Endocrines, Behavior, and Population

Social and endocrine factors are integrated in the regulation of growth of mammalian populations.

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For several decades the spectacular increase and decrease of certain arctic mammals has stimulated research on populations. The crashes of rabbits were dramatized by Seton (*1*), and the suicidal movements of lemmings were publicized by many authors. However, as is so often the case, the conspicuous features turn out to be merely an extreme case of a very general phenomenon—namely, the fluctuations of a population. Investigators first sought an explanation for the "crash," but now most of them search for a description and understanding of the interaction and relative importance of the many factors that influence the ups and downs of populations.

In this article we describe the current status of our understanding of population fluctuations, emphasizing the regulatory features that prevent populations from destroying the habitat. The research discussed is limited to work with mammals, since the mechanisms are best known for that class. It is assumed that the reader has knowledge of ecological principles such as density dependence and limiting factors.

For many years it was assumed that epizootics, famine, and climatic factors terminated the explosive rises in population size and precipitated the often spectacular crashes (*2*). However, by the early 1940's it had become apparent that none of these mechanisms explained some of the observed declines in population, and it was suggested that factors intrinsic to the population were involved in its regulation (*3*). The skepticism toward earlier explanations was reflected further in a review by Clarke in 1949 (*4*), as well as in Elton's classic earlier work (*5*). Probably the greatest shift in emphasis has occurred since 1949; there has been an upsurge of investigations in which density-dependent changes in the animals themselves have been explored, and of theories in which the observed phenomena of population growth and decline (*6–9*) are explained in terms of biological mechanisms intrinsic in the populations and not only as results of the action of external factors. It is clear that food, climatic factors, and disease may cause population change. Indeed, it would be foolish to state that these factors do not, under certain circumstances, limit population growth or produce spectacular decline. The early investigations of Emlen, Davis, and their co-workers (*8*) on populations of Norway rats demonstrated clearly that environmental factors can reduce a population. For example, a drought followed by excessive rain resulted in a notable decline in rats in Baltimore (*8*). However, as early as 1946 spectacular declines in rat populations were found to be coincident with social disturbances rather than with environmental changes.

The suspicion that social phenomena were involved prompted a search for mechanisms that could regulate the growth of populations in a density-dependent manner. No longer is attention focused exclusively on spectacular crashes and the causes of death. Instead, an attempt is made to integrate the social actions and the well-known habitat factors into a scheme that will explain the changes in populations. Since social or behavioral features are density-dependent, they become evident only at high population levels. Nevertheless, such features are present in low populations, but inconspicuous. Purely ecological factors, such as food and climatic conditions, also affect populations and, indeed, may prevent a population from attaining a level where social forces can become important. Hence, examination was begun of a theory which states that, within broad limits set by the environment, density-dependent mechanisms have evolved within the animals themselves to regulate population growth and curtail it short of the point of suicidal destruction of the environment (*6, 10–13*). Milne (*12*) has summarized this point of view as follows: "The *ultimate* capacity of a place for a species is the maximum number of individuals that the place could carry without being rendered totally uninhabitable by utter exhaustion or destruction of resources. . . . The environmental capacity cannot be greater than ultimate capacity; it could, conceivably be equal to ultimate capacity but . . . is usually somewhat smaller." We would modify the "somewhat" to "considerably," in view of the situation most often observed for mammals (here we are talking primarily of herbivores and rodents). Milne goes on to say that "the one and only perfectly density-dependent factor [is] intraspecific competition."

While some investigators ascribe all regulation and limitation of populations to direct effects of environmental factors, others recognize that a feedback control of population growth exists. However, there is not complete agreement on the mechanisms by which these results are achieved. In the rest of this article we review the more recent results of experiments made to test the hypothesis that a behavioral-physiological mechanism operates to control population growth in mammals, and we consider criticisms of this view in the light of the evidence on which they are based. The acceptability of the hypothesis should be considered from the viewpoint of what would constitute disproof. To prove that behavioral mechanisms *never* affect population growth is of course impossible. To cite one or more cases in which some habitat factor controlled the population is merely an elaboration of the obvious. Thus, proof or disproof of the hypothesis reduces to the problem of finding how frequently and under what circumstances

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the behavioral mechanism does operate. The discovery of other physiological mechanisms [for example, pregnancy block caused by the proximity of strange males (*14*) or direct block of reproduction organs in *Peromyscus* (*15*)] does not alter the situation. Similarly, the absence of the mechanism in certain mammals would not prove its absence in rodents. The problem, then, is not that of proving the existence of a behavioral-physiological mechanism but that of proving the importance of such a mechanism in the regulation of populations.

Physiological Mechanisms

On the basis of the knowledge of pituitary-adrenocortical physiology available prior to 1950, it was proposed (*16*) that stimulation of pituitary-adrenocortical activity and inhibition of reproductive function would occur with increased population density. It was suggested, further, that increased adrenocortical secretion would increase mortality indirectly through lowering the resistance to disease, through parasitism or adverse environmental conditions, or, more directly, through "shock disease," although it soon became evident that unwarranted emphasis was being placed on "shock disease." Implicit in this theory and in the design of experiments to test it was the theory that behavioral factors (aggressive competition, for example) comprised the only stimulus to the endocrine responses which would invariably be present in every population. Experiments to test the theory were conducted on animals which were provided with (or known to have) more food, cover, and other environmental assets than they could utilize, and were thus in populations either totally free of predation or having a minimum degree of predation (*17–19*).

The endocrine responses were first assessed through measurement of changes in the weights of the adrenals, the thymus, the reproductive organs, and certain other organs. Interpretations of adrenal weights are reliable and simple in species that have been adequately studied in the laboratory—for example, in rats and mice, whose adrenal physiology and morphology have been examined in detail under a variety of circumstances. In particular, the immature zonation (X-zone) of mice and its changes with respect to age and sex had been thoroughly explored (*20*). An important point was the lack of evidence of function for this zone. Where adrenal weight could be reliably interpreted in terms of function, it seemed better, in the study of populations, to use an indicator of long-term conditions, rather than indicators highly sensitive to acute stimuli. For example, concentrations of ascorbic acid in the adrenal gland and concentrations of corticosteroid in plasma respond very rapidly to acute stimuli. Furthermore, the interpretation of changes in adrenal weight was supported by other morphological criteria of increased corticosteroid secretion, such as involution of the thymus, though the possible role of other factors in the alteration of these other organs was not overlooked. Nevertheless, even in rats and mice, changes in adrenal weight can only be considered strong presumptive evidence of changes in adrenocortical function until validation is obtained by direct functional studies.

Adrenal weights are not valid indices of function unless certain precautions are observed. The presence of immature zones (X-zones) complicates the use of adrenal weights as indices of function, since evidence that such zones contribute to cortical function is lacking. Another complication is the possibility of weight loss with sudden or excessive stimulation. Moreover, there may be a misleading increase in adrenal weight due to accumulation of lipids with cessation of adrenocorticotropic hormone (ACTH) stimulation. Also misleading is the hypertrophy of the adrenal medulla which occurs in some instances, but this usually is not important (*21*). In addition, qualitative changes in the corticosteroids secreted may require modification of interpretations based on adrenal weight. Finally, sexual maturation or activity may alter cortical function and adrenal weight. Androgens involute the X-zone or decrease adrenal weight in adult animals, whereas estrogens commonly increase adrenal weight. It is axiomatic that, in comparing changes in adrenal weight with changes in population, one must consider adrenal changes due to reproductive condition, and that only adrenals from animals of similar reproductive status can properly be compared.

In addition to these physiological considerations, there is the problem of obtaining adequate samples. Since there are two sexes and at least two age groups, the sample must contain enough animals in each of four categories for appropriate analysis. This requirement may seem obvious, but it often has been neglected.

The foregoing principles regarding the interpretation of adrenal weights have been presented because in many studies one or more of these principles has been neglected. Earlier work on physiological responses to changes in populations has been reviewed elsewhere (*6, 17–19*) and is only summarized here. In experiments with mice in the laboratory, progressive adrenocortical hypertrophy and thymic involution were observed to occur with increasing size of population. Somatic growth was suppressed and reproductive function was curtailed in both sexes. Sexual maturation was delayed or, at higher population densities, totally inhibited. Spermatogenesis was delayed, and the weights of the accessory sex organs declined with increasing population density. In mature females, estrous cycles were prolonged and ovulation and implantation were diminished; intrauterine mortality of the fetuses increased. Recent results in rabbits show an increase in intrauterine mortality in association with increased population density, especially in the fetuses of socially subordinate females (*22*). In another study a similar increase in intrauterine mortality was noted, but no difference in rate of resorption of embryos relative to social rank was observed (*23*). Increased resorption of embryos also followed grouping of *Peromyscus* (*24*). However, in mice, the importance of resorption of embryos in regulating birthrates may vary considerably from population to population (*17*). Also, increased population density resulted in inadequate lactation in mice, so that nurslings were stunted at weaning. This effect was seen again, though to a lesser degree, in animals of the next generation not subjected to additional crowding (*25*). It has since been found that crowding of female mice prior to pregnancy results in permanent behavioral disturbances in subsequently conceived young (*26*). Particularly interesting in this regard is the observation that increased concentrations of corticosterone may permanently affect the development of the brain in mice (*27*). Increased population size also delayed or totally inhibited maturation in females, as well as in males, so that in some populations no females reached normal sexual maturity. The combination of these responses, be-

lieved to result from inhibition of gonadotrophin secretion, resulted in a decrease in birthrate, or an increase in infant mortality, or both, as populations increased, until increase of the population through the production of young ceased. Concentrations of gonadotrophins in relation to changes in population size have not been measured. However, increase in the number of rats per cage was found to alter responses to injected gonadotrophins, even when the area per rat was kept constant (*28*).

Increased population density may affect reproductive function in male and female house mice differently in different populations. The growth of one population was slowed and eventually stopped mainly by a decline in birthrate due to (i) failure of the young to mature and (ii) decrease in the reproductivity of mature animals (*17*). Infant mortality was a negligible factor in this population. In several others a decline in the survival of nurslings was largely responsible for a slowing and stopping of population growth, although a lowering of the birthrate also occurred (*17, 19*). In most populations both a decrease in birthrate and a decrease in the survival of nurslings contributed importantly to slowing of the rate of population growth and limitation of numbers, but, as one might expect, the relative importance of these two factors varied among populations. In populations in which a change in birthrate was the main regulating factor, other measurements indicated that it was the males which were primarily affected by increased population density, the effect on females being slight. When increasing mortality of nurslings was the main regulating factor, the females were severely affected and the males were relatively less affected than in other populations (*17*). These results imply that effects on the male may be important in producing declining birthrates, although failure of females to mature also would contribute to a decline in birthrate in any population and cannot be excluded. Final conclusions regarding this problem must await further investigation.

For many years it has been known that disease sometimes becomes rampant when populations reach peak levels (*5*). However, the belief that disease usually is a primary cause in the reduction of populations has not been supported (*5, 11*). A change in host resistance has been suggested as an underlying condition leading to increased mortality from epizootics (*6, 11, 17*). It is well known that glucocorticoids reduce resistance to infectious disease by inhibiting the normal defense reactions. They may also be involved to some extent in the pathogenesis of other disease, such as glomerulonephritis as seen in woodchucks (*17*). Furthermore, grouping, presumably through adrenal stimulation, augments adrenal-regeneration hypertension in rats (*29*). Experiments have shown that, with increased population density, there is a marked depression of inflammatory responses, of formation of antibodies, and of other related defenses, with a resultant increase in susceptibility to infection or parasitism. For example, in a confined population of rabbits a highly lethal epidemic of myxomatosis occurred coincident with attainment of a high density (*22*). During this epidemic dominant animals and their descendants had the highest survival rate, implying a breakdown in host resistance following increased social competition. Similar results were observed in a population of deer, associated with high densities and subsequent decline in population (*30*). Increased density also enhances mortality from other causes —for example, radiation, amphetamine toxicity, and toxicity due to other pharmacologic agents (*31*). Decreased resistance to amphetamine following grouping is probably due to increased secretion of epinephrine and not to increased secretion of corticosteroids (*32*). Emotional stress also enhances mortality from disease, probably through the same endocrine mechanisms (*33*). These results suggest that at high population densities an epidemic occurs in part because resistance is lowered. Thus, disease is a consequence of high population rather than a primary cause of a decline in population.

Behavioral Aspects

What basic behavioral factors result in these profound effects? It seemed to us that any density-dependent effects would be related to social rank. Experiments made to test this hypothesis showed that adrenal weight and somatic growth were related to social rank (*18, 34*). Other experiments, in which adrenocortical function was assessed from counts of circulatory eosinophils (*35*), confirmed these results. Adrenal cortical activity is similarly related to social rank in rats and dogs, as determined by lipid and cholesterol concentrations in the adrenals of rats and by hydrocortisone secretion in dogs (*36*). In several somewhat related experiments it has been shown that the degree of response to changes in population size is dependent on the behavioral aggressiveness of the strain or species involved (*19, 37*). In the highly aggressive house mouse (*Mus musculus*), changes in adrenal weight, ascorbic acid content, and cholesterol content demonstrated the important role of behavioral factors in the responses to changes in population density. In contrast, deer mice (*Peromyscus maniculatus bairdii*) failed to respond, due to behavioral characteristics and not to an inherently unresponsive endocrine system (*37*). The two species responded equally when exposed to trained fighters of their own species or when subjected to cold.

In most studies of social rank an indirect measure of adrenocortical function was used, such as the weights of adrenal and thymus, cholesterol and ascorbic acid content of the adrenal, and numbers of circulating eosinophils. Recently, a number of investigators have observed increases in adrenocortical function with increases in population density. There is an appreciably greater in vitro production of corticosteroids by adrenals in grouped mice than in singly caged mice (*38*). Albino laboratory rats show an increase in plasma corticosterone concentrations from 6.7 to 22 micrograms per 100 milliliters when they are maintained in colonies rather than in groups of four to a cage (*39*). There was also a fivefold increase in the in vitro production of corticosteroids by the adrenals of the colony-maintained rats. Barrett and Stockham (*40*) reported a 73-percent increase in plasma corticosterone concentrations, as measured fluorometrically, in albino rats kept in groups of 20 as compared with concentrations in singly caged animals. Pearson (*41*) found that, in general, plasma corticosterone levels increased with increasing density in freely growing populations of mice, although there was considerable scatter in the results, possibly because of capture and handling procedures. Thus, direct measurement of corticosteroid levels confirms conclusions from experiments in which morphological criteria were used to assess adreno-

cortical function in Norway rats and house mice.

Increases in the weight of the spleen in response to increased population density have been reported in mice and voles (*6, 42, 43*). In house mice the increase in splenic weight is due to increased hematopoiesis involving all blood-forming elements, and not solely to erthyropoiesis, as in voles (*43*). The increase probably is related to social rank (*44*), although a response to injuries from fighting could not be ruled out.

The problem of the role of food invariably arises in discussion of changes in population. A shortage of food might have the direct effect of causing starvation or an indirect effect by increasing competition among animals. Contrary to a widely held belief, chronic inanition per se (as opposed to acute starvation) appears not to result in increased adrenal weight or increased cortical function in rats, mice, and men (*45, 46*). Experiments with mice showed that chronic inanition had no effect on adrenal weight, either directly or indirectly (*46*). However, inanition curtailed reproductive function independently of its effects on the pituitary-adrenocortical system. In some species, limitation of the food supply apparently increases competition (*22, 47, 48*), and thus subordinate animals are more affected by the shortage than dominant ones. Resistance to starvation (and thus survival) is greater in dominant or older animals than in subordinate or younger animals (*22*). Also, the decreased need for protein seen in deer during winter and early spring is frequently overlooked (*49*). It is possible that some microtines or other rodents also have mechanisms for taking advantage of bacterial protein synthesis during periods when proteins and natural plant foods are scarce. On the basis of existing evidence (*11, 50*), the direct effect of food shortages cannot be considered a common denominator in the regulation and limitation of growth of populations of herbivorous mammals. Studies of populations of *Clethrionomys* (*51, 52*), lemmings (*53*), voles (*11, 19*), woodchucks (*54*), *Apodemus* (*52*), and other mammals have shown that a deficiency of food either was not a factor in population decrease or else had an effect complementary to behavioral changes associated with changes in population density (*47*). From evidence currently available it appears that the effects of restricting water intake over a long period can be regarded in the same fashion as the effects of chronic inanition. In a thorough study of food requirements and availability of food in relation to populations of small mammals, it was shown that food was not a limiting factor in the area studied (*50*). More critical studies of this sort are needed before a final evaluation can be made of the relative importance of food shortages in limiting population growth and of the degree to which such limitation, when it does occur, is associated with increasing competition within existing hierarchical structures.

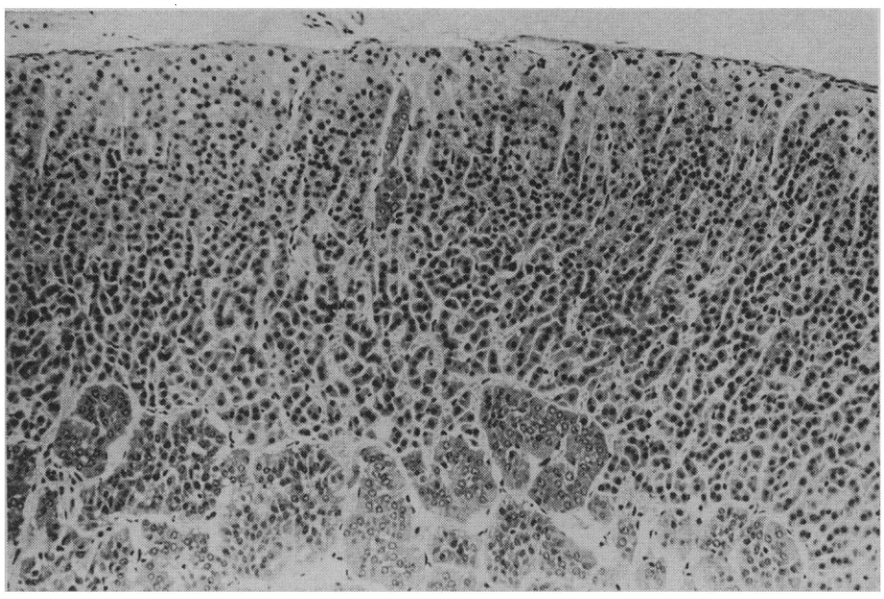
The important point, in assessing the effects of behavioral factors on adrenal function, is the number of interactions between individuals rather than density of population per se. Thus, age, sex, previous experience, local distribution, and other factors may be critical in producing effects (*6, 17–19, 55*). The development of the adrenal responses may be produced by very brief encounters with other animals. Experiments showed that 1-minute exposure to trained fighter mice 1, 2, 4, and 8 times a day for 7 days produced increases in adrenal weight and increases in adrenal and plasma concentrations of corticosterone (*56*). As few as two 1-minute exposures per day resulted in a 14-percent increase in adrenal weight, and eight exposures daily resulted in a 29-percent increase. Plasma corticosterone increased by 67 percent. Adrenal levels of corticosterone increased in proportion to adrenal weight, so corticosterone concentrations per gram of adrenal tissue remained constant. These results validate, for mature male house mice, the use of adrenal weight as an index of cortical function. Thus, a few short daily exposures to aggressive mice produced a greater increase in adrenal weight than caging male mice of the same strain together in groups of eight continuously for a week (*37, 56*). These results should serve as an answer to the criticism that laboratory experiments on populations are not realistic because of artificially high densities.

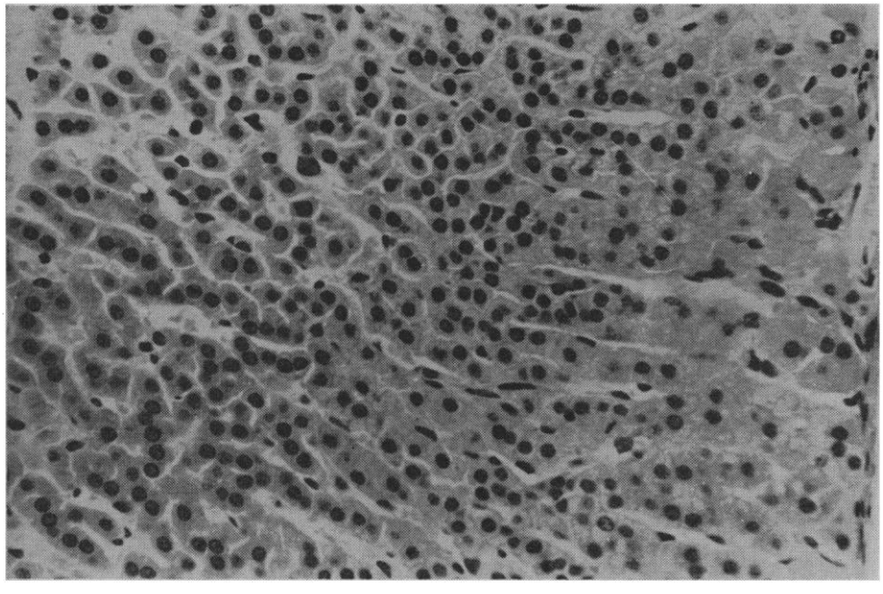
Differences in basic aggressiveness of the strain or species must be considered in a comparison of relative population densities. For example, albino mice are extremely docile in contrast to some strains maintained in the laboratory (*57*). *Peromyscus maniculatus bairdii* also is nonaggressive—even more so than albino *Mus* (*37*). Recently Southwick has demonstrated the importance of behavioral factors in eliciting an adrenocortical response in *P. leucopus* by showing that grouped animals had no adrenal response when they were "compatible" but did if they were "incompatible" (*58*). Thus, to compare absolute densities in the laboratory with those of feral populations is not a justifiable procedure.

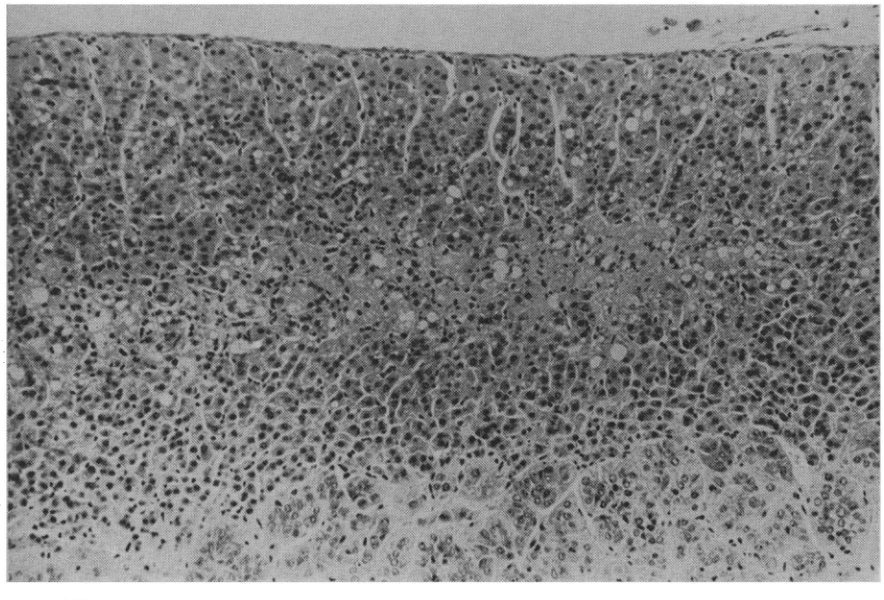
It is often said that fighting per se, or injury from fighting, produces the endocrine changes that occur with change in rank and number (*59*). However, data from a large number of populations of mice demonstrate that the endocrine responses to grouping are identical whether or not there is fighting or injury (*6*). Fighting is another symptom of social competition. It seems clear that the basic stimulus to the endocrine changes are sociopsychological, or "emotional," and not physical in nature. Pearson has made the interesting observation that in freely growing populations a few excessively submissive, thoroughly beaten-up, badly scarred mice have low plasma concentrations of corticosterone (*41*). This result agrees with our observations that mice that sink to this level are so abjectly submissive that the more dominant animals no longer pay any attention to them. Because they no longer interact with other members of the population, they cease to be part of it. Also, their continuing existence is probably the result of an artificial situation created by confinement, as in natural populations such animals would doubtless have been forced to move continually; hence most of them would have become mortality statistics. Such submissive animals have been observed and repeatedly captured in a population of woodchucks.

Criticisms of Theory

The criticism has been made, as stated earlier, that results from studies on populations in the laboratory cannot be extrapolated to natural populations because of the excessive densites in the laboratory (*11, 60–62*). The work cited above (*56*) showed that mice exposed to crowding for very short periods each day had an increase in adrenal function. In addition, data on density for most natural populations are often misleading, as many







species of rodents, especially rats, voles, and mice, often occur in local "colonies" that may be rather crowded even though areas around them may be very sparsely inhabited. Localized groups of rats in natural populations apparently behave like independent populations, with different degrees of crowding, until the numbers and movement increase sufficiently to fill the general area, at which time the colonies lose their identity and become part of a larger population (*6*). Furthermore, comparable endocrine changes have been observed in natural populations of a number of other species—voles, rats, Japanese deer (sika), woodchucks, and rabbits (*30, 53, 63–65*). Increased social strife produced by the introduction of aliens into a population of rats will induce movements, increase mortality, and, if the original population was high, cause a striking decline from original densities (*18, 66*). Conversely, artificial reduction of a population or alteration of its social structure in a way that

Fig. 1 (top left). Adrenal of an immature 15-gram male *Microtus pennsylvanicus*, trapped 15 June, illustrating zonation of the cortex. The cortical zone next to the medulla is composed of compact, lipid-free cells with moderately hyperchromatic nuclei. Between this zone and the typical fasciculata is a zone of small cells containing some lipid (its distinctiveness is more clearly apparent in the original sections than in black and white photomicrographs). These two zones appear to differ morphologically from the X-zone of *Mus*, although both involute with attainment of sexual maturity. Spermatogenesis had nowhere advanced beyond primary spermatocytes in the testes of this vole. The seminal vesicles and coagulating glands together weighed 2.3 milligrams. (Five-micron section stained with hematoxylin and eosin; × 143)

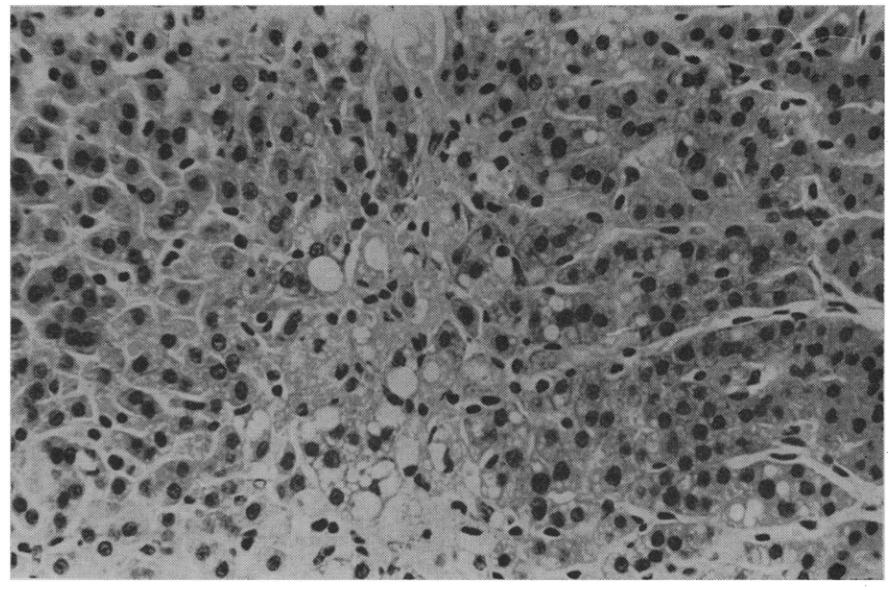
Fig. 2 (center left). Same adrenal as in Fig. 1 at higher magnification, showing cellular details more clearly. Outer cortex at the right. (× 358)

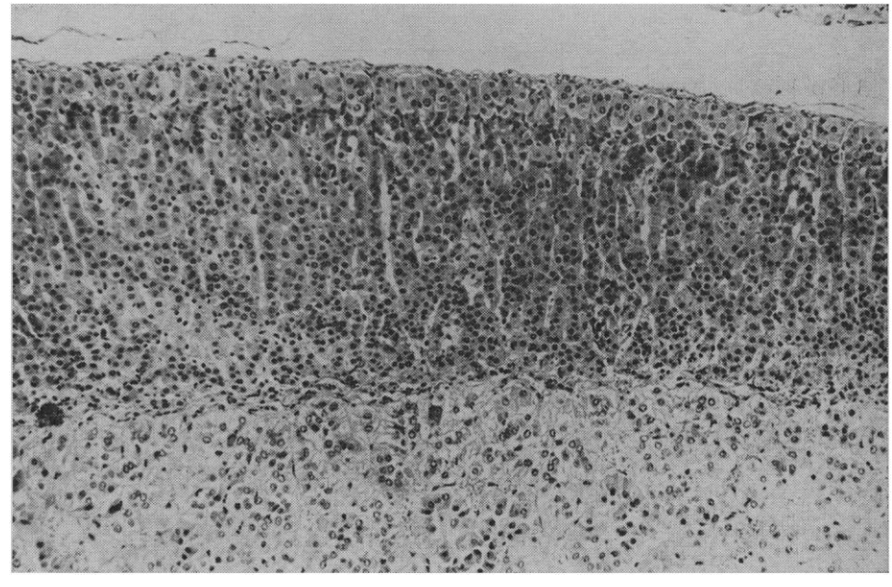
Fig. 3 (bottom left). Adrenal of a more mature male *Microtus pennsylvanicus* than that of Fig. 1. Two distinct cortical zones of degeneration may be seen, one juxtamedullary and the other midcortical. The midcortical zone results from involution of the central cortical zone shown in Figs. 1 and 2, while the juxtamedullary involution arises from involution of the innermost zone. This involution occurs when spermatogenesis is complete, with sperm in the epididymis, but before the seminal vesicles have attained mature size. The seminal vesicles and coagulating glands together weighed 434 milligrams. (Five-micron section stained with hematoxylin and eosin; × 143)

reduces competition will reduce adrenal weight and incidence of disease accordingly (*17, 22, 67*). This reduction has been observed in rats, deer, and woodchucks (*30, 65, 67*).

In some situations no correlation has been shown between adrenocortical function and changes in population, but so far the cases fall into two categories. The first is that where the sample is too small to demonstrate any correlation. For instance, Negus (see *61*, Table 4) studied only 98 animals over a 2-year period, of all ages and both sexes (*61*). A second cause of lack of correlation is inaccuracy of population measurement, primarily because currently available census methods are notoriously poor and confidence limits of the estimates have been disregarded (*61*).

Since changes in adrenal weight occur with reproductive activity, several authors have concluded that adrenal weight cannot be used as an index of adrenocortical function in the study of populations (*68, 69*). It was implied in these accounts that these changes in adrenal weight with changes in reproductive status were overlooked when conclusions concerning population were drawn from changes in adrenal weight in earlier studies of house mice or other species (*62, 68, 70, 71*). Our published data show that these factors were taken into consideration in our studies (*64, 72*). On the other hand, a number of workers may have failed to find a correlation between population status and adrenal weight because changes with sexual function were disregarded. It is well known that adrenal weight increases during pregnancy or with estrogen





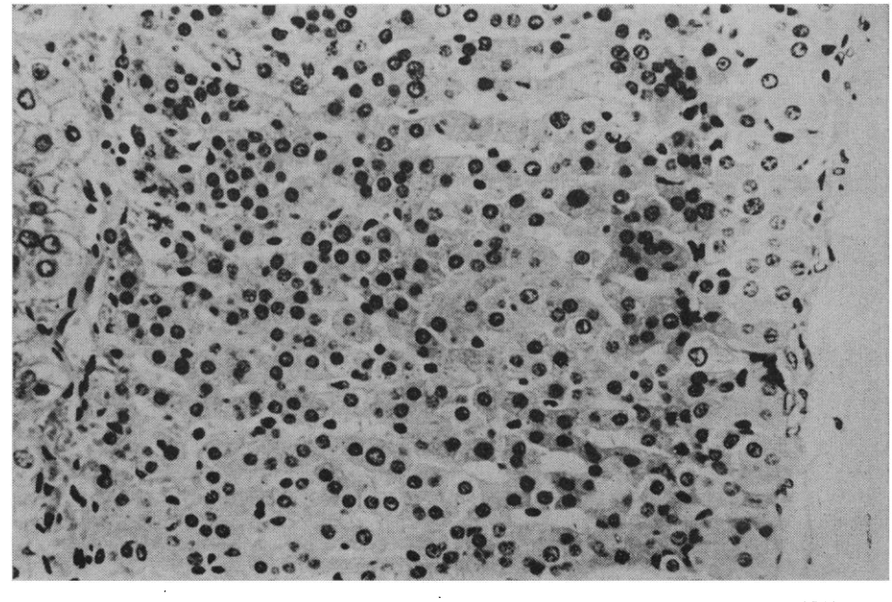


Fig. 4 (top right). Same adrenal as in Fig. 3, showing more clearly the unique midcortical zone of degeneration which closely resembles the fatty type of degeneration of the X-zone often seen in female *Mus.* Outer cortex at the right. (× 358)

Fig. 5 (center right). Adrenal of a fully mature male *Microtus pennsylvanicus* captured on 15 June, typical of a mature adrenal cortex in males of this species, having a conspicuous zona glomerulosa and zona fasciculata and a central, rather thin zona reticularis. The seminal vesicles and coagulating glands together weighed 1479 milligrams. (Five-micron section, stained with hematoxylin and eosin; × 143)

Fig. 6 (bottom right). Same adrenal as in Fig. 5 at higher magnification, showing more clearly the details of zonation of the mature cortex of *Microtus pennsylvanicus.* Outer cortex at the right. (× 358)

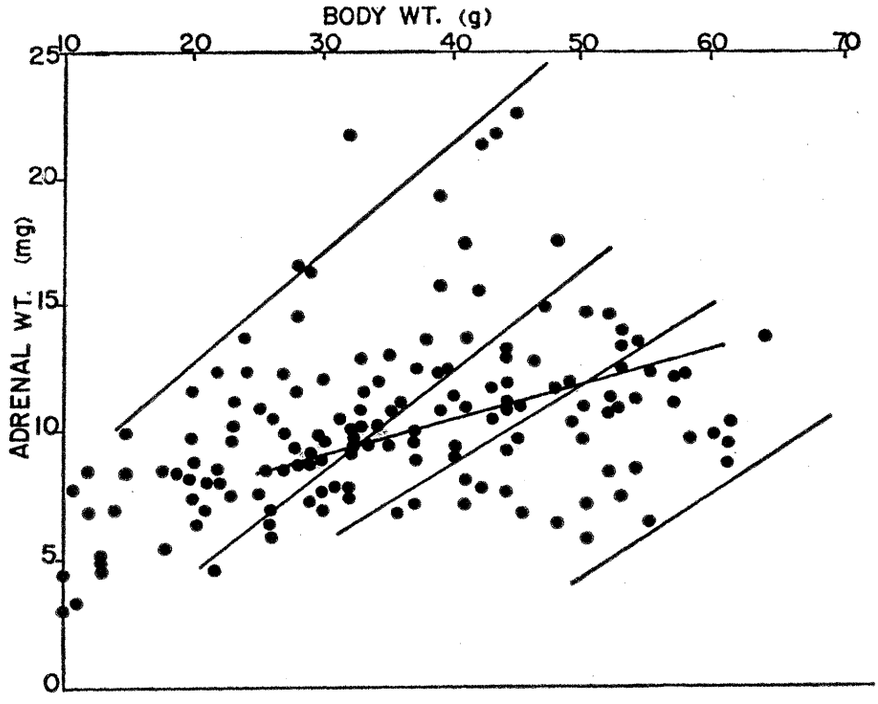


Fig. 7. A plot of adrenal weights (in milligrams) against body weights (in grams) for male *Microtus pennsylvanicus*. The lines were not fitted but were drawn in approximately as follows. The two parallel lines at upper left enclose points for immature animals whose adrenals showed typical immature zonation, as shown in Figs. 1 and 2. The two parallel lines at lower right enclose points for fully mature animals resembling those of Figs. 5 and 6. The points between (and inevitably to some extent some points enclosed by the parallel lines) are for animals in the process of maturing. The single line corresponds roughly to the mean adrenal weights of maturing animals; however, this is not a fitted line and only suggests the direction of transition. It was found impossible to fit regressions of adrenal weight relative to body weight (or body length) for these data in defining starting or end points of zonal involution.

stimulation in some species, but it is not always remembered that changes in adrenal weight due to population changes can be superimposed on these increases (*19, 64, 65, 70*). Changes in adrenal weight with change in reproductive status fall into two categories: (i) change in weight when there is immature zonation which later disappears, and (ii) change in weight in fully mature animals which is associated with reproductive activity. Obviously, only changes in adrenal weight or function in animals in the same reproductive condition can be properly compared or correlated with changes in population. Chitty and Clarke (*71*) have claimed that a marked increase in the size of the adrenal in female voles (*Microtus agrestis*) is restricted to pregnant animals. However, McKeever reported similar increases in nonpregnant, nulliparous, but sexually mature, females of *M. montanus* (*69*). Our results with *M. pennsylvanicus* are similar, although mature nonpregnant, nulliparous females are scarce, as one would expect. It appears, at least in the North American voles, that the striking increase in the size of the adrenal is associated with maturation and estrogen secretion and is not limited to pregnancy. However, we have long been aware that adrenal size increases during pregnancy in many species and that this must be considered in using adrenal weights as indices of adrenal function. In other cases, a change in adrenal weight is related to seasonal behavioral changes (*64*), as originally suggested for muskrats (*73*) and later for *Microtus* (*70*).

Further criticism of the theory that behavioral-endocrine mechanisms are operative in the control of population growth is based on recent reports of a lack of correlation between adrenal weight and changes in population size, from which it has been concluded that endocrine mechanisms do not affect population growth (*61, 68, 69*). In another report it was stated that there is no evidence of a "stress mechanism" in a collapse of a lemming population, as no related changes in adrenal weight were found (*74*). First, it must be noted that failure to demonstrate a correlation, without consideration of pertinent relationships, is not disproof of a correlation. Second, these criticisms have been based on observed adrenal weights in voles or rice rats (*Oryzomys*), primarily in the former, without critical evaluation and validation, microscopic or otherwise, of the weight changes. While such conclusions may eventually prove correct in some instances, the inappropriate use, in the studies reported, of adrenal weight as an index of adrenocortical function in these rodents invalidates the conclusions. A basic error in the studies was failure to recognize that many rodents have zones in the adrenal cortex which in many ways resemble the X-zone in house mice, and that these zones are without known function. The use, as indices of function, of the weights of adrenals which include these zones is not appropriate. Delost has published numerous reports on the existence of an "X-zone" in the adrenals of voles (*Clethrionomys, Pitymys*, and *Microtus*) which involutes at maturity in males and regenerates during sexual quiescence (see *6*). Chitty and Clarke (*71*) have further explored this problem in *M. agrestis*. On morphological grounds and because we have observed two immature zones in male *M. pennsylvanicus*, we do not entirely agree with Delost that these should be called X-zones, but the basic observation that in immature voles there are zones which later involute, spontaneously or on administration of testosterone, remains valid. Male *M. pennsylvanicus* appears to have two distinct zones which involute at maturity (Figs. 1–6), neither one of which appears to be entirely comparable morphologically to the X-zone of house mice. The male *Pitymys, Synaptomys*, and *Clethrionomys* that we have examined, and possibly other voles, have similar zonation, although the probability of differences between species or genera must be kept in mind. These zones persist with inhibition of maturation, so that in such voles adrenal weight is relatively much greater in immature than in mature males (Fig. 7). The converse is true for the adrenals of female voles (Figs. 8–10), which undergo a striking hypertrophy at maturity, probably as an exaggerated effect of estrogens, as described for many species, although this has not been tested as yet (*74a*). McKeever (*69*) has demonstrated changes in adrenal weight with age and maturation in

Microtus, illustrating changes occurring with maturation, but he failed to recognize the zonal changes and probably typical, but enhanced, responses to estrogen, and so arrived at unjustified conclusions. In addition, the picture is confounded by the fact that all gradations between the immature and the fully mature condition of the adrenals occur, as shown in Figs. 8 to 11.

Further complicating the picture is the fact that most small mammals born in the fall, and probably even those born at the end of the spring and in the early summer breeding season in a period of relatively high population density, overwinter in the im-

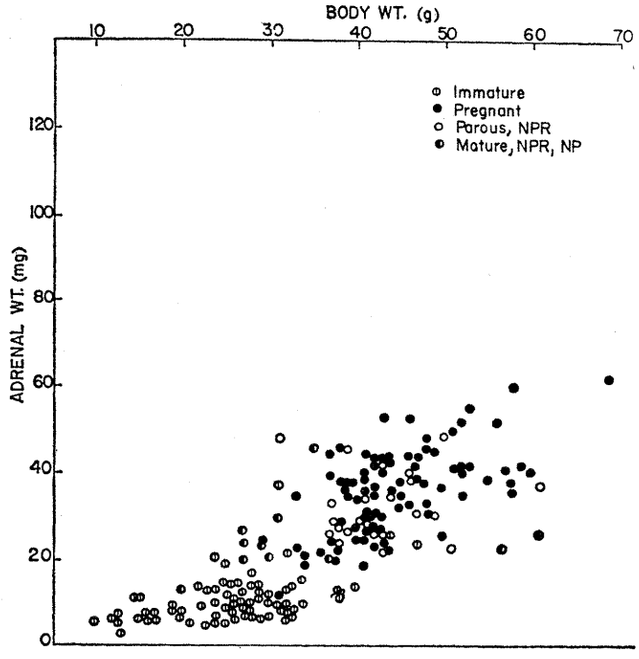


Fig. 8 (top left). A plot of adrenal weights (in milligrams) against body weights (in grams) for female *Microtus pennsylvanicus* captured at all seasons of the year. Reproductive status is indicated as shown (NPR, nonpregnant; NP, nulliparous). It may be seen that adrenal weight increases sharply with sexual maturation whether or not the animal is pregnant or parous, although most were pregnant. As may be seen in Fig. 9, most of the immature animals were captured in the late fall and early winter and mainly represent suppressed maturation in young of the preceding breeding season.

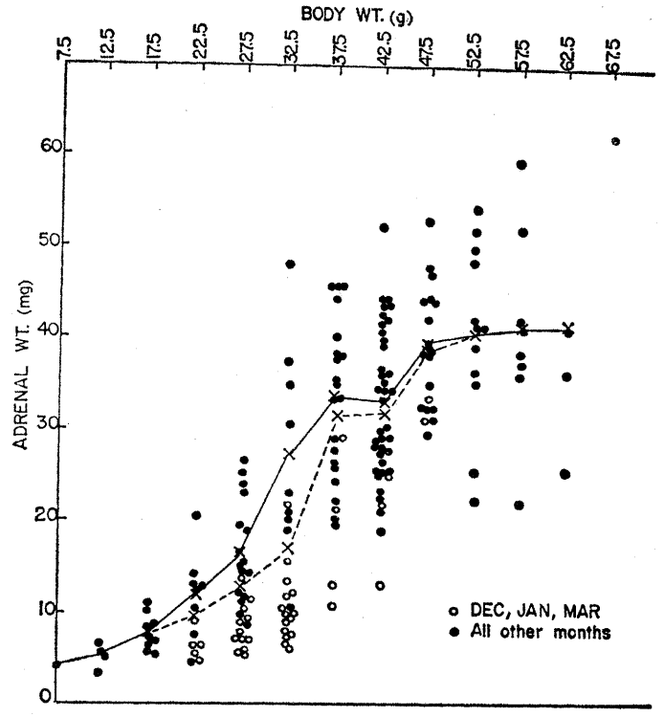


Fig. 9 (top right). Weights of adrenals from the animals of Fig. 8 plotted against body weights, with season of capture indicated. A large number of the adrenal weights for immature females are for animals captured between December and March, as indicated in Fig. 8. (Solid line) Mean adrenal weight for animals captured in any month other than December, January, and March; (dotted line) mean adrenal weight for all animals. Figures 8 and 9 show that only the weights of adrenals from mature animals can properly be used for comparing changes in weight with changes in population; in the main, this means that only the weights of adrenals of animals weighing more than 35 grams can be used, but in the winter one finds a few immature females even in this weight range. For this reason the values for mean adrenal weight that we previously published (*18*) for female *Microtus montanus* captured in winter are probably too low, although we used only weights of the adrenals of animals weighing 37.5 grams or more in the study, thus largely, but not entirely, avoiding this pitfall.

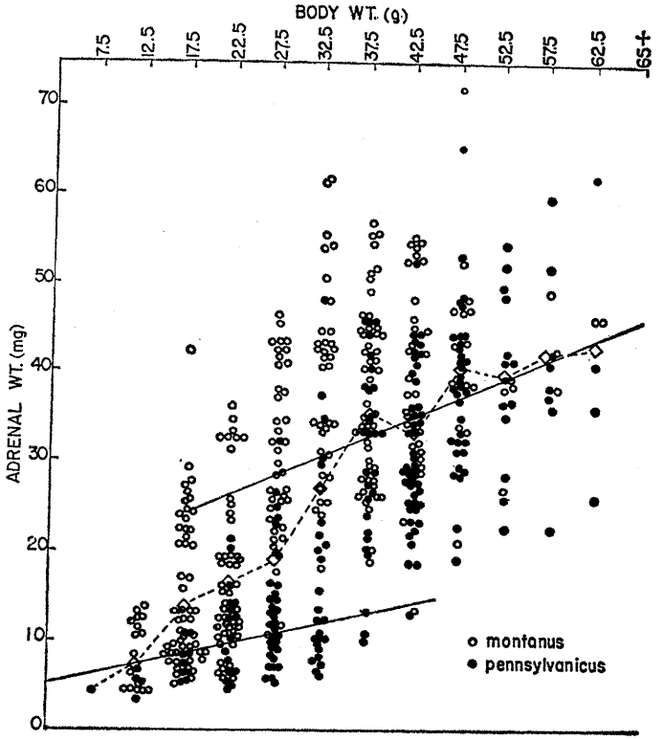


Fig. 10 (right). Plot of adrenal weights against body weights for female *Microtus pennsylvanicus* and *M. montanus*. Regression curves were fitted to points for fully mature females (upper curve) and to points for immature females (lower curve). Weights of adrenals from maturing females form a continuum between these end stages. This plot again illustrates the problems one encounters in using adrenal weight of voles to assess adrenocortical function in relation to population changes unless one uses only fully mature animals. It appears from this diagram that female *M. montanus* mature somewhat earlier than female *M. pennsylvanicus*, but a number of other factors, including differences in populations, confound the data and make it impossible to draw a definite conclusion.

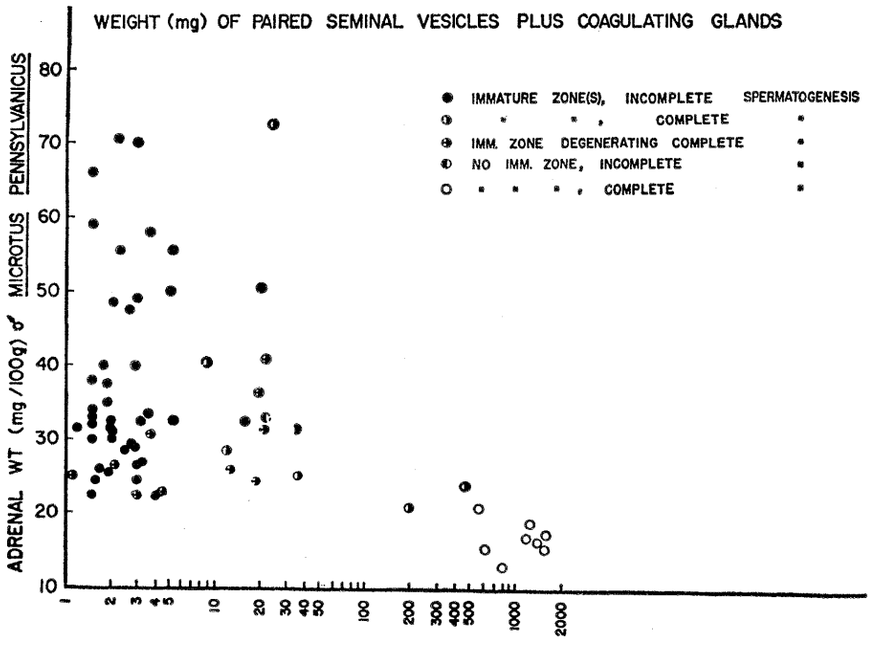


Fig. 11. Plot of adrenal weight (in milligrams per 100 g of body weight) for male *Microtus pennsylvanicus* against the logarithms of values for combined weights (in milligrams) of seminal vesicles and coagulating glands. The state of sexual maturity is indicated in the key. This plot depicts the difficulties encountered in using adrenal weight to assess adrenocortical function in male microtines because of the presence of immature cortical zones.

mature condition (*17, 19, 75, 76*), so that a persistence of immature zonation in males and, in females, the small size of the adrenals unstimulated by estrogen (or whatever factors stimulate the hypertrophy associated with maturation) would be expected (Figs. 8 and 9). The basic error in the conclusions of several investigators was the assumption that adrenal weight is always synonymous with cortical function. In addition, nothing is yet known about the steroids secreted by these species or the possible relation of steroid secretory patterns to changes in zonation. Obviously, if adrenal weight is to be used as an index of adrenocortical function in these species, comparisons can be made only between animals in the same state of reproductive function and with the same degree of involution of immature adrenal zones. Thus, for practical purposes, comparisons are limited to fully mature, sexually active animals. This means, in our experience, that in *Microtus* (*pennsylvanicus* or *montanus*) one usually is limited to the use of animals weighing 35 to 40 grams or more and having uninhibited reproductive function. The relationship between adrenal weight and reproductive function in terms of the weight of seminal vesicles in *M. pennsylvanicus* is shown in Fig. 11. These data illustrate problems one encounters in attempting to make comparisons of adrenal weight for other than fully mature, sexually active males (Figs. 7 and 11).

Another cause of failure to demonstrate a correlation between adrenal weight and population density is failure to consider the social rank of individuals in the samples examined. Since high-ranking individuals generally do not have enlarged adrenals, comparisons of high-ranking individuals at low and high population densities will reveal no changes in adrenal weight or function. McKeever may have made this error when he divided animals into sexually nonactive and active categories (*69*). At high population densities maturation of subordinate animals would be delayed, and these animals would be called nonactive. McKeever's Table 2 (*69*) may simply show that high-ranking animals have similar adrenal weights at low and high population densities, and that low-ranking animals do also. However, comparisons between sexually inactive animals in this case are very probably invalid because of the persistence of immature zonation. Another example of failure to consider social rank is Rudd and Mullen's consideration of only the survivors from groups of pocket gophers (*77*).

In most instances, failure to find a correlation between adrenal weight and population density is due to inclusion of immature animals in samples in progressively larger numbers with seasonal progression. Seasonal or maturational changes in the adrenals do not invalidate the use of adrenal weights as indicators of adrenocortical function if the weights are used critically, but comparisons must be made between comparable animals at comparable times. For example, it has been possible to show a significant decrease in the size of adrenals of woodchucks with alteration of social structure and diminution of competition during the time of rapid increase in adrenal weight by making the appropriate adjustments (*64, 65*); however, there is no complicating zonation in this mammal.

So far we have discussed primarily the restriction of increases of populations due to the effects of high densities. In addition, this explanation should provide some understanding of the increased mortality of young that occurs in subsequent generations. One of the striking aspects of both a natural and a confined population is the observation that young animals have a higher mortality than adults coincident with high population and, in natural populations, also after population density has fallen to relatively low levels (*7*). Chitty (*7*) explained these losses of young in two ways: losses in the year of peak population he attributed to attacks by adults, and losses in the following spring he attributed to some unknown congenital condition acquired *in utero*. Evidence consistent with this view was presented by Godfrey (*78*). Body weights that were low as compared with those in the peak year have been reported in these studies (*79*), and we have observed a similar nonoccurrence of large animals following a peak in population (*19*).

Chitty (*79, 80*) invoked genetic selection to explain how later generations might be influenced by conditions existing before they were born. Therefore, he postulates an effect of social behavior different from that proposed by us (*17, 19*). Thus, he and his colleagues—for example, Krebs (*74*) and H. Chitty (*70*)—differ from us on the *kind* of physiological and behavioral changes they postulate, but not on the question of whether behavioral changes play an essential part in the regulation of numbers. We find

Chitty's explanation for the events in natural populations difficult to accept because it requires genetic selection acting rapidly for a year or two with a subsequent return to, or close to, the original genetic status. In contrast, we believe there is ample evidence of endocrine mechanisms which have the prolonged effects necessary to account for the increased mortality of young during, and for a considerable time after, episodes of maximum density. We have mentioned some of these effects, but we should also call attention to the life-long effects on reproductive function of single injections of androgens into mice or rats less than 10 days old (see *81*); the behavioral effects produced *in utero* reported by Keeley (*26*); the effects of the injection of corticosteroids or other hormones during pregnancy on later behavior (*82*); and the effects of corticosteroids on brain development (*27*). Undernutrition during nursing also has profound and permanent effects on offspring (*83*), which are consistent with the observed reduced growth at high population levels. Actually neither the endocrine nor the genetic selection explanations have been adequately tested, but there appears to be more evidence in support of the former. However, selection must play a long-range role, if not a short-term one (*19*). Whatever the mechanisms accounting for the observed increased mortality of young during and following episodes of high density, it seems evident that the altered status, which we believe to be physiological, will increase susceptibility to adverse environmental conditions, and that behavioral factors are of primary importance in the genesis of the altered status. It is clear that, in a general way, we arrive at the same ultimate conclusions as Chitty, but we place more emphasis on decreased productivity than on increased mortality, although one would anticipate various combinations of these two factors to occur in different populations and under different circumstances. One would expect altered reproductive function to be of greater importance in mammals with a high reproductive rate than in those with a much lower reproductive rate, such as woodchucks. Woodchucks exhibit decreased reproductive function with increased social pressure, brought about by an increased failure to mature in their first year, and increased intrauterine mortality (*84, 85*), but this is less important in regulating their population than movement of young or mortality (*17, 84*). Of interest in this regard is the finding that young woodchucks become more seriously affected by renal disease at high population densities, and that this probably results in appreciable mortality (*17*).

These comments lead to consideration of another recent discovery of direct pertinence to the question of the greater effects of high population density on young than on adult mice. First, we repeat that the young in general are subordinate animals and thus, other things being equal, more seriously affected by crowding. However, immature house mice secrete appreciable quantities of 17-hydroxycorticoids, especially hydrocortisone, and, when they are grouped, not only does the total adrenal corticosteroid production increase but the hydrocortisone-corticosterone ratio increases as well (*38, 86*). With sexual maturation of male mice, the ability to produce hydrocortisone is greatly reduced. Also, if there is delayed maturation accompanying increase in numbers, the secretion of appreciable amounts of hydrocortisone is prolonged. The importance of this finding is that hydrocortisone is a much more potent glucocorticoid than corticosterone, which is the principal compound secreted by adult mice, adult rats, and probably a number of other adult rodents (see *6*). Therefore, similar degrees of stimulation of the adrenals of immature and adult mice should result in more profound effects in the immature animals even if there were no difference in social rank. This difference has been observed biologically in the much greater degree of thymic involution and growth suppression produced in immature mice either by ACTH or by grouping than can be produced in adults by similar treatment or by the injection of relatively high amounts of corticosterone (*18, 19, 87, 88*). Similarly, gonadotrophin secretion is suppressed by much smaller doses of steroids in immature than in mature mice and rats (*89*), so that inhibition of maturation of the young in experimental and natural populations may be explained on this basis.

In attempting to explain the mechanisms of the progressive inhibition of reproductive function with increasing population density we postulated that increased secretion of adrenal androgens in response to increased secretion of ACTH might be sufficient to inhibit gonadotrophin secretion, especially in immature mice, and thus explain the observed declines in reproductive function (*6, 90*). Indeed, the injection of adrenal androgens at nonvirilizing physiological concentrations suppresses gonadotrophin secretion and inhibits normal maturation in immature female mice (*91*). Injection of ACTH in intact immature mice also totally inhibits normal maturation (*87*). Surprisingly, ACTH has a similar effect in adrenalectomized mice maintained on hydrocortisone (*88, 92*); thus it appears that ACTH has a direct suppressive effect on reproductive function and therefore on maturation (the site of action is as yet unknown) of immature female mice. Consequently there are at least two distinct mechanisms capable of inhibiting maturation, whose relative importance in the intact animal is unknown. There also remains the distinct possibility that the central nervous system, in response to emotional stimuli, may inhibit gonadotrophin secretion even more directly. In any event, there is ample explanation, including both behavioral and physiological mechanisms, for the differences in the effects of high population levels or increased competition on reproduction, growth, and mortality of the young in contrast to adult animals.

Conclusions

The experimental results suggest that there are mechanisms for the regulation of many populations of mammals within the limits imposed by the environment, including food. We subscribe to the view that density-dependent mechanisms have evolved in many forms, and probably in most mammals (*11–13, 19, 93*). Thus, mammals avoid the hazard of destroying their environment, and thus the hazard of their own extinction. We believe that the evidence, as summarized here, supports the existence of endocrine feedback mechanisms which can regulate and limit population growth in response to increases in overall "social pressure," and which in turn are a function of increased numbers and aggressive behavior. Neither increased numbers nor increased aggressiveness can operate wholly independently. Furthermore, we believe that environmental factors in most instances probably act through these mechanisms by increasing competition. A good example of this would be the situation described by Errington for muskrats (*94*). A drought causes the animals to concen-

trate in areas of remaining water, with the result that competition and social strife are greatly increased. It follows that increased strife, with increased movement, will also increase losses through predation, another way of increasing mortality of subordinate animals (*22, 47, 94*).

Finally, we might paraphrase Milne's statements (*12*) regarding density-dependent regulation of population growth as follows: Environmental factors (food, predation, disease, physical factors) may limit population growth, but if they do not, as appears more often than not to be the case in mammals, the physiologic mechanisms outlined above will. And finally, the action of these mechanisms is always proportional to changes that depend on changes in population density, behavior, or both. The fact that a sigmoid growth form requires the operation of such a "density-dependent damping factor" supports this conclusion, whereas external limiting factors, unless they operate through the density-dependent damping mechanism, will characteristically truncate a growth curve. Truncation is seldom seen, but the best example of such a curve for mammals that we have seen is that given by Strecker and Emlen (*95*).

In summary, we believe that the behavioral-endocrine feedback system is important in the regulation of populations of rodents, lagomorphs, deer, and possibly other mammals. One would expect other factors to occasionally limit population growth, but, when these fail to do so, the feedback mechanism acts as a safety device, preventing utter destruction of the environment and consequent extinction. Because of time-lag effects, this feedback system should not be expected to work perfectly in every situation.

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74*a*. *Note added in proof*: Results from a recent study of the relationships between sexual maturity, the adrenal glands, and population density in female *M. pennsylvanicus* from a natural population suggest that *female* voles of this species have no X-zone as it is defined for house mice (*20*). Apparently it is a hypertrophic reticularis and inner fasciculata [resembling the adrenals of woodchucks in this respect (*54, 64*)] which have been labeled an X-zone. There is no involution at pregnancy. The cells contain lipids, and the hyperplasia occurs with maturation, as pointed out by Chitty and Clarke (*71*). Adrenal weight relative to body weight is a discontinuous function in these animals as a result of the sudden increase at maturation. Therefore, regressions of adrenal weight relative to body weight or body length are invalid if the data come from both immature and mature females. When these facts are taken into account it is clear that there is no change in adrenal weight relative to body weight with reproductive status in mature females, and that there is a remarkable parallelism between mean adrenal weight of mature females and population size.

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