methods collectively can be used to treat a social disease—human carelessness. Since man's provisions are necessary for the survival of the rat, we must attempt to curb man's carelessness. Yet, undoing all of man's bad habits is unlikely for economic and social reasons; therefore, we believe that in regulating rodent population members at lower levels we must employ techniques similar to those used by the rodents themselves. Such methods have the advantage of stemming off immigration from the outside and of protecting the public from the economic, food, and health hazards of pest proliferation.

Like most other studies, this one began as a result of serendipity. The study's progress has been the result of patient observation, hard work, and a conviction that new information would be valuable to our understanding of rodent populations in general and would be applicable to rodent control specifically. We, like Richter, were reluctant rat catchers. But, we have learned from this intelligent, fastidious little animal about the management of its social affairs and even its physiological economies. We have only begun to understand the biology of this animal and the impact that chemical and biological warfare can have in its management. We believe that a deeper understanding of the habits and physiology of this little beast would be invaluable to the protection of resources so needed by the human population.

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