Thesis Approved

By

__________________________
Richard J. Andrews
Major Advisor

__________________________
Dean
A STUDY OF PATHOLOGICAL CONDITIONS IN WILD RODENTS (RATTUS NORVEGICUS) WITH RESPECT TO SEASONAL VARIATIONS AND ENDOCRINE IMBALANCE

BY

JOHN G. SOUTHARD

A THESIS

Submitted to the Faculty of the Graduate School of the Creighton University in Partial Fulfillment of the Requirements for the Degree of Master of Science in the Department of Biology

Omaha, 1971
ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to all of those who were instrumental in developing this thesis. I am especially grateful to Dr. R. V. Andrews and Dr. R. W. Belknap for their ideas and effort throughout the entire study, Steve Hess for his technical cooperation, Dr. J. F. Sheehan for his assistance with the photomicrography, my wife Leslie for typing the rough draft and Betty McPartland for the typing of the final manuscript. I would also like to express appreciation to the National Institute of Health for their financial support.
# TABLE OF CONTENTS

I. Introduction ....................................................
   A. Factors Maintaining Population Density ............... 6
   B. Ecological Factors Affecting Population Density .......11
   C. Behavioral Factors Affecting Population Density ......14
   D. Physiological Factors Affecting Population Density  
      and the General Adaptation Syndrome ....................18

II. Statement of the Problem ......................................38

III. Materials and Methods .......................................39
   A. Field Procedures ..........................................39
   B. Laboratory Procedures .....................................40

IV. Results ........................................................43
   A. Adrenal Function .............................................43
   B. Reproductive Status of the Population ...................56
   C. Incidence and Severity of Pathologic Conditions .... 62

V. Discussion and Conclusions ..................................66

VI. Bibliography ...................................................92
# TABLE OF FIGURES

Figure 1....................................................... 4
General Adaptation Syndrome.

Figure 2................................................................. 9
Components of reproduction in polyoestrous mammals.

Figure 3..................................................................45
Dose responsiveness of isolated rat adrenal glands to exogenous ACTH.

Figure 4................................................................. 47
Basal secretory rates of isolated rat adrenal glands throughout the trapping period.

Figure 5..................................................................49
Dose responsiveness of isolated rat adrenal glands to exogenous ACTH.

Figure 6..................................................................58
A comparison of plasma corticosterone levels in juvenile, sub-adult and adult animals throughout the trapping period.

Figure 7..................................................................81
Rat kidney section. Osmotic nephrosis.

Figure 8..................................................................83
Severe necrotizing glomerulonephritis.

Figure 9..................................................................85
Acute necrotizing glomerulonephritis.

Figure 10................................................................. 87
Nephrosis of kidney from winter trapping period.
Table of Figures (continued)

Figure 11

Pathologic conditions characteristic of animals trapped in early spring.
TABLE OF TABLES

Table 1.................................................................51
Demographic features of a "stable" population of Wild Norway Rats.

Table 2.................................................................53
Demographic features of a "stable" population of Wild Norway Rats.

Table 3.................................................................55
Demographic features of newly established populations of Wild Norway Rats.

Table 4.................................................................60
Physical characteristics of mature male rats from a "stable" population.
I. INTRODUCTION

Numerous studies of rodent populations have contributed invaluable information with respect to ecological and environmental, behavioral and physiological interactions on population dynamics. Some of these observations include seasonal changes in breeding (Venables and Venables, 1952; Perry, 1945; Watson, 1950; Harrison, 1951; Davis and Hall, 1948, 1951; Newson, 1963; Kalela, 1962; Mullen, 1964; Beveridge, 1965; Chitty and Phipps, 1966); behavioral alterations (Calhoun, 1950, 1952; Chitty, 1957; Southwick, 1964; Sadlier, 1965; Krebs, 1964; Christian and Davis, 1964; Ader, 1967; Christian, 1955; Elton, 1942; Lack, 1954); ecological variations (Davis, 1953; Thompson, 1955; Pitelka, 1957; Lidicker, 1966; Kalela, 1957); adrenocortical function (Bronson, 1967; Louch and Higginbotham, 1967; Dougherty, 1953; Christian and Davis, 1956; Christian, 1963a; Bronson and Eleftheriou, 1963; Andrews, 1968a); and mortality (Calhoun, 1949; Chitty, 1964; Krebs, 1964; Sadlier, 1965; Beck and Rodeheffer, 1965; Chitty and Phipps, 1966; Lidicker, 1966).

For the most part, studies of the wild rat (Rattus norvegicus) have been concerned with its ecology and social interactions (Calhoun, 1962). Through attempts to arrive at an effective rat control method, investigators have revealed valuable information with regard to social interactions, mortality, reproduction, social rank and social stress, and movements. Depending upon the nature
and the objectives of the investigation, several approaches to the study of wild rat population dynamics and related phenomena have been effected. Some of the significant studies concern reproduction rates in rodent populations (Eaton and Stirrett, 1928; Asdell, 1941; Davis and Hall, 1948, 1951; Davis, 1951a, 1951d; Emlen and Davis, 1948; Harrison, 1951; Perry, 1945; Watson, 1950); migratory habits of rats (Creel, 1951; Silver, 1927; Davis, Emlen and Stokes, 1948; Emlen, Stokes and Winsor, 1948; Chitty, 1946; Spencer and Davis, 1950); and infections and disease conditions common in wild rat populations (Habermann, Williams and Thorp, 1954; Cram, 1928; Price and Chitwood, 1931; Davis and Huan-Ying, 1952; Childs and Cosgrove, 1966; Ader, 1967; Tobach and Bloch, 1956; Christian and Ingle, 1948).

The concept that pathological tissue-response to traumatic environmental insults may reflect hormonal imbalance has been used to investigate the relationship between population dynamics, disease and endocrine function. Such tissue responses may be used as an index of stress and may be accompanied by decreased resistance to metabolic and infectious disease. In 1936, Selye demonstrated that animals respond in a systematic manner to a wide variety of seemingly unrelated, noxious agents such as infections, heat, cold, fatigue, irradiation, trauma, toxic substances and nervous strain. Although the primary actions of these agents were quite different, they shared the common feature of placing
the body in a state of systemic stress. Selye defined stress as the sum of all non-specific changes caused by altered function or damage. Among the most dramatic of these changes is an enlargement and increased secretory rate of the adrenal cortex.

Further investigation led Selye to develop the concept of the 'General Adaptation Syndrome' (G.A.S.), Fig. 1. This concept divides the over-all response of the organism into three stages: the "alarm reaction", in which the adaptation is not yet acquired; the "stage of resistance", in which adaptation is advantageous; and the "stage of exhaustion", in which the acquired adaptation is lost. Of these three stages, the stage of resistance is the most sensitive to secretions of the adrenal cortex, resulting from an increased secretion of the adrenocorticotropic hormone (ACTH) from the anterior pituitary.

The sequence of events within the adaptive mechanism proposed by Selye describe a model with significant cellular involvement which may affect systemic integration of individual organisms and thereby be equally applicable to animal population dynamic adjustments. Whether the emphasis, regarding adaptive responses, is placed at the molecular and cellular level or at the organismic and population levels of integration, adaptation is characterized by ordered structure and functional coordination. If, in conjunction with an adaptation to a stressful condition, the system must maintain internal equilibrium, it must have some regulatory
Cerebral Cortex

Hypothalamus

Ant. pituitary nerve stress:
Proinflammatory, either
may cause tissue physical
sensitization to or psychic
stress: results

stimulation

impulse

either

body

response

specific

local

response

increased

secretion

in a specific local
response

or non-
specific

body-wide

response

or both.

increased production of

ACTH

Adrenal medulla increase in sympathetic activity

Adrenal Cortex

Adrenocortical Hormones

Adrenal gland stores cholesterol which can be converted into hormones during stress.

Salt hormones increased production of ACTH
protein metabolism disturbed.
electrolyte and glucocorticoids suppress water balance the inflammatory process.
disturbed

Retention of Na permeability of capillary
and Cl ions and membranes increased.
water.

Excess secretion carbohydrate metabolism is disturbed. Use of glucose by of K ions.
tissues decreased. Lysis of eosinophils and lymphoid tissues.

Selye found certain changes that always occurred: atrophy of the thymus, enlargement of the adrenal cortex, haemorrhage into gastric mucosa, death results from exhaustion.

Fig. 1. General Adaptation Syndrome - G.A.S. - or reactions by which the organism adapts.
mechanism which is capable of responding to changes from without by appropriate adjustments from within. If this is accomplished with an equal but opposing force, the integrity of the whole is maintained.

Although the factors, which maintain an organism or population at equilibrium with its environment, act in such a way as to be outstanding at any particular time, it must be emphasized that any single, overt response is not the result of a simple reflex system concerning only the apparent stimulus and obvious response. Instead it is the integration of many stimuli which continuously moderate (either synergistically or antagonistically) the organism's behavioral and physiological adjustment. The problem of manipulating such a system, to discover how it functions, lies in the preservation of its complex integrated organization.

Selye proposed the hypothesis, based on the General Adaptation Syndrome, that the pathogenicity of local and systemic stressors depends upon the function of the pituitary-adrenocortical system, which may either enhance or depress the organisms defense reactions. According to Selye, an imbalance in this physiologically precise adaptation syndrome is the significant factor in the initiation of 'diseases of adaptation'. An understanding of this concept and its relative significance required some knowledge of the system under investigation. The following observations are discussed with the intention of ascertaining those conditions that influence
a population of wild rats.

Wild rats (*Rattus norvegicus*) demonstrate marked stability at population supporting capacity levels. However, fluctuations in this equilibrium state result in patterned eruptions in the dynamics of the population. These changes reflect numerous extrinsic and intrinsic factors acting to compensate for altered environmental conditions. Although alteration of rat population densities accompanies alterations in extrinsic factors such as habitat, harborage changes, nutritional limitations, predator pressures, disease factors and climatic changes, intrinsic factors operate in density adjustment toward the carrying capacity for a given environmental circumstance. The intrinsic factors which contribute to migrations and reproductive-mortality interactions, include social modifications as well as reproductive alterations with respect to the pituitary-adrenal-gonadal axis.

A. Factors Maintaining Population Density.

Populations must necessarily remain within the physical limitations of their environment. Several studies have emphasized the importance of density-dependent factors acting as moderators for 'normal' population growth and maintenance of a desirable number in a particular environmental circumstance (Christian and Davis, 1964; Calhoun, 1948, 1949, 1950; Cazanove, 1931; Davis, 1951b, 1951c, 1951d, 1952b; Jackson, 1951; Leslie, Venables and Venables, 1952; Solomon, 1949; and White, 1914). If a population should
exceed the supporting capacity of its environment, the resources of that environment would soon be depleted. Therefore, factors working to attain an equilibrium between population numbers and environmental resources must regulate, in a compensatory manner, the oscillations of animal populations about a satisfactory number. If controlling factors should be ineffective or delayed, extremes of variations from the norm could demand further adjustment requirements, of which many would lie beyond the inherent capacity of the control systems involved.

In order to understand more clearly the factors regulating population dynamics, it must first be determined which factors are involved in maintaining populations at desirable density levels. Then factors influencing growth and reduction in population numbers may be investigated when equilibrium conditions are upset.

1. Reproduction.

In time, even the most precisely regulated systems go out of control. Several inter-related factors, capable of affecting those misalignments, must then act in a compensatory manner if the system is to regain its equilibrium state. Of all the density-dependent factors concerning a population, the most noticeable to the casual human observer happens to be reproduction. To be sure, the deep significance of reproduction lies not in its dramatic nature but in its reflections upon the balance of the total population structure.
As is suggested by the diagram (Fig. 2), the factors which contribute to the regulation of reproductive efficiency are complex and varied. However, the net effects of the reproductive process with respect to population density is the sum of the consequences of each interacting factor.


In contrast to the process of reproduction, and often influenced by reproductive efficiency, mortality plays an important role in the regulation of population numbers. Although mortality rate is dependent to some extent upon several behavioral, ecological, and physiological phenomena acting in any particular circumstance, the result of these interactions is dramatized by the fact that each becomes obvious only through a decrease in over-all numbers of individuals.

The result of an increased mortality rate beyond the reproductive capability of a population would obviously reduce the number of individuals within that population in the absence of immigrations. Alternatively, a decreased mortality rate below the rate of recruitment, would result in population growth. Therefore, in isolated, non-cyclic populations which remain stable for long periods of time, in the absence of drastic environmental eruptions, a steady-state equilibrium is primarily a result of the balance between reproductive and mortality rates.

An investigation of the mortality rate of a population must
Total Yearly Reproduction

<table>
<thead>
<tr>
<th>Total yearly embryo reproduction (per mature female)</th>
<th>Number of animals breeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population Size Sex ratio Age at maturity</td>
</tr>
<tr>
<td></td>
<td>Length of breeding season</td>
</tr>
<tr>
<td></td>
<td>Litter size Pregnancy rate</td>
</tr>
</tbody>
</table>

Fig. 2. Components of reproduction in polyoestrous mammals (Krebs, 1964; p. 22).
take into consideration not only post-natal death, but also the occurrence of pre-natal mortality. Failure to investigate the reproductive state of a population with respect to pre-natal deaths would not only overlook a possible mortality factor, but could leave an actual increase in reproductive potential unaccounted for. Mortality rate has been shown to be affected by a variety of factors including supersaturated populations (Calhoun, 1948, 1952, 1957), inter-specific competition (Crombie, 1947), age and sex ratio (Asdell, 1941; Davis, 1951b; Schein, 1950; White, 1914) and pregnancy and disease (Davis, 1951c, 19518; Davis and Jensen, 1952).

3. Movements.

Emigration and immigration modify the reproductive and mortality factors in a population. Numerous factors are involved in the initiation of movements within a population such as changes in harborage, food availability, predator-prey pressures, and inter- and intra-specific strife which may or may not be a reflection of an altered population density.

If reproductive and mortality rates are to be based upon estimates of numbers within a population, valid assumptions can be made only if the migratory habits of the population are known. It is obvious that if immigration were to equal emigration, no net change in population density would result. However, as a result of altered environmental conditions one of these two often predominates, resulting in noticeable density changes.
Migratory patterns are frequently characteristic of the species or population under investigation, and the movements of a population need not necessarily reflect altered environmental conditions that are density-related. The task of separating characteristics of a population from altered environmental conditions which modify those characteristics is essential to a clear understanding of the nature of the dynamic structure involved.

Dynamic populations of wild rats reveal definite patterns which reflect alterations of several extrinsic and intrinsic factors. These modifying factors may, for discussion, be categorized as ecological, behavioral, and physiological.


Extrinsic factors which affect and modify population densities are those which have their actions outside the physical animal. The interactions of extrinsic and intrinsic factors allow ecological variation to play a significant role in population regulation. Among those factors demanding adjustment are climatic changes (photoperiod, temperature, etc.), food, harborage, predator-prey relationships, parasitism, and natural catastrophies (Calhoun, 1950; Christian and Davis, 1964; Pitelka, 1961; Kalela, 1957; Chitty, 1968).

Changes in climatic conditions are the most dramatic of the extrinsic factors, because other extrinsic (as well as some intrinsic) factors are affected by or dependent upon alterations in
climate (Bohanan, 1939). Food and harborage are directly affected by seasonal changes in temperature and weather conditions. The degree of predator-prey pressures is directly affected by food and harborage availability. Suitable environmental conditions are necessary for intermediate stages of parasite development, and weather conditions often govern the extent and nature of natural catastrophes. Seasonal climatic changes in temperature and moisture are among the major environmental hazards confronting animal life.

Factors favoring population growth can be of either genetic or physiological-ecological origin, or both. Genetic factors include a hereditary change of birth rate tending toward larger litter sizes, shorter gestation periods with more frequent litters, or an increase in the reproductive season over a given time span.

Ecologic factors affect the genetic factors as well as having an over-all effect on population size. A genetic change to produce a second litter in the same year might seem advantageous, but it would ultimately be deleterious for the population as a whole if the young were born in a time of year when the climate was severe. The young, less able to survive because of their dependence, might pre-empt harborage sites or critical food supplies for the population as a whole. Therefore, a second litter might cause a reduction in the population because of increased mortality resulting from additional numbers in the population.
Ecologic effects on populations are usually considered under two headings: those that result from the population size itself and those that are independent of the population. Density-dependent factors favoring an increase in population numbers would include such items as harborage availability, food, etc. Density-independent factors that are of importance in population growth include favorable climatic conditions such as prolonged seasons suitable for reproductive success, rainfall, and food production.

These same genetic and ecologic factors can work toward a decrease in the reproductive rate or an increase in mortality with a concomitant decrease in the population size. In general, more is known about the factors that limit population numbers than those resulting in an increase. The most probable reason for this emphasis on factors which limit population growth is that the activities of larger populations are more noticeable, and the stimulus for investigating population dynamics stems from a desire to control unwanted animal populations.

The genetic factors that cause a reduction in population numbers include hereditary decreases in litter sizes, low viability of young, and increased prevalence of lethal genes in a population. Such density-independent factors as climate and natural catastrophies can cause population reduction by such means as crop-failures, excessive heat or cold, and drought.

The density-dependent factors that result in decreased
population size are usually interrelated and complicated by secondary effects. When a population is large with respect to its environmental carrying capacity, factors that are normally inconsequential assume roles of major importance. As a population increases, its predators generally increase in number as well. Predation then becomes a major factor influencing the reduction of a population (Calhoun, 1948, 1949; Jackson, 1951).

The crowded conditions resulting from a large population provide another mortality factor by increasing the probability of disease and parasite transmission. The greater the number of contacts among individuals in a population, the more frequent are the chances of transmitting diseases that are fatal or that weaken the animals' ability to resist normal limiting mortality factors. Parasites are not necessarily fatal, but do account for a drain on the host system which results in increased food consumption (competition for food in overcrowded populations thus, would limit the supply needed for maintaining a reasonably healthy state).


Social organization benefits the species as a whole (Lloyd, 1967; Healey, 1967). It provides a greater degree of assurance that at least one pair of individuals will get enough food, protection, and territory to enable them to produce young and thus continue the species. Moreover, the dominant individuals in a social population have greater disease resistance than do those
lower in the social hierarchy.

The role of both social rank and stress becomes increasingly important as the population reaches and exceeds its environmental supporting capacity (Calhoun, 1963). With limited food and harborage, intra-specific competition emphasizes dominant-subordinate relationships, which determine an individual's social success. An individual forced to consume a sub-optimal diet, as a result of his inability to compete with the more dominant individuals in the population, will also be at a disadvantage with respect to other physical needs such as mates and harborage sites. As a result, those animals which are subordinate in the population will be under more social stress and less resistant to factors enhancing mortality (disease, predator-prey pressures, etc.). Calhoun (1957) indicated that negative social interactions (stressors) are partially responsible for the consistent antagonistic behavioral patterns characteristic of stressed populations.

The sigmoid growth and associated species competition equations normally described for freely-growing populations of wild rodents assume that the degree of crowding in the population is suitably indicated by total population numbers, and that there is a linear response to crowding in each animal in the population. However, social interactions may influence the relationship between a population and its environment and will alter the population pattern through intra-specific competition (Hutchinson, 1947).
All animals that have definite territorial boundaries and clear spatial limitations have a pre-determined growth pattern dependent to a large extent on the behavior of individuals. The mean population size, fecundity, and mortality rates may be legislated by altered environmental factors; however, oscillations about any predicted mean will be greater in a population of socially interacting animals. The resulting dominant-subordinate relationships will tend to increase the complexity of influencing factors of population dynamics (Bronson, 1965).

Territorial behavior has been recognized in Amphibia, fish, reptiles, birds, ungulates and rodents (Andrewartha, 1961). Two features common to these classes of animals are home range and the development of an intolerance to over-crowding. It has been found that the selective value in territorial behavior is that animals which have established definite home range habitats are more secure against predator pressures. The strife that develops during defense of territories against inter- and intra-specific competitors usually leads to the eviction of one of the competitors with the emergence of dominant-subordinate relationships, or to a demand for physiological adjustments in the population. The factors which enhance growth of the population are dampened as a result. Successful breeding populations tend to live in home-ranges where their security is greatest (Andrewartha, 1961). Predators are then least successful in diminishing population numbers when the prey
manifest territorial behavior.

Most of the fighting that takes place among wild rodents is intra-specific and occurs most frequently in species with highly integrated societies. However, Calhoun (1949) added foreign rats of both sexes to well-defined populations of Rattus norvegicus, and after retrapping over a period of two or three months, found that only sixteen per cent of the strange rats remained; the rest were either killed or forced to emigrate. Calhoun (1950) demonstrated degrees of conflict in a rat population subjected to a single feeding area. He found that there were definite reflections of altered growth and fecundity which could be attributed to persecution and conflict directly. Increased social strife may be an important controlling factor in population growth when such necessities as available food and harborage are limited. Barnett (1963) describes in detail the conditions for conflict, consequences of strife on behavioral adjustments in wild rat populations, and their importance as controlling factors in the dynamics of the population.

Dominant-subordinate relationships are a result of social interactions including inter-specific and intra-specific competition, territorial behavior, and competition for food and harborage. There is a great deal of evidence suggesting that rat populations form social hierarchies, since dominant-subordinate relationships are tested in the same individuals on numerous encounters (Calhoun, 1950). Although crowding has been shown to be an important factor
regarding individual conflicts in a population, it does not in itself lead to conflict. On several occasions rats have been observed who would not eat after severe social suppression even though food was plentiful.

Aggression in rodent populations has been found to be dependent upon a number of factors. Southwick and Clarke (1968) described interstrain differences to be characteristic in four inbred strains of mice. Healey (1967) and Sadlier (1965) found that male aggressiveness affected the growth and survival of juveniles. Because aggressive behavior is more easily observed in crowded or saturated populations, the frequency of aggressive behavior has been positively correlated with increased density levels. Conflicting hypotheses regarding causes of increased infant mortality have therefore been suggested by several investigators (Lloyd and Christian, 1967). Both population density levels and aggressive behavior will surely be found to be closely related if not equally influential in population adjustments in most circumstances.


Chitty (1952) suggested that the 'crashes' that recur in natural populations of voles (Microtus agrestis) may not be a direct result of weather, predator-prey interactions, food availability or other seemingly obvious environmental factors, but only to increased vole population density. He noted that the offspring
that were reared in large (saturated), or declining populations were more susceptible to disease and other mortality-related factors than at times of lower density levels. Increases in organ weights of animals taken from saturated populations were attributed to a physiological imbalance in specific organs (spleen) due to more frequent conflict in the population as well as associated disease conditions such as hemolytic anaemia. The data of Clarke (1954), Dawson (1956), Chitty (1957), Strecker and Emlen (1953), and Southwick (1955a, 1955b), suggest that stress is the outcome of crowding. This results in histologically perceptible altered physiological disturbances.

Studies of the physiological compensations for environmental oscillations and stresses allow meaningful assumptions to be made concerning the physiological machinery that regulates such adaptations (Christian, 1963). Animals have, as a part of their genetic endowment, the ability to compensate for environmental change within limits that are specific for the individual and characteristic of the species (Lewontin, 1957). Animals not only demonstrate tolerance and resistance in this regard but also the capability for acclimation and acclimatization (Booker, 1960; Carlson, 1960). The best descriptive term characterizing the sum of environmental pressures which require physiological compensations is stress. Selye (1950) gives a detailed evaluation of various stressors and the responses they elicit in the adapting organism. A discussion of
these concepts will be dealt with subsequently.

In the vertebrates, the anterior pituitary (through the action of its gonadotropic hormones) links the neurosecretory centers of the brain to the endocrine tissues of the gonads. This link between the external environment and the reproductive system has an important mediator, the hypothalamus. Hypophysectomy is always followed by regression of the reproductive organs; other variables remaining constant. Furthermore, gametogenesis is blocked at the spermatogonial or oogonial stages (Hoar, 1966). Numerous reproductive phenomena have been shown to be dependent upon pituitary-gonadal hormone interaction (Hoar, 1962). Mammalian sexual cycles of regular rhythmicity have been shown to be unpredictably oscillatory with altered environmental condition (Asdell, 1946; Parkes, 1960; Barrington, 1963).

A survey of the literature investigating compensatory physiological adjustments to density-dependent environmental conditions in the wild rat (*Rattus norvegicus*) reveals persistent yet vibratory patterns displayed in response to both extrinsic and intrinsic modification. The complexity of those interactions which determine the precise mechanisms for compensatory responses has made the elucidation of the individual mechanisms responsible difficult as well as the extent of their interdependence. The animal's ability to appreciate a variety of external phenomena better equips it to adapt to changes in its environment. However, in many instances
the adaptability of the organism becomes obvious only when the constancy of its homeostatic steady-state has been disrupted. In the early 1900's Walter B. Cannon extended the observations of Claude Bernard on the "milieu interieur" and reinforced the already strong indications that emotional and physiological adjustments to stress situations were necessary to maintain the dynamic constancy of physiological behavior.

An increased secretion of the glucocorticoids has been demonstrated in animals subjected to acute and sudden exposure to cold by a number of investigators. In 1964 Eleftheriou demonstrated increased levels of corticosterone in two subspecies of deer mice (Peromyscus maniculatus bairdii and P. maniculatus gracilis) that were exposed to cold extremes. His data are in good agreement with that of Sellers (1957), in which lowered ambient temperatures were shown to elicit an activating response of the pituitary-adrenal axis. Under conditions of fluctuating climatic conditions Birmingham (1953), and Haynes (1959) showed that in vitro steroid production was maximal in white rats during the winter months. Under these fluctuating seasonal conditions, the adrenal cortex was shown to remain active, increasing in mass and steroid production. Schonbaum (1960) suggested that acute exposure to cold in male Wistar rats caused a transient rise in adrenocortical activity within the first thirty minutes of exposure in vivo when availability of ACTH is unlimited. However, each of these investigators
found reduced adrenocortical activity with extended exposures (several months). In conjunction with these studies it has been suggested that the adrenal ascorbic acid acts as a trigger mechanism in acute cold stress (Schonbaum, 1960). It has been demonstrated by these and other investigators that increased adrenocortical activity in the rat may be a mediator in the initiation of increased thermogenesis resulting from an increase in metabolic processes in the adapting animal. It has been clearly demonstrated in the laboratory rat that cold acclimation increases non-shivering thermogenesis and that norepinephrine is one of the important mediators (Carlson, 1960). The involvement of the endocrine system in an adaptive response to such altered environmental conditions leaves open the suggestion of altered endocrine patterns resulting from acute stress situations, for which the adapting organism is unable to compensate.

Christian (1950) proposed the hypothesis, based on Selye's General Adaptation Syndrome, that a reduction in numbers of saturated populations could be a direct result of variations in pituitary-adrenal functions due to stressful conditions. Calhoun (1962) found significant reductions in resident populations of Norway rats when foreign rats of the same species were introduced into their limited areas. Differences in both adrenal structure and weight have been demonstrated with regard to alterations in population structure (Southwick, 1964; Lloyd et al., 1964). With regard to
adrenocortical function, Andrews et. al., (1965, 1968, 1970) found, by direct measurement of adrenal secretory activity, variation in steroidogenesis during and following the lemming 'crash' of 1965. These secretory levels were twenty to sixty times higher than in non-crises circumstances, regardless of seasonal variations. These data suggest that neuroendocrine stimulation by environmental and other density-dependent factors (crowding etc.) may be responsible for, or at least involved in, physiological adjustment requirements during stress conditions.

It has been known for a long time that the adrenal gland is closely associated with the organism's ability to resist various types of stressors. Tepperman (1943), accumulated a great deal of data concerning causative agents in adrenal hypertrophy, among which were listed exercise, pregnancy, cold exposure, hyperthyroidism, prolonged insulin treatment, diabetes, hypoxia, shock-producing agents and both acute and chronic infections. The wide variety of factors eliciting the same general response in the adrenal cortex was difficult to explain even though the adrenal cortex was known to be resisting the disturbances in physiologically imbalanced organisms. Adrenal hypertrophy and morphological changes were not only associated with various non-specific stressors, but also with metabolic and tissue disturbances.

Selye (1936a) first described whole body changes which were recognizable as a regular and common response to a variety of
noxious stimuli regardless of their nature. These disturbances of Cannon's "homeostasis" were recognized by the organism as a common threat to its existance. Selye dedicated his life work to investigating these reactions to physiological disturbances, describing the reactions and symptoms of several organs and organ systems as a part of his General Adaptation Syndrome and diseases of adaptation (Selye, 1946). Probably the most important of Selye's deductions were those derived from morphological changes in tissues during noxious stimulation. Largely under the influence of Selye the term 'stress' has been associated with any threat to metabolic equilibrium of homeostasis in the organism which eventually results in noticeable pathological aberrations. Determination of which reactions are a result of the stimulus and which are elicited by the resulting stress is difficult. In discussing the stress reaction, it is essential to limit stress responses only to those which can be demonstrated to be common to a wide variety of stimuli.

One of the earliest of such stress responses is that of decreased circulating lymphocytes (Harlow and Selye, 1937). It has been demonstrated that in adrenalectomized animals this altered blood picture does not result with application of stressful stimuli (Valentine et al., 1948). It was, deduced from this that lymphopenia was due largely to prolonged adrenal cortical stimulation in animals. At the same time, as was first suggested by Selye, there was also a fall in the circulating eosinophils. This
observation was confirmed by Hills et al., (1948). Hills showed that administration of ACTH promptly causes a reduction in circulating eosinophils, but no change results when administered to sufferers of Addison's disease.

Sayers and Sayers (1949) reported that gradual changes in the internal or external environment, such as mild seasonal changes in temperature, gradually increased the cortical hormone demand but were sufficiently slow to allow normal adrenal cortex function. However, intense and continuous stress resulted in adrenal hypertrophy and irreplaceable depletion of cholesterol and ascorbic acid content.

Selye's concept of disease conditions resulting from a variety of noxious agents (stressors) is not in dispute even at the present time. However, the elimination of a number of variables as causative agents and the placement of emphasis upon abnormal pituitary-adrenal function as the sole avenue for effecting the pathogenesis of disease has provoked several disputes and much opposition from a number of investigators. Although the pituitary-adrenal system should be appreciated as being of major importance in identifying certain stress phenomena and should not be overlooked or underestimated, it cannot be considered the sole indicator of the stress response mechanism.

Awapara (1949), and Thorn (1949), have suggested that 11-dehydrocorticosterone, corticosterone, 17-hydroxy
11-dehydrocorticosterone, and 17-hydroxycorticosterone all have at least one similar action in initiating increased glucose synthesis with concomitant reductions in protein synthesis by diversion of amino acid building blocks. Other functions assigned to these carbohydrate regulating hormones are the utilization of fat depots and the control of lymphopoiesis (Dougherty, 1947).

Although specific actions have been assigned to the hormones of the adrenal cortex, the sum of their actions in the intact organism is not without doubt. Some of the more fundamental, accepted functions of the adrenocortical hormones with respect to blood pressure regulation and metabolism are discussed briefly below.

1. Regulation of arterial blood pressure.

A discussion of the regulation of arterial blood pressure must of necessity consider the action of the adrenocortical hormones on cardiac output and peripheral vasoconstriction. The hormones of the adrenal cortex act upon the circulating blood volume through electrolyte and water distribution in the kidney. Selye induced hypertension as a result of nephrosclerosis by prolonged administration of ACTH and desoxycorticosterone. Selye (1942) demonstrated that desoxycorticosterone acetate (DCA) exhibits a kidney enlarging effect with concomitant increased arterial blood pressure and overall hypertension. This experiment has since been confirmed by several investigators (Ludden, 1941;
Korenchvesky, 1941; Durlacher, 1942). These studies indicate that the steroids caused hypertrophy of the parietal layer of Bowman's capsule and kidney enlargement due to hypertrophy of proximal and distal convoluted tubule cells. Adrenalectomy prior to steroid administration prevented the development of such lesions, suggesting primary steroid action (Polonsky, 1950).

2. Metabolism.

The adrenocortical hormones play an important role in the regulation of carbohydrate, fat and protein metabolism as well as the control of blood glucose levels and gluconeogenesis. Their influence on renal function (electrolyte and water metabolism) is effected by their ability to control the renal excretion of sodium and potassium, an important factor in the maintenance of urinary volume. Kidney function has been shown to be related to the androgenic hormones (Polonsky, 1950). Administration of sufficiently high concentrations of androgenic hormones causes hypertrophy of kidney tubules and acts as a protective agent against nephrotoxins which induce nephrosclerosis (desoxycorticosterone, Henderson, 1948; Selye, 1946). It is not a new concept that the stresses that are forced upon the organism by the various stressor agents mentioned previously may, in fact, have an important role in the pathogenesis of a number of diseases which are considered to have unknown etiologies. The General Adaptation Syndrome concept has led to the realization of how several non-specific stressors (muscular exercise,
burns, radiation, nervous excitement, exposure to extremes of heat and cold, and social stresses) initiate physiological imbalance and its resulting pathology, "disease". Selye has emphasized the importance of excessive adaptive reactions to the environment and the concomitant decreased resistance to disease factors. However, it must be emphasized that the alterations common to the General Adaptation Syndrome are not in themselves pathological changes. Only when the response to an environmental stimulus becomes distorted and excessive will it produce the important "diseases of adaptation". If environmental stimuli continue to persist, even the well adapted organism's resistance will wear out, and morphological lesions characteristic of Selye's "alarm reaction" appear. Further stimuli make subsequent adaptation responses impossible (O'Connor, 1947). The clinical significance of the General Adaptation Syndrome was not fully recognized, until it has been demonstrated by Selye that the nonspecific damaging agents actually produced hypertension, glomerulosclerosis, and nephritis with both an enlargement of the adrenal cortices and increased corticoids in the blood. It has been further suggested by Selye, on the basis of his experiments, that the blood pressure rises immediately after initiation of the alarm stimulus. With this transitory alteration in blood pressure, and in Selye's "stage of resistance", hypertension and nephrosclerosis develop. Carbohydrate metabolism is severely affected by a temporary overproduction of active corticoids which
are instrumental in increasing gluconeogenesis.

According to O'Connor (1947), when an organism has acquired a high degree of adaptation to a particular stressor agent, it is less resistant to other damaging agents. It is possible therefore, to deplete the organism's adaptation energy. In this case the adrenocortical function may terminate in a final breakdown with symptoms characteristic of or perhaps attaining the well known effects of adrenal insufficiency. When acute adrenal insufficiency develops, the observer must be cognizant of the complexity of physiological changes that are taking place in the organism. It is a common practice to attribute special physiological roles to particular hormones on the basis of their observable effects. However, such superficial views are far too simple to explain the complexity of adrenocortical hormone actions.

A discussion of abnormal hormonal secretion and its place in the pathogenesis of a variety of internal diseases must necessarily resolve itself around three major issues: (1) the abnormal secretion of one or more of the adrenocortical hormones and associated phenomena, (2) the significance of the adrenal cortex in the pathogenesis of disease conditions mimicked by cortisone and ACTH treatment, (3) the role of the adrenal cortex in Selye's Adaptation Syndrome. Selye (1946) suggested the adrenal cortex as the mediator of the organism's response to stress. To understand more precisely the significance of the adrenal gland, with respect to
hypertension and physiological imbalance in the organism, it is necessary to define its normal and abnormal functions in particular organ systems.

Selye (1946) demonstrated that a variety of animal species respond to anterior pituitary extracts as well as corticoid hormones with increased hypertension, renal changes and accompanying cardiovascular lesions. According to Selye (1945) the effects of anterior pituitary hormone preparations may be subdivided into two distinct types: those having renotrophic action and those inducing nephrosclerosis. The renotrophic action is characterized by general hyperplasia and hypertrophy of the kidney tubule cells. In contrast, the nephrosclerotic action damages the kidney structure, manifesting itself by hyalinization of renal glomeruli and acute nephrosclerosis. Beland (1944) showed that testosterone elicited renotrophic responses only while Selye and Pentz (1943), and Selye and Stone (1943) showed deoxycorticosterone acetate elicited nephrosclerotic responses. Selye found the renotrophic effect to have essentially a kidney growth-stimulating effect upon microscopic examination. Excessive proliferative activity was found to accompany overdosage with potent renotrophic hormones and their combinations. This activity was assumed to be detrimental to renal tubule function. Although growth of kidney mass was noted as the most obvious effect of renotrophic hormone overdosage, the fact that tumorous growths may be initiated with prolonged doses
was not completely ruled out. The nephrosclerotic hormones had their most pronounced damage in the pelvic area of the kidney, with an initial formation of edema in the adipose tissue of the hilum. Selye proposed that the degenerative changes of the large renal arteries were probably of the nature frequently produced by other nephrosclerotic compounds and resembling periarteritis nodosa.

The adrenal control of water balance and electrolyte metabolism is mediated chiefly through the action of 11-deoxycorticosterone (DOC) and deoxycorticosterone-like compounds. Although it is known that these hormones act specifically to control sodium metabolism (favoring sodium retention), the mode of action is not sufficiently understood. DOC, in physiological amounts, reduces chloride ion and water excretion, while its 'primary' action is to increase potassium excretion. Soffer (1948) suggested that potassium, for the most part intracellular, is regulated primarily by plasma sodium concentration, but to some extent by direct hormonal action. Deoxycorticosterone tends to reduce the plasma concentration of potassium by renal clearance and increased diffusion into kidney tubule cells.

Conn (1949) found deoxycorticosterone to have an equal effect on sweat glands and kidney urine excretions with respect to sodium, chloride and potassium balance, and suggested their measurement as an index of adrenocortical function in salt regulation. Forsham
(1948) demonstrated that while single doses of adrenocorticotropic hormone (ACTH) caused potassium, sodium and chloride excretion, prolonged administration of ACTH reversed these effects. The explanation was that the short term affect of ACTH was eventually everted by DOC activity (DOC being increased higher levels of ACTH).

Selye (1942) demonstrated that deoxycorticosterone acetate (DCA) exhibits a kidney enlarging effect, which has since been confirmed by several investigators (Ludden, 1941; Korenchvesky, 1941; Durlacher, 1942). These studies indicated that the adrenal cortex steroids cause hypertrophy of the parietal layer of Bowman's capsule (particularly in mice) and kidney enlargement due to hypertrophy of proximal and distal convoluted tubule cells. The kidneys of DCA treated animals displayed abnormal renal weights, distended tubule cells and hypertrophy and hyperplasia of both the parietal and visceral lamina of Bowman's capsule. Most of the glomeruli were abnormally small with obvious signs of sclerosis. The above experiment was designed by Selye to demonstrate the ability of the steroid hormones to produce nephrosclerosis. It was Selye's interpretation that overdosages with corticoids may not only be instigatory in inducing nephrosclerosis, but that this may be an explanation for the pathogenesis of nephrosclerosis already demonstrated in hypertensive (stressed) animals. In 1951 Selye noted that animals treated with DCA in concentrations found during stressed conditions, showed typical malignant nephrosclerosis with
periarteritis-nodosa-like changes of the small renal arterioles. The glomeruli appeared abnormally large and permeable to plasma proteins; since proteinaceous material was found in the spaces of Bowman's capsule. However, the extracts of the anterior-pituitary used in these experiments were quite impure, leaving some doubt as to the mechanisms responsible for the changes. It has been suggested, and commented upon further, by Selye (1950) that the actions may have been simply an allergic response of the body to these possible toxic substances. In view of this fact Selye (1950) performed a similar experiment using pure, natural, 11-desoxocortisone, and, in fact, produced the same disease conditions as were noted previously, but with greater intensity. He interpreted this data to substantially support his evidence that the naturally occurring corticoids in above normal doses may be involved in the pathogenesis of diseases of adaptation which respond to the therapy of ACTH administration.

Woods (1960) found that rats with deoxycorticosterone-saline induced hypertension exhibit marked renal vascular damage with concomitant increased susceptibility to experimental pyelonephritis. Goldblatt (1957) suggested that malignant hypertension could develop from benign hypertension due to superimposition of renal infections. Rapid development of hypertension in the albino rat with overdosage of corticoids and the accompanying vascular lesions is well documented (Gardner, 1960; Selye, Hall and Rowley, 1943).
Since the kidney is one of the chief excretory organs of the body and a regulator of blood pressure, it is not surprising that it plays a significant role in the organism's adaptation to stress. Although morphological changes in the kidney are not manifested independently of various other organ system reactions (cardiovascular system; hepatic hyalnosis syndrome etc.) they have been shown to be a good index of stress and its intensity.

Morphologic examination of kidneys taken from animals under a variety of stress conditions reveal several features common to all types of non-specific stress. Upon gross examination, the cortex appears anemic, the medulla hyperemic, with the boundary often indistinguishable. Microscopic examination shows dilated tubules, degenerating epithelial cells and often complete necrosis. Bywaters and Beall (1941) feel that these degenerative changes involve only the proximal convoluted tubule, while Moon (1948) suggests that all portions of the convoluted tubules are affected. The interstitial tissue is usually edematous and lymphocytic. Polymorphonuclear leucocyte infiltration is common (Selye, 1950). Exposure to cold and infectious diseases produces a nephritic condition in the kidney (Bell, 1947). Corticoids have been shown to initiate nephritis in rats, and adrenocortical tumors have been associated with glomerulonephritis in mice (Kirschbaum, 1949). The fact that no infectious organisms are present in the kidneys of many animals exhibiting glomerulonephritis suggests that an excess of corticoids
Renal insufficiency influences the metabolism of the steroids in many ways. This factor becomes increasingly important when accumulative affects are considered. A reduction in the efficiency of renal function may lead to retention of steroids (especially 17-hydroxycorticosteroids). With prolonged retention of biologically active steroids, significant increases in renal insufficiency already present may result (Henderson, 1948). Resulting tensions in the cardiovascular system, due to blood pressure disturbances, not only alter metabolic processes and normal systems function, but eventually result in increased hypertension, an increase in compensatory steroid secretion, and their associated disorders (Selye, 1950).

Hall and Hall (1959) demonstrated an augmentation of hormone-induced cardiovascular disease by simultaneous exposure of the organism to stress. Hall noted the fact that although all of the stressors used by Selye et al., (1958) and Crane et al., (1958b), were known to act upon the pituitary-adrenal axis, the action of adrenal hormones upon the cardiovascular system was governed by a variety of unaccounted circumstances, and that cold was the only stressor used which has been successful in producing hypertensive cardiovascular disease in rats, (Selye, 1943; Selye, 1957; Ingle and Baker, 1957). These investigators showed that stress alone increased blood pressure only slightly. However, administration
of DCA during stress situations was particularly effective in producing hypertension and cardiovascular disease.

Corticosterone was the first biologically active hormone to be isolated from adrenal gland extracts (Mason, 1937). Corticosterone is one of the major adrenocortical secretory products in rodents (Bush, 1953), and is used extensively as an index of stress intensity, although relatively little is known about its possible toxic effects at levels demonstrated under stress conditions. Coar (1963) attributed a mineralocorticoid excess syndrome to excessive secretion of corticosterone. Coar presumed that the adrenocortical hyperactivity associated with severe electrolyte disturbances to be due to excess corticosterone secretion in combination with relatively weak mineralocorticoids, (eg. cortisol), and normal amounts of strong mineralocorticoids (eg. aldosterone). Corticosterone processes the electrolyte-regulating activity of deoxycorticosterone as well as the potential for carbohydrate regulation attributed to cortisone and hydrocortisone.

Chang (1965) and Kass (1955) demonstrated the ability of the glucocorticoids to suppress immune mechanisms and inhibit the tissues responses to injury. Both hydrocortisone and corticosterone, through their suppression of the defense mechanism, can increase the pathogenicity of a wide variety of potential pathogens (Frenkel, 1962; Kass, 1953). Extremes of temperatures, trauma and infectious diseases stimulate increased adrenocortical activity and may be
influential in increasing susceptibility to pathogenic agents (Funk, 1967; Yamada, 1964). Christian (1958) demonstrated the adverse effects of overcrowding on mice. One of the important features noted was an increased adrenocortical function and concomitant decreased resistance to parasitism and infectious diseases. Several other investigators have since confirmed these observations (Davis, 1958; Vessey, 1964).
II. STATEMENT OF THE PROBLEM

A number of investigators have studied the social, behavioral and ecological features characteristic of wild rat population dynamics. At present, there is a lack of information regarding physiological adjustments to altered behavioral and ecologic conditions.

This study was conducted to define the endocrine and reproductive status of a population of wild Norway Rats (Rattus norvegicus), and to determine the significance of adrenal hyperfunction in the pathogenesis of discrete parenchymatous, renal and hepatic diseases.
III. MATERIALS AND METHODS

The methods used in this study are divided into field procedures and laboratory procedures. All animal collections were taken from a geographically isolated population of wild rats (Rattus norvegicus) colonizing a three acre landfill site. Monthly samples were taken beginning April, 1970, and terminating February, 1971. In addition 10 pairs of animals, taken from the landfill site, were introduced into each of three pens in August, 1970. Monthly samples of each of the pen populations were taken using methods similar to those described for the landfill area.

A. Field Procedures.

Sherman live-traps were employed to obtain animals from the landfill and pen sites. Continuous dumping of refuse and plowing of the trapping area during the course of this study prohibited the establishment of permanent trap lines. Traps were placed near runways whenever possible to enhance trapping efficiency. Traps baited with peanut butter were set in the early afternoon and collected the following morning when weather conditions permitted. During winter months, when temperatures dropped below freezing, the traps were checked every hour to assure no undue exposure to cold and trap mortalities.

During frequent trapping periods the animals developed 'trap shyness'. To enhance trapping efficiency during these periods, traps were baited and left open for three days prior to the
scheduled trapping date. Occasional changes of bait from peanut butter to fruit during the summer months also increased trapping efficiency.

Capture-recapture periods usually preceded scheduled trapping dates. This allowed an estimation of population density (by Lincoln index) in each of the three pens. Captured animals were weighed, sexed and marked by a variety of combinations of ear punches. Capture-recapture periods contributed useful information regarding demographic features of the three pen populations as well as animal distributions within the pen enclosures. Food (purina rat chow) and tap water were placed in centrally located receptacles in each of three pens, ad libitum.

B. Laboratory Procedures.

1. Handling and sacrifice procedures.

All animals captured were returned to Creighton University where they were held overnight in their respective traps to minimize adrenal hyperactivity resulting from capture trauma. Animals collected in the morning were sacrificed that same morning. All animals were sacrificed between the hours of 8:00 a.m. and 11:00 a.m. by mild etherization followed by a 1.0 cc injection of pentobarbitol and cervical dislocation. Immediately following cervical dislocation, and prior to removal of organs, approximately 3.0 ml. of blood were drawn into heparinized syringes. A blood smear was obtained from each animal for examination at a later date.
2. Tissue processing.

Adrenal glands were extirpated immediately following sacrifice, debrided and temporarily placed in Puck's nutrient medium. After weighing and halving, the glands were placed in flasks containing Trowell's nutrient medium (Trowell, 1954) and 0 m U, 100 m U and 200 m U of ACTH. Following a 2 hour incubation period in a Dubnoff shaker-bath at 37°C and in an atmosphere of 95% O₂ and 5% CO₂, the medium was sampled as described below.

Blood samples were taken directly from the heart immediately following sacrifice. 100 μl plasma samples were processed for steroid determination in a manner described elsewhere (Strohbehn, 1970).


Quantitatively collected medium and blood plasma samples were processed by (A) solvent partitioning (peroxide-free ethyl acetate: water), (B) thin layer chromatography, (C) elution with absolute ethyl alcohol and (D) quantitation of selected "spots" as described elsewhere (Andrews, 1968c). Estimates of corticosterone were made following the procedure and fluorescence methods outlined by Silber et al. (1958).


Representative sections of liver, diaphragm, heart, kidney and duodenum were taken from all animals collected. Testis, prostate, seminal vesicle and epididymus were taken from males while
ovaries and oviducts were removed from all females collected. All tissues were fixed in 10% buffered formalin, sectioned (6 μ), mounted, and stained with allochrome stain for later examination of the incidence of pathologic conditions. When gross morphological aberrations were observed in the spleen and lung tissues, representative sections were prepared in the manner described above.

Sections of small intestine as well as liver and kidney cysts were taken and immediately examined for parasitic and other tape-worm infections. Results regarding percentage parasitic infestation and detailed descriptions of parasite types will be given in a subsequent paper.
IV. RESULTS

The results of this study are divided into three categories; (A) a summary of adrenal function and blood plasma levels of corticosterone, (B) the reproductive status of the population, and (C) the incidence and severity of renal and hepatic pathologic conditions.

A. Estimations of Adrenal Function.

Estimations of adrenal function demonstrate marked seasonal differences in the rat populations studied (Figs. 3; 4; 5). Comparisons of the "stable" landfill population and freely-growing pen populations suggest that the onset of adverse weather conditions in the early winter had an equal effect on both groups of animals with respect to adrenal function and blood plasma levels of corticosterone. Indications of adrenal hyperactivity were also noticeable in the early summer trapping period (Figs. 3; 4; 5). Immediately following these periods of adrenal hyperfunction, increased stress periods were indicated by refractory dose-responses to media containing OmU ACTH, 100 mU ACTH and 200 mU ACTH (Fig. 3; 5).

The summer and winter periods in which refractory responses to exogenous ACTH were noted, correspond to periods of little reproductive activity, as is suggested by the demographic data for both "stable" and newly-established wild rat populations (Tables 1; 2; 3). However, during the peak breeding season the "stable"
Fig. 3. Dose responsiveness of isolated rat adrenal glands to exogenous ACTH. Slope and intercept values for each group were estimated by the least squares method; vertical bars represent mean plasma concentration of corticosterone for each group of animals.
Fig. 4. Basal secretory rates of isolated rat adrenal glands throughout the trapping periods. Male (♂), Female (♀) and gravid Female (♀️).
B /100 mg ADRENAL Wt/h.

KEY
1. SPRING
2. EARLY SUMMER
3. LATE SUMMER
4. FALL
5. EARLY WINTER
6. LATE WINTER
+ NO ANIMALS CAPTURED

μg B/100 mg ADRENAL Wt/h.
Fig. 5. Dose responsiveness of isolated rat adrenal glands to exogenous ACTH; vertical bars represent mean plasma corticosterone concentrations for each group of animals.
TABLE 1. Demographic features of a "stable" population of Wild Norway Rats, illustrating seasonal changes in population structure and seasonal variations in reproductive activity.
### Demographic Features of a "Stable" Population of Wild Norway Rats

<table>
<thead>
<tr>
<th>Sampling Period</th>
<th>N</th>
<th>Mean Body Weight (gms)</th>
<th>% Females</th>
<th>% Gravid</th>
<th>Mean Litter Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Gravid Female</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>52</td>
<td>218</td>
<td>255</td>
<td>334</td>
<td>65</td>
</tr>
<tr>
<td>Early Summer</td>
<td>32</td>
<td>157</td>
<td>194</td>
<td>323</td>
<td>45</td>
</tr>
<tr>
<td>Late Summer</td>
<td>38</td>
<td>248</td>
<td>163</td>
<td>329</td>
<td>63</td>
</tr>
<tr>
<td>Fall</td>
<td>32</td>
<td>302</td>
<td>304</td>
<td>478*</td>
<td>47</td>
</tr>
<tr>
<td>Early Winter</td>
<td>30</td>
<td>311</td>
<td>274</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>Late Winter</td>
<td>27</td>
<td>267</td>
<td>206</td>
<td>354*</td>
<td>19</td>
</tr>
</tbody>
</table>

* = only one specimen of this type caught during this period.
TABLE 2. Demographic features of a "stable" population of Wild Norway Rats; illustrating population structure changes throughout the trapping periods.
Demographic Features of a "Stable" Population of Wild Norway Rats

<table>
<thead>
<tr>
<th>Sampling Period</th>
<th>% Juveniles</th>
<th>% Sub-Adults</th>
<th>Gravid $\frac{\phi}{\text{Mature } \phi \times 100}$</th>
<th>Litter Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Spring</td>
<td>0</td>
<td>6</td>
<td>19</td>
<td>10.0</td>
</tr>
<tr>
<td>Spring</td>
<td>20</td>
<td>10</td>
<td>60</td>
<td>10.4</td>
</tr>
<tr>
<td>Early Summer</td>
<td>19</td>
<td>25</td>
<td>25</td>
<td>11.4</td>
</tr>
<tr>
<td>Late Summer</td>
<td>8</td>
<td>39</td>
<td>48</td>
<td>10.9</td>
</tr>
<tr>
<td>Fall</td>
<td>3</td>
<td>6</td>
<td>6*</td>
<td>3.0*</td>
</tr>
<tr>
<td>Early Winter</td>
<td>7</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Late Winter</td>
<td>0</td>
<td>0</td>
<td>20*</td>
<td>13.0*</td>
</tr>
</tbody>
</table>

* Only one animal of this type caught during this period.
TABLE 3. Demographic features of newly established Wild Rat populations with seasonal distribution of juveniles (0-150 gms.), and sub-adults (150-250 gms.).
Demographic Features of Newly Established Wild Rat Populations

<table>
<thead>
<tr>
<th>Sampling Period</th>
<th>% Juveniles</th>
<th>% Sub-Adults</th>
<th>Gravid $\frac{#}{\text{Mature} , #} \times 100$</th>
<th>Litter Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Summer</td>
<td>18</td>
<td>25</td>
<td>80</td>
<td>8.5</td>
</tr>
<tr>
<td>Fall</td>
<td>8</td>
<td>57</td>
<td>8</td>
<td>9.0</td>
</tr>
<tr>
<td>Winter</td>
<td>0</td>
<td>86</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Early Spring</td>
<td>0</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
population demonstrated marked adrenal hyperfunction; a fact further strengthened by increased plasma corticosterone levels during this period (Fig. 6). An examination of adrenal secretion of corticosterone throughout the annual investigation indicates a seasonal fluctuation in the basal secretory rates (Fig. 3; 5).

B. Reproductive Status of the Population.

The fluctuating body-weight distribution of the animal population samples indicates a larger percentage of adult animals emerging from winter (Table 4). With the recruitment of juveniles resulting from late winter breeding, and the increased reproductive activity in the early spring, the juvenile component of the "stable" population became more pronounced in the spring trapping period. As the juveniles matured to sub-adult size in late summer, the sub-adult component of the population became more pronounced, resulting in a shift in the populations social structure (Tables 1; 2; 3).

Examination of the "stable" population of wild rats regarding seasonal variations in fertility and fecundity revealed a number of interesting features. The fertility rate (and also the organ-weight/body-weight ratios of gonads and sex accessory organs) was highest in the spring trapping period (Table 4). Because no significant differences in litter sizes were found during either of the breeding seasons, coupled with the fact that the percentage of juveniles trapped in early summer were less than expected in view
Fig. 6. A comparison of corticosterone concentrations in the plasma of juvenile, sub-adult and adult animals throughout the trapping periods.
I. SPRING
2. EARLY SUMMER
3. LATE SUMMER
4. FALL
5. EARLY WINTER
6. LATE WINTER
+ NO ANIMALS CAPTURED

KEY

**ug B-PLASMA**

**JUVENILES**

**SUB-ADULT**

**ADULT**

μg B-PLASMA

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4. Physical characteristics of mature male rats from a "stable" population. All weights shown are in grams.
## Physical Characteristics of Mature Male Rats from a "Stable" Population

<table>
<thead>
<tr>
<th>Sampling Period</th>
<th>R Body Wt. (gms)</th>
<th>Adrenal Wt. x 10^{-4}</th>
<th>Testis Wt. x 10^{-3}</th>
<th>Sem. Ves. Wt. x 10^{-3}</th>
<th>Prostate Wt. x 10^{-3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring</td>
<td>363</td>
<td>2.6</td>
<td>10.8</td>
<td>5.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Early Summer</td>
<td>267</td>
<td>3.9</td>
<td>9.4</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Late Summer</td>
<td>323</td>
<td>2.0</td>
<td>9.2</td>
<td>4.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Fall</td>
<td>334</td>
<td>3.3</td>
<td>7.8</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Early Winter</td>
<td>352</td>
<td>3.6</td>
<td>8.3</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Late Winter</td>
<td>356</td>
<td>2.8</td>
<td>9.7</td>
<td>4.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>
of the high percentage of gravid females in the spring sample, it is suggested that neonatal mortalities were of some significance in reducing the number of juveniles surviving in the early summer months. With the emergence of the surviving juveniles in early summer, fertility rates dropped considerably (Table 1).

The fall samples suggested an increase in fertility rate, above summer conditions, which was depressed with the onset of winter and which remained depressed until the late winter and early spring breeding period.

In contrast to the "stable" population, the freely-growing pen populations maintained a high rate of fertility throughout the early fall season. The onset of severe weather conditions in winter (as was also demonstrated in the "stable" population) effected decreased reproductive activity in the pen populations.

Gross examination of gonads and sex accessory tissues as well as actual weights of the tissues (Table 4) correlate well with the suggested periods of reproductive activity determined by percentage age (body-weight) distributions throughout the study. A high degree of development of gonads and sex accessory tissues was noted both in gross examination and histological preparations of samples taken during the spring and fall periods. Decreased functional activity was noted during the summer months, and complete anatomical and functional regression occurred shortly after the brief period of reproductive activity in the fall. Increased development and
function of gonads and sex accessory organs were observed in both late winter and early spring samples of the following year (1971).

C. Incidence and Severity of Pathologic Conditions.

Both gross and histological examinations of renal and hepatic tissues revealed combinations of severe glomerulonephritis, glomerulosclerosis, osmotic nephrosis of both proximal and distal convoluted tubules, non-inflammatory necrosis, ischemic glomeruli and renal tubules, fractionated glomeruli, sloughed and broken tubule cells and the absence of parietal epithelial layers in Bowman's capsule in the kidney. In addition, focal necrosis, abnormal mitotic activity and indications of obstructive jaundice in the hepatic tissues in all animals captured were observed. Variations in the incidence and severity of these pathologic manifestations correlate very well with peak stress periods as is indicated by refractory adrenal dose-response curves (Figs. 3; 5).

The period of highest incidence and greatest severity was evidenced in the fall and early winter samples. Late winter and early spring animals demonstrated less severe pathologic aberrations, with an increase in both incidence and severity throughout the summer trapping periods.

Kidney-weight/body-weight ratios were significantly higher in the more acutely diseased animals, with noticeable increase in inflammatory masses of connective tissues. Great variation was noted regarding the extent of kidney lesions. Animals taken in
the fall demonstrated necrosis which covered a major portion of the organ and the entire epithelial layer of the convoluted tubules, while animals captured in the spring showed signs of a limited focal necrosis in limited regions.

Gross appearance of the kidneys revealed a pale and thickened cortex with obliteration of the normal cortical markings. Animals taken prior to the fall sample demonstrated swelling of the laminal epithelial cells covering the glomerular capillaries. In some cases there were indications of exfoliation of both parietal and laminal epithelial cells, at which time noticeable aggregations were seen in Bowman's capsular space. This swelling, proliferation and exfoliation of capsular cells is indicative of early stages in glomerulonephritis.

The kidney tubule lesions present in animals with less severe (probably initial) stages of abnormalities, were found to be largely degenerative. Albuminous and fatty materials sloughed into tubule lumens were found to result concomitantly with swollen and slightly fractionated convoluted epithelial cell layers. The sequence of degenerative events appeared to be an initial degradation of Bowman's capsule and associated glomerular capillaries, followed by degeneration and fractionation of first the proximal and then distal convoluted tubules.

Animals involved with more severe pathologic abnormalities (probably a later stage of the early nephritic condition,
complicated by additional excitants which result from the disease condition itself as well as a number of associated metabolic disturbances) demonstrated complete obliteration of glomerular capillaries in many cases, with an increased thickening of Bowman's capsule. In the most severely affected animals a combination of the nephritic condition outlined above, and focal induration of a cyanotic type was evident. Well defined kidney tubules were often absent, giving the appearance of Selye's "endocrine kidney".

Minute regions of necrotic liver cells (focal necrosis) were found scattered throughout the majority of animals collected. Peaks of severe hepatic infections followed the peaks of severe renal abnormalities by a period of approximately one month (period between successive trapping dates). November and December samples taken from the "stable" population showed the greatest degree of damage with respect to hepatic tissues. The degree of damage, as with the kidney, was least in early spring, progressively increasing in the summer, fall and winter samples. More extensive necrosis, particularly around central veins in the lobules was found in animals collected in the late fall and early winter; however, in the majority of cases the necrotic tissue was limited to peripheral areas. Pigmentation of the liver cells in necrotic areas and distorted lymph and interstitial spaces were assumed to be indicative of obstructive jaundice. In addition, sections taken to include bile-ducts were found to frequently demonstrate various degrees
of parenchymatous and interstitial connective tissue inflammation. Not infrequently livers were found to contain fat-laden parenchymal cells, especially in livers that were markedly fibrotic. This latter condition being either an indication of liver starvation or severe metabolic disorders. In most instances the severity of hepatic dysfunction was paralleled by an equal degree of disease manifested in the kidneys of the same animal.

The seasonal variations in pathologic conditions found in renal and hepatic tissues become even more interesting when compared with the degree of cardiac hypertrophy noted in animals with particularly severe tissue disorders. The pattern of tissue injury, when compared to the periods of adrenal hyperactivity resulting partially from seasonal climatic changes, social-behavioral and physiological maladjustments due to altered population structure, becomes quite distinct, etiologically, from the usual abnormalities of the infectious type.

Numerous parasites (roundworms) were frequently found in the duodenal-ileal segment of the small intestine as well as tapeworms in the form of liver cysts. Although of some contributory value regarding strains on adequate nutrition, these were accepted as of minor importance (correlation of parasitic infestation and the more severe tissue disorders was highly unlikely).
Adaptability has, since the development of the 'general adaptation syndrome' by Selye, been considered an important functional characteristic of all living organisms. It has been the contention of many investigators whose interests lie in the elucidation of the complex mechanisms involved in the maintenance of homeostasis in the organism, that the lack of adequate adaptability to altered extrinsic and intrinsic factors is directly concerned with social-behavioral and physiological disturbances. However, within the past 20 years, the concept of stressor-induced pathological manifestations has been accepted as being of true etiological significance. The importance of the general adaptation syndrome went unnoticed until several investigators had proven that exposure of organisms to a variety of non-specific stressor agents actually produced such conditions as nephrosclerosis and severe metabolic disorders. Noticeable enlargements of the adrenal cortices, with concomitant oversecretion of adrenocortical hormones during stress periods, have been discerned as a compensatory facilitation of the adaptation reaction. Pituitary-adrenocortical mediation of pathologic conditions during prolonged stress conditions is suggested when the facilitory oversecretion of adrenocortical hormones becomes, instead, overdosage.

Chronic overdosage of adrenocortical hormones and their direct degenerative effects on the target organs is not however, the sole

V. DISCUSSION AND CONCLUSIONS
agent responsible for all of the physiologic and pathologic changes which occur in the course of the general adaptation syndrome. Naturally occurring pathological abnormalities and physiological disturbances of the types demonstrated in the conduct of this study are a result of maladjustments to altered behavioral, ecologic and physiological conditions. It is probable that a number of the abnormal tissue responses noted were elicited directly by the stressor agents. The fact that the severity of pathological conditions in both renal and hepatic tissues closely follows seasonal climatic changes as well as adrenal hyperfunction and population structure changes is highly suggestive of the complexity of interacting factors. In this respect the concept of stress suggested by Selye (1950) is sometimes oversimplified and often misinterpreted regarding the interrelationship between the stressor and the stress-response.

The postulates of earlier investigators, which suggested that behavioral phenomena and their resulting stress reactions were intimately involved in the adaptation of animals to a continuously changing environment, prompted a search for a socially-induced, behavioral-endocrine feedback mechanism that could be responsible for regulating population densities (Christian, 1964). Although there are several factors which are unquestionably important in limiting population growth (predator pressures, disease, food availability, etc.) the behavioral-endocrine feedback system
supplies a constant input of cues regarding altered environmental conditions (most of which require compensatory activation of physiologic processes). The consequence of such a system is an immediate activation of adrenocortical function with concomitant inhibition of fecundity. Christian (1968) noted that overcrowding of mice suppressed sexual development in immature animals and significantly reduced reproductive function in adults. Several investigators have recently noted that in wild mammalian populations which form complex social hierarchies (eg. rats, mice), pituitary-adrenocortical function usually increases and reproduction and growth decrease with decreasing social rank (Davis, 1957; Christian, 1963; Christian, Lloyd and Davis, 1965; Bronson, 1967; Louch, 1967).

The factors responsible for individual variation are probably the most difficult of biological phenomena to interpret and understand regarding population dynamics. Several studies have emphasized the complexity of this phenomenon. Some of those of interest here include determinants of individual behavioral differences (Christian, 1964; Denenberg, 1962; Richter, 1954), pituitary adrenocortical response to stress (Christian, 1964; Levine, 1962, 1964; Metcalf, 1960), altered adrenocortical function with abnormal litter sizes (Grotta, 1969; Broadhurst, 1963) and differences in age and sex regarding response to stress (Zarrow, 1966, 1967). Levine (1969) suggests that one factor, which might influence adult stress physiology due to genetic variation, is differences
in maternal behavior during the neonatal period of development. Richter (1954) and Christian and Davis (1964) noted that wild house mice respond to overcrowding with a greater degree of adrenal hyper-trophy than do albino laboratory mice. These data suggest not only intraspecific variation within a particular population, but also wide variations between populations. With these wide individual differences, care must be taken to emphasize the importance of individuality when discussing the factors responsible for the dynamic features of a population and potential pathogenic agents.

Adrenal response patterns displayed by wild Norway rats collected in this study revealed marked differences which may be attributed to seasonal change, the physiological status of the animals and the seasonal severity of pathologic conditions due to ecologic, behavioral and parasitically induced stress.

A high recruitment period in early spring resulting in overcrowded conditions and increased social contact, in combination with extremes of heat in mid-summer and cold in early winter, resulted in peak stress period suggested by the refractory dose-response curves (Figs. 3; 5) characteristic of animals captured during these periods.

It has been suggested by a number of clinical animal investigations that certain stressful conditions (over-crowding, extremes of temperatures, etc.) can elicit such latent disease manifestations as glomerulocapsular nephritis, cardiac hypertrophy and
necrosis, renal hypertension and gastric ulcers, while others which are more closely associated with physical trauma (wounds, shock etc.) actually suppress potential pathogens (Guillemin, 1955; Bajusz, 1961). Investigators have repeatedly demonstrated that the pituitary-adrenocortical system is activated by a variety of stressor agents, whether of extrinsic or intrinsic origin. An essential feature of the animals physiologic role in stress response and especially of adaptive endocrine mobilization (which in prolonged or severe stress circumstances operates in a manner which tends to deplete other physiologically important regulatory processes) appears to be the employment of specific conditioning factors. The animals ability to maintain these conditioning factors at levels high enough to supply an adequate 'energy for defense', will ultimately determine the severity of the subsequent disease manifestations. Although the term 'conditioning factor' is an elusive as the stress response itself, it has been generally accepted as being any hormonal or other intrinsic or extrinsic factor which modifies the pituitary-adrenocortical response to noxious stimulation (Bajusz, 1969; Selye, 1950).

It is suggested that in addition to ecologic and behavioral factors, severe endocrine disorders resulting in physiologic imbalance played key roles in the initiation of the pathologic aberrations of renal and hepatic tissues. The highest incidence of pathologic abnormalities in the kidney (glomerulosclerosis,
ischemic glomeruli and renal tubules, fractionated glomeruli and glomerulonephritis) and in the liver (focal necrosis, obstructive jaundice and abnormal mitotic activity) appeared in early fall, shortly after the peak stress period of mid-summer. Selye (1950) proposed that during prolonged exposure to nonspecific stressors the adrenal cortex may secrete an excess or imbalance of corticoids which play an etiologic role in such disease manifestations as hypertension, nephritis, nephrosclerosis, etc. Although it is not likely that the mechanism regulating adrenocortical activity would spontaneously become distorted, and in itself result in the pathologic conditions found in this study, it is highly probable that a combination of extrinsic and intrinsic disorders could upset normal homeostatic balance. Excess corticoids can induce a variety of renal and hepatic disorders. These factors should not be overlooked, but simply recognized as of secondary importance. It appears that the primary action of adrenocortical hyperactivity, with respect to pathogenicity, is to alter the dynamics of the circulation and metabolic processes.

Arterial blood pressure is a result of interactions between cardiac output, peripheral vasoconstriction, the circulating blood volume and the capillary bed volume. The adrenocortical hormones are capable of altering each of these factors. Selye (1946) noted the relationship between arteriolar vasoconstriction and adrenocortical function by repeatedly producing renal hypertension and
nephrosclerosis in rats by injection of above physiologic doses of desoxycorticosterone.

The liver responds to increased levels of adrenal glucocorticoids by decreased protein synthesis and increased gluconeogenesis. Because this elevated state of metabolic activity cannot be maintained indefinitely, the degeneration of hepatic cells is unavoidable during prolonged stress stimuli.

The dramatic decline in the severity of pathologic conditions noted in all samples taken after November is attributed to the onset of severe winter conditions. Animals affected by extremes of disease conditions were least resistant to the adverse temperature changes and severe weather conditions experienced throughout the winter trapping periods. This reduction in animal numbers in the population during the winter is also reflected by the increased recruitment of early spring, the season with the highest percentage of captured juveniles as well as gravid females. The seasonal variations in male gonad and sex accessory organ-weight/body-weight ratios correlate very well with the suggested periods of high reproductive activity in the spring and fall samples. Testis, prostate and seminal vesicle-weight/body-weight ratios are all highest in the spring sample, then decrease gradually through the summer with a slight increase prior to and during the short period of reproductive activity in early fall (Table 3). Male reproductive organs taken during the winter sampling periods were lucid
and showed little functional reproductive activity either grossly or histologically. Normal stages of follicular and ovarian development were noted throughout the entire study; however, follicular development in ovaries taken during winter trapping periods were less pronounced when compared to spring, summer and fall samples.

It was previously suggested that neonatal mortalities were partly responsible for the reduction in the number of juveniles noted between the spring and summer trapping periods. It is a well known fact that the constancies of psychological and physiological states are not as immutable in the juvenile as they are in the adult. Therefore the resistance to environmental stressors are not so rigorously developed during the neonatal periods. This observation is interesting in view of the fact that only the juvenile males and gravid females (as expected) demonstrated refractory responses to doses of ACTH during the early summer period. Previous literature regarding the response of the neonatal rat to stressor agents (eg. heat, electric shock) demonstrate an inability of stressful stimuli to evoke a pituitary-adrenocortical response (Leeman, 1963; Jailer, 1950; Schapiro, 1960). Among the noxious stimuli which have been found to be ineffective in activating the adrenal cortex during the neonatal period are extremes of heat and cold (Adolph, 1957). Pituitary-adrenal adaptation mechanism is non-functional during early development which suggests the
possibility of such detrimental repercussions as were evident in the present population investigation.

The probability that the adrenocortical dysfunction noted in this study is directly related to the pathologic conditions immediately following such derailments is strengthened by a great number of experimental facts now reported in the literature (Britton, 1932a, b; Seckel, 1940; Long et al. 1940; Leon, 1965; Selye, 1950). Although determinations of the exact mechanisms responsible for the pathologic conditions observed during the course of this investigation have not been attempted, a discussion of the possibilities of several mechanisms, as well as the general roles played by renal and hepatic tissues in response to systemic stressor agents may enhance such determinations in future stress-related studies.

As Selye has noted (1950) the liver plays a key role in most of the systemic stress reactions in which the whole organism is involved. The liver can perform many key chemical reactions through its specific enzymes by regulating intermediary metabolism. Although specific changes in liver cells and tissues may be noted upon exposure of the organism to noxious stimuli, the severity and characteristics of each depend, to a large extent, upon conditioning factors (eg. heridity, diet, age, previous stress exposure etc.), (Selye, 1950). Usually (and most pronounced in this study) the liver undergoes severe atrophy, fatty infiltration, leukocytic infiltration and focal necrosis. Exposure
to heat causes fatty degeneration and scattered areas of focal necrosis in the rabbit, with necrotic areas located around central lobule veins (Gore, 1949). Observations of mice exposed to extremes of cold indicate that this species responds with marked fatty infiltration of the hepatic parenchyma (Levin, 1955). This cold induced fat deposition was ascribed to stress with the pituitary-adrenocortical system suggested as the mediator. Animals examined in this investigation demonstrated severe degenerative changes in hepatic tissues in the fall sample and increased fat depots in late winter and early spring. Again, animals suffering more severe metabolic disorders probably succumbed to the adverse climatic conditions experienced in the winter months. This fact may account for the less severe pathologic conditions found in animals captured in late winter and early spring. In addition, animals captured in early spring showing degenerative changes such as hepatic focal necrosis were of the sub-adult class (150-200 gms.) and were probably a result of sporadic late winter reproductive activity and so were not affected by the earlier extremes of cold. The fatty infiltration most characteristic of winter-trapped animals is probably somewhat indicative of malnutrition. The degree of fat infiltration and parenchymatous inflammation was greater in the "stable" landfill population than in the newly-established pen colonies. Since the "stable" populations food supply depended entirely upon city refuse collections (which were burned immediately
after dumping during the winter months) food availability during this period was scarce. The freely-growing pen populations were given balanced diets of continuously supplied food. This may be partly responsible for less severe incidence of fat infiltration and parenchymatous inflammation seen in the pen populations. However, increased social pressures resulting from intra-specific competition for such limited food resources were probably of equal significance in this regard. The diet is a very important conditioning factor regarding the response of the liver to systemic stresses. As was noted by Selye (1950), malnutrition may act as an alarming stimulus and, in fact, elicit hepatic manifestations typical of various other non-specific noxious stimuli.

There is considerable evidence of both a morphological and physiological character in agreement with the view that liver cells themselves are damaged by maladjustments of the organism to a variety of altered intrinsic and extrinsic factors (Judah, 1965; Leites, 1962; Selye, 1950; Brown, 1954). Necroses in the liver may occur under various conditions and in many forms. Focal necrosis is found irregularly scattered (or in the immediate vicinity of large veins) through the liver in a number of acute infections, and may be artificially induced by exposure of animals to a number of toxic agents which tend to endanger systemic homeostasis (Foglia, 1938).

Microscopical examination of animals demonstrating varying
degrees of degeneration and destruction of liver cells revealed a number of interesting features in agreement with similar conditions found by Selye and Dosne (1940), Selye and Hall (1943), Foglia and Selye (1938), and Leblond, Gross and Lauqier (1943). These portions of hepatic tissue having a ischemic appearance were most evidently degenerated. Necrotic cells were somewhat disintegrated, and in their place were irregular collections of fat droplets. In the more acutely affected animals demonstrating zonal or central necrosis there was also associated hypersplenism, glomerular as well as parenchymatous degeneration of the kidneys and frequently noticeable ventricular cardiac hypertrophy. It is probably not entirely misleading to suggest that the combination of pathologic conditions noted above had its initiation as a result of both direct affects of the stressor agents themselves and indirect (constant interruption of the steady-state performance of the pituitary-adrenal axis) insults to the animals physiologic processes. It is not difficult to imagine that as a result of such disturbances, faulty cell metabolism and the more or less pronounced indications of cell autolysis evidenced in the majority of trapped animals, might occur.

There is little doubt that various forms of stress may have a marked affect on the potentially toxic properties of the adrenocortical hormones; especially when there is an accumulation of these hormones in greater than physiologic amounts. Stress has its
primary effect on kidney circulation, and as is noted by Hoff et. al., (1951), may in itself produce degenerative changes. Christian (1964) produced combinations of severe glomerulosclerosis and nephritis in mice with chronic ACTH treatment.

The similarity between experimental renal hypertension and renal hypertension resulting from stress has been a source of much controversy since the importance of the urinary organs in the stress response was first proposed by Selye. The kidneys are constantly subjected to stresses which tend to disturb the organism's internal environment. Because the kidney is the primary excretory organ of the body and a precise regulator of blood pressure, its role during adaptation to systemic stress is evident. Although Selye has given a thorough account of the general morphologic and functional changes that occur in the kidney during the animal's overall adaptation to systemic stress, there is a lack of information regarding kidney abnormalities resulting from naturally occurring stressors in wild mammalian populations.

Exposure to extremes of cold is very effective in producing nephrosclerosis, probably because of increases in thyroxin secretion resulting in an abnormally high basic metabolic rate. Selye has suggested that renal enlargement during chronic exposure of the rat to cold is due to an increased catabolism of extrarenal tissue which augments the excretory load. Heat exposure has its primary action on the tubular epithelium; however, a number of renal
disorders are thought to be complicated by severe heat stress (Haam, 1939).

Typical of the animals examined in this study was a condition resembling osmotic nephrosis in both proximal and convoluted tubules (Fig. 7). Damage of this type showed very little seasonal variation. The fact that this condition was found in juvenile as well as adult animals suggests a site of origin for more severe kidney diseases encompassing both medullary and cortical portions. The more severely affected animals captured in the fall were characterized by an acute necrotizing glomerulonephritis (Figs. 8; 9; 10). Gnarled destruction and degeneration of the glomerular architecture resulting from a variegated fibrinoid necrosis of the endothelium and proliferation and exfoliation of both glomerular and tubular epithelium were the most obvious characteristics of these animals, in addition to the general tubular abnormalities mentioned above. The pathologic manifestations characterizing such animals are a result of a number of complex and interacting factors (systemic insults resulting from extremes of temperature changes, metabolic and circulatory disorders, parasitic infections and severe endocrine disorders directly associated with altered behavioral and ecologic conditions).

The relation of cardiac hypertrophy to renal hypertension in the presence of such pathologic aberrations is of importance in view of the fact that progression of the disease conditions may
Fig. 7. Section of rat kidney (cortex) demonstrating osmotic nephrosis, sloughed parietal epithelial layers and fractionated proximal and distal convoluted tubule cells. Characteristic of animal trapped during summer period. (6μ; 400x).
Fig. 8. A combination of severe, necrotizing glomerulonephritis and the initiation of glomerular and tubular necrosis. Fibroblastic infiltration of arteriolar-glomerular junctions. (6 μ; 400x).
Fig. 9. Acute necrotizing glomerulonephritis with both tubular and capsular necrosis. Degenerating glomeruli and massive thickening of tubules gives the appearance of Selye's "endocrine kidney". Characteristic of animals trapped during the fall period. (6μ; 350x).
Fig. 10. Nephritic condition seen in all animals trapped during the winter periods. Fractionated capillary tufts with little or no evidence of function. (6μ; 600x).
result in complete obstruction of capillary blood flow (especially in glomeruli) and increased arterial hypertension due to inflammation of the renal parenchyma and occlusion of arcuate arterioles. In many cases there was little evidence of capillary blood flow to entire kidney cortices.

Using animals caught in the spring as the most "normal" with respect to disease manifestations (Fig. 11), and then noting the progression and development of those conditions to the most severe disorders found in the fall trapping periods, a pattern of renal and hepatic changes evolved. Glomerular lesions progressed from a diffuse proliferative glomerulonephritis characterized by hyperplasia of the endothelial cells and 'cloudy swelling' of parenchymatous tissue to a more acute necrotizing glomerulonephritis involving both the glomerular structure and Bowman's capsule. These changes were accompanied by fractionation and degeneration of both proximal and convoluted tubules in late summer. Animals captured in the fall and early winter trapping periods evidenced nephrosclerosis similar to that produced by anterior-pituitary extract in the rat by Selye (1946). The diffuse peripheral necrosis found in the hepatic tissues of animals captured in the spring progressed in midsummer to more widespread necrosis with signs of fatty infiltration. Animals taken in early winter showed a marked increase in cell death with peripherally necrotic areas as well as destruction circumscribing centrally located veins. Fatty infiltration and
Fig. 11. Section through the cortical region of the kidney. These less severe pathologic conditions were typical of spring-caught animals. Lack of proximal tubule brush border, sloughed parietal epithelium, and swollen glomerular capillaries. (6μ; 650x).
parenchymatous inflammation were also more pronounced at this time.
BIBLIOGRAPHY


Asdell, S. A. (1941) The influence of age and rate of breeding upon the ability of the female rat to reproduce and raise young. Cornell University Agric. Exp. Sta. Mem. 238: 3-28


Awapara, J. et. al. (1949) Quantitative relation between certain amino acids and glycogenesis. Endocrinol. 44: 378


________________ (1952) The social aspects of population dynamics. J. Mammal. 33: 139-159.


---


Eleftheriou, B. E. (1964) Bound and free corticosteroid in the plasma of two sub-species of deer mice (Peromyscus maniculatus) after exposure to a low ambient temperature. J. Endocrinol. 31: 75-79.


Habermann, R. T., Williams, F. P. and Thorp, W. T. S. (1954) Common infections and disease conditions observed in wild Norway Rats kept under simulated natural conditions. Amer. J. Veterinary Research. 15: 152-156.


Korenchresky, B. and Hall, K. (1941) Correlation between sex hormones and deoxycorticosterone as judged by their effects on the weights of organs of gonadectomized rats. Biochem. J. 35: 726.


