# INCIDENCE OF PEPTIC ULCERS IN ADAPTATION TO FORCED EXERCISE AND ANXIETY - PRODUCING ELECTRICAL STRESS IN ADULT MALE ALBINO RATS

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ABSTRACT

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By

Katherine Hawks

The purpose of this study was to determine the incidence of peptic ulcers in adaptation to a program of forced exercise and anxiety-producing electrical stress in male albino rats.

Twenty animals were randomly assigned to a single housing condition and four experimental groups. The treatments comprised forced activity in controlled-running wheels for 35 minutes, and anxiety-producing electrical shocks administered sporadically on an average of four per minute over a two-hour period. Both treatments were administered singly to two of the groups and in combination to a third group. The fourth group received neither treatment and acted as the controls. Treatments were administered seven days a week for 18 days.

The animals were sacrificed at the termination of the study by decapitation. The interior of the rumen and

glandular portion was surveyed for peptic ulcers with the aid of a dissecting microscope.

The results indicated that neither the forced exercise nor the anxiety-producing electrical shock, either singly or in combination, was severe enough to induce peptic ulcers in adult male albino rats.

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Katherine Hawks

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DEDICATION

To my family, for their indirect inspiration to work harder, travel further, and search beyond in my quest for life.

To Paul, for his constant friendship.

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TABLE OF CONTENTS

LIST OF FIGURES

# CHAPTER I

# THE PROBLEM

## Introduction

With increasing stresses in daily human life, more attention has been paid to the incidence of peptic ulcers. Studies tend to indicate that the incidence of peptic ulcer has reached a peak and is beginning to fall in this decade, but science has not come significantly closer to identifying the stimuli provoking an ulcerous response. According to Sun (41), a systematic manner is needed for gathering data on the relation of man's heredity and environment to the pathogenesis of peptic ulcer.

The problem of stress, as presented by Selye (36), is that physical exercise is interpreted by the body in the same manner as other stressors. He has stated that any type of stressor will cause an increase in size of the adrenal gland, an involution of the thymus, and ulcers in the gastrointestinal tract (36).

An avoidance-behavior situation was used by Porter *et al.* to produce ulcers in the "executive" monkey (27). Mikhail induced ulcers in male albino rats by isolation and preconditioned anxiety of shock and light (24).

One of the existing research programs in the Human Energy Research Laboratory at Michigan State University is the forced-exercise training of male albino rats. Electrical shock is used as a stimulant in an avoidance-type situation. The rat will not receive shock if the correct amount of physical exercise is performed in the animal running wheels. Situated beside the exercised rat in a small cage is another animal which acts as the electrical stimulation control. This animal is exposed to the same shock as the performer but is not allowed to run or control the shock received. In two pilot studies, 36 prepubertal male Sprague-Dawley rats were taken from an investigation concerning a vegetarian diet and exercise and 12 adult male Sprague-Dawley rats were taken from a cyclical study concerning the effects of exercise on the histochemical properties of muscle fiber. The animals were investigated after eight weeks of treatment and no peptic ulcers were found.

Several researchers (24, 27, 36) have induced ulcers in animals by isolation, electrical stress, avoidance tasks, and exhaustive muscular exercise. Further information is needed on the degree of forced exercise and anxiety-producing shock that can be imposed on adult male albino rats without inducing ulcers.

## Statement of Problem

The purpose of this study was to determine the incidence of peptic ulcers in adaptation to a program of forced exercise and anxiety-producing electrical stress in male albino rats.

## Limitations of the Study

1. The results of this study are applicable only to male albino rats of the Sprague-Dawley strain under similar conditions of exercise and electrical stress.
2. The total number of 72 animals might be considered minimal.
3. The experimental period of 18 days may not have been adequate for the establishment of significant patterns of ulcers.
4. Animals trained during another season in the year might respond with a different ulcer incidence.
5. Other weights or ages of animals might be expected to respond differently to the program.

## Importance of the Study

The significance of this study is in assessing the stress, as measured by an ulcerous response, of the various environmental variables and experimental treatments used in laboratory research with adult male albino rats.

# CHAPTER II

# RELATED LITERATURE

## Exercise and the Adaptation Syndrome

In recent years, tremendous advances have been made towards a better understanding of the effects of exercise. In spite of this advancement in many exercise areas, little has been done to understand the effects of physical exercise as a stressor on the gastrointestinal tract.

Selye (36), indicates that the body may react to all types of stressors by an increase in the size of the adrenal gland, an involution of the thymus, and peptic ulcers of the gastrointestinal tract. The body reacts to these physical, mental, or emotional stressors through the pattern of an adaptation syndrome. This adaptation syndrome is characterized by a decrease in specific resistance to the agent stressing the body during the "alarm reaction phase." The specific resistance then increases and reaches its maximum during the second "stage of resistance." Later, it may again fall below normal and finally, death may ensue during the final "stage of exhaustion." In a study using forced physical exercise as the stressor, the

resistance of rats was decreased enough during the "alarm reaction stage" to impose acute gastric ulcers (35). Supposedly, the rat will then gain resistance to the exercise during the "stage of resistance" and rid itself of the ulcer. There is some suggestion as to such a sequence of events in the literature by Mikhail (23, p. 66) who indicates that the recovery from ulcers, rather than their formation, may indicate the strength of conditioned fear. If the stressor continues to impinge upon the body and remains too great for the animal to handle, the animal enters the "stage of exhaustion." This was demonstrated by the appearance of gastric ulcers after 30 days of exposure to cold (35).

The non-specific resistance to a second stressor is likewise characteristically influenced by the general adaptation syndrome. While an animal acquires specific resistance to one agent during the alarm reaction, its non-specific resistance to other agents is altered. The lung edema, normally produced by adrenalin, is prevented in animals in which an alarm reaction previously has been elicited either by adrenalin or by other agents such as exercise (34).

## Normal Anatomy of Rat's Stomach

The stomach (Figure 1) is divided into two portions by a prominent white transverse ridge, the limiting ridge, which separates the upper two-fifths, the cardiac portion,

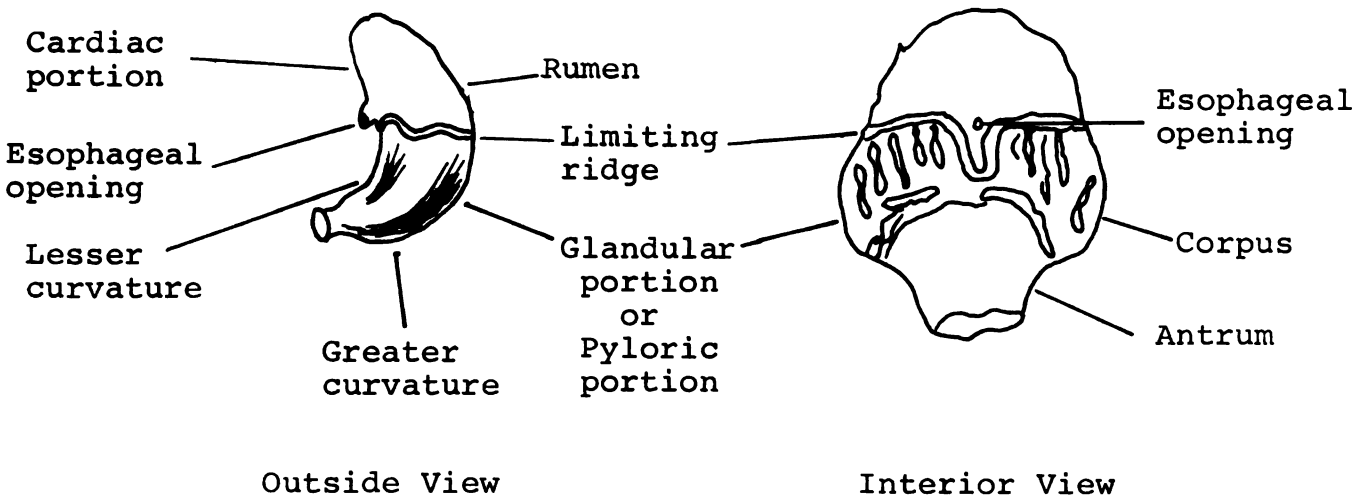


Figure 1. Rat's Stomach

from the lower three-fifths, the pyloric portion (17). The entrance of the esophagus is located at the lesser curvature. The limiting ridge can be seen easily from the outer surface of the stomach.

The rumen (38) or cardiac portion is the non-secretory portion of the stomach. It is translucent and thinner than the glandular (38) or pyloric portion. The mucosa is smooth, pearly grey, and is covered by a thin, stratified squamous epithelium. Beneath the epithelium is a thin layer of connective tissue. Beyond the connective tissue layer is a well-developed muscularis mucosa which is separated by another layer of connective tissue from the true muscularis.

Below the limiting ridge is the glandular or secretory portion which is composed of two clearly defined areas. Each is histologically different. A rough semi-circular area straddling the lesser curvature below the limiting ridge is the antrum. It is relatively thin, translucent and has a slightly irregular inner lining. Its mucosa consists of relatively short simple glands lined by mucus-secreting columnar epithelium. The remainder of the lower two-thirds comprises the corpus. It is believed that this part of the rat's stomach both anatomically and functionally is analogous to the body of the stomach in man (38). It straddles the entire greater curvature below the ridge except for a small area above the pylorus. This is the thick opaque portion of

the rat's stomach. Its mucosa is thrown into prominent folds which contain closely packed long, narrow, tubular glands. The line of demarcation histologically between this mucosal pattern and that of the antrum is gradual.

## Animal's Relationship with His Environment in the Production of Gastrointestinal Ulcers

### Conflict

Sawrey and his co-workers focused on the hypothesis that peptic ulcer results from conflicts between the drives of the subject and the environmental opportunities for satisfaction. Their experimental model consisted of a food-deprived rat which had to cross an electrified area in order to obtain food and water. The treatment was maintained for 47 of every 48 hours. During the 48th hour the animal was allowed to obtain food and water without being shocked. When these conditions were imposed for varying periods, gastric erosions of both the glandular part of the stomach and the rumen occurred (32). The results indicated that the conflict per se contributed significantly to ulcer formation. Weight loss was significantly related to the variable of shock. The combination of food deprivation and electrical shock contributed to lesion formation, but only in interaction (31).

Sawrey and others have found additional factors which are influential in the formation of gastric ulcers. Genetic factors have been shown to play an important role.

Sprague-Dawley rats develop erosions more readily in a conflict situation than Nebraska Hooded rats (31). The effect of nuture was emphasized by Ader's report that rats weaned at 15 days of age are more vulnerable to gastric lesions than those weaned at 21 days of age (2). The handling of a rat during its first 10 days of life was shown to increase its resistance to erosions when placed in an experimental situation later in life (3). Bonta observed that female rats displayed a significantly higher ulcer response than male rats (7). The same article indicated a seasonal variation whereby the peak of ulcerous response was reached in April and May and a low was reached November and December (7).

Restraint

A second model for producing ulcers in rats employed restraint. Since the normal 24-hour activity of the rat corresponds to about 12 miles of walking (20), immobilization of the animals for several hours strongly upsets them and works as a potent stress favoring the development of ulcers. The work of Bonfils in France has established that there is an inverse relationship between the number of erosions and the volume of space permitted the animal, and that the method of immobilization is unimportant (6). The lesions are restricted to the mucosa of the glandular portions of the stomach. The erosions heal rapidly and there is no tendency toward chronicity. Repeated

immobilizations decrease the number of erosions but increase the mortality (18).

As in the first model, the susceptibility to restraint-induced erosions was genetically controlled (40), and early handling increased the inherited resistance to this lesion (42).

Ader took advantage of the variations in intensity of "activity drive" in rats and demonstrated that restraint during periods of high spontaneous activity produced more erosions than restraint occurring during periods of low spontaneous activity (1). Senay showed that two stresses, cold and restraint, together produced an even higher percentage of stress ulcers in rats (37).

In the Sawrey and Sawrey (33) experiment, it was reported that rats exposed to fear conditioning prior to being restrained for 48 hours developed greater ulceration than controls when the conditioned stimulus was periodically presented during restraint. A similar method was employed by Mikhail in order to test the hypothesis of Sawrey and Sawrey that conditioned anxiety of short duration should promote ulcer formation (24). Rats were deprived of food before and after being subjected to the conditioning treatment of simultaneous light and shock or light and buzzer. Following the conditioning, all were placed in corsets as stress treatment for inducing ulcers. The experimental group was exposed to the conditioned stimulus of either the light or the buzzer during the 24

hours of restraint. Mikhail concluded that the short exposure to conditioned anxiety did not increase gastric acidity nor ulceration. In an earlier study, Mikhail found that rats with ulcers recovered when they were exposed to several procedures of conditioned anxiety (23).

Contrary to the first model of conflict, observations of gastric secretion have been made during the restraint situation. Gastric hyperacidity was produced in the rat by pyloric ligation (11) which demonstrated a decrease of secretion with restraint (22). Chronic fistula rats showed a decrease in secretory volume, an increase in acid concentration, and no change in acid output (10).

Since Pincus suggested that the vascular component was particularly important in the production of lesions in man (25), the disturbances and anatomy of the vascular system in the rat's stomach should be considered. Bonfils et al. reported that the "capillary pits" which appear in the gastric mucosa within 30 minutes of restraint (5) suggest important vascular disturbances which may be related to the gastric erosions. Anatomically, it has been found that there is a relative paucity of arteries and collaterals in the rat stomach as compared with other species (4). Further investigation of these observations has lagged.

Brooks et al. extended the restraint situation to the Spider monkey (12). In this primate, three hours of restraint inhibited gastric acid output. If restraint was

prolonged for 24 hours, gastric secretion remained stable at the initial level and the normal nocturnal fall in acid secretion seen in the unrestrained monkey was abolished. Possible gastric pathology was not ascertained.

Conditioned Avoidance

The third situation that has been used to produce gut lesions was a type of conditioned avoidance behavior described by Sidman (39). The task required pressing a lever to avoid receiving electric shocks to the foot. Each lever press postponed delivery of the shock for 20 seconds. This has been used extensively by Porter et al. in their "executive" monkey studies. In the experiment, four pairs of Macaca iris monkeys were placed in an avoidance situation (27). The "executive" animal of each pair had access to a lever which postponed the shock for 20 seconds. The other monkey received the same number of shocks as his "executive" partner, but his lever presses had no effect on the delivery of shocks. The avoidance situation was programmed so that six-hour test sessions alternated with six-hour rest sessions on a round-the-clock basis.

At the end of two to eight weeks, all the "executive" monkeys developed gastric lesions and ulcers (9). Three of four "executive" monkeys died during the experiment. The fourth monkey was sacrificed in moribund condition. All of their partners remained in good health, were

sacrificed at the time of the "executive's" death, and were found to have no gastric ulcers. In a subsequent study (26) of nine Macaca mulatta on the same experimental schedule for four weeks, none died. All were sacrificed at the end of the experiment, and only two monkeys had duodenal erosions. In this experiment, gastric juice was sampled hourly during a six-hour off-period for three days each week, and acid concentration was determined. There were slight changes in acidity, but the variability was considerable. Foltz and Millet (16) attempted to duplicate the schedules of performance as described by Brady et al. (9). They imposed the same behavioral situation on six male Macaca mulatta for 60-128 days. All the "executive" monkeys survived. Confinement in the chair was felt to be insufficient to produce gastric ulceration. Only one out of the six monkeys with nonfatal gut lesions was given visceral examination.

## Evaluation of the Ulcer Response

A common problem independent of species or production technique, is the evaluation of the ulcer response. The detection of the lesion is carried out either with the naked eye (7, 21), or under slight magnification (13, 38). A recent method makes ulcer detection more objective than hitherto (30). This technique consists of oral treatment of the rats with $FeCl_3$ one hour before sacrificing them and at autopsy immersing the stomachs in a solution of

potasium ferrocynaide. The ulcers are stained dark blue, whereas the mucosal background retains its normal pink color.

Numerous variations in methods exist concerning the quantification of the detected ulcers. Hambourger and his associates (19) divided the stomachs into five grades. The principle of the "all or none" response (stomachs with ulcers and "clear" stomachs) was also applied (13, 21). Several authors used scoring systems (28, 29) and calculated ulcer indices. The latest method used was a "blind" ranking evaluation whereby the observer ranked the stomachs in order of severity of general pathological condition (8).

# CHAPTER III

## METHOD

The purpose of this study was to determine the incidence of ulcers in adaptation to an existing program of forced exercise and electrical stress in male albino rats.

### Subjects

Twenty male albino Sprague-Dawley rats from another investigation of the effects of physical activity and anxiety-producing stress on ADH secretion were used as subjects. The animals were received at 80 days of age and sacrificed for inspection of ulcers at 128 days of age. They were purchased from Hormone Assay Laboratories in Chicago, Illinois, in June, 1970.

### General Animal Care

The animals received a diet of Wayne Lab blocks and water ad libitum. The animals were handled daily. The temperature in both the animal quarters and the treatment room was maintained between 70 and 72 degrees Fahrenheit and between 60 and 70 per cent relative humidity.

The rats were housed in 8 1/2 × 4 1/2 × 4 1/2-inch sedentary metabolism cages with temporary access to attached spontaneous activity drums, 5 inches wide and 14 inches in diameter.

The animal quarters were lighted 24 hours a day.

## Treatment of Animals

The animals were divided randomly into four groups of six. The groups were randomly assigned to the following experimental regimens:

1. Control Group. These animals received no experimental treatment but were placed in the anxiety cages for two hours and in the holding cages for two hours every day seven days per week, in order to equate all environmental variables.

2. Anxiety Group. These animals received sporadic electrical shock for two hours per day in anxiety cages. Following the anxiety treatment, each animal was placed in a holding cage for two hours.

3. Forced-exercise Group. These animals were placed in the anxiety chambers for two hours but received no electrical shock. They then were forced to run a medium-endurance type program in controlled-running wheels for 30 minutes. Subsequently, they remained in the wheels for a holding period of 90 minutes.

4. Anxiety plus Forced-exercise Group. These animals received sporadic electrical shock for a period of

two hours and were forced to run a medium-endurance type program in controlled-running wheels for 30 minutes. Following the running treatment, they remained in the wheels for a 90-minute holding period.

## Research Method

The first phase of the experiment consisted of four weeks of general environmental adaptation and foot conditioning during which each animal was permitted free access to the spontaneous activity drum which was attached to his cage.

At the commencement of the treatment period and thereafter, access to the activity drums was denied.

The treatment program was conducted for four hours a day, seven days a week. A peak period of ADH activity was expected so the experiment was continued on an open-ended basis (14, 15). The study was terminated when the data leveled off for five continuous days.

The anxiety-producing stress consisted of electrical shocks (60 volts, 15ma), preceded by a pleasant tone audible at conversational level. The tone lasted for .5 seconds and was given .5 seconds before each electrical shock. The shock, which lasted .5 seconds, was administered randomly on a 100-second time basis. Ninety-five per cent of the stimulations were from 5 to 20 seconds apart; 5 per cent of the stimulations were from 20 to 80 seconds apart. The average number of shocks on a random

basis was four per minute. The duration of the treatment each day was two hours. The stimulations were received through a stainless-steel grid which served as the floor of individual cages.

The training wheels used for the forced-exercise treatment employed avoidance electrical stimulus (1.2ma) operant conditioning, utilizing a light (60 volts, 120 watts) as the conditioned stimulus. The animals were forced to run at a speed of 2 foot per second for 10 seconds. They repeated this run 30 times with a rest interval of 10 seconds between repetitions. The program consisted of three bouts with a rest interval of 5 minutes between each bout. The total running time was 35 minutes. All animals were able to satisfactorily complete this exercise program.

## Ulcer Assay

The animals were randomly sacrificed by decapitation at the end of the 18-day period. The interior of the rumen and glandular portion was surveyed for punctured areas, red spots, or lesions. Any questionable area was further investigated through the use of a dissecting microscope. An ulcer is normally identified by the absence of the overlying epithelium. An ulcer was recorded according to the area in which it was observed.

# CHAPTER IV

## RESULTS AND DISCUSSION

The purpose of this study was to investigate the effects of physical activity and anxiety-producing electrical stress on the incidence of peptic ulcers in adult male albino rats. Twenty animals were randomly assigned to a single housing condition and four experimental treatments. The rats received treatments seven days per week, four hours each day, for a period of 18 days. The animals were sacrificed at the termination of the study by decapitation.

### Results

The animals were sacrificed at the end of the experiment and inspected for peptic ulcers. The portion of the digestive system from the esophageal opening to below the antrum was removed. The interior of the stomach was surveyed with the aid of a dissecting microscope. The rumen appeared smooth and white with no trace of punctures. The glandular portion contained the normal cryptic folds which were routinely inspected for eruptions. The antrum was thin and translucent with no lesions. The results

indicated that neither the forced exercise nor the anxiety-producing electrical shock, either singly or in combination, was severe enough to induce peptic ulcers in adult male albino rats.

## Discussion of Results

This study and previous work by Porter et al., Selye, and Sawrey and Sawrey used the experimental treatments of avoidance task, electrical anxiety, and physical exercise to produce gastrointestinal ulcers. There is some suggestion by Selye (36) that exhaustive exercise alone can induce ulcers. However, Selye's literature does not describe the method or degree of physical stress necessary to produce stomach ulcers. Porter et al. (27) used an avoidance task that required a monkey to pull a lever to avoid electrical shock as a means of inducing peptic ulcers. Increased incidence of ulcers in restrained rats was found by Sawrey and Sawrey (33) who used a preconditioned anxiety period of six hours of electrical shock and a buzzer.

Treatment similarities between the present study and those of Porter et al., Selye, and Sawrey and Sawrey made this author question the possible stress being imposed upon the gastrointestinal tract in this investigation. However, visceral examination showed no evidence of an ulcerous response to the forced exercise and anxiety-producing electrical shock. Apparently, the environmental

variables and experimental treatments used in this experiment do not act as stressors upon the gastrointestinal tract of adult albino rats.

# CHAPTER V

# SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

## Summary

The purpose of this investigation was to determine the incidence of peptic ulcers in adaptation to a program of forced exercise and anxiety-producing electrical shock in adult male albino rats.

Twenty 110-day-old male albino Sprague-Dawley rats were randomly assigned to one of four treatments. The animals in the control group received no experimental treatment but were placed in the same housing as those of the other groups prior to and during treatment. The anxiety group received sporadic electrical shock for two hours per day. The animals in the forced-exercise group were forced to run a medium-endurance type program in controlled-running wheels for 30 minutes each day. The anxiety plus forced-exercise group received both the sporadic electrical shock for two hours and the forced running for 30 minutes each day.

The animals were housed in sedentary metabolism cages with the quarters lighted 24 hours per day. The

treatment program was conducted for four hours a day, seven days a week, and continued for 18 days.

The anxiety-producing electrical stress was designed with electrical shocks (60 volts, 15ma) administered sporadically on an average of four per minute over a two-hour period.

The forced-exercise program was designed as a mild exercise with only 30 minutes of medium-duration, moderate-intensity activity.

The rats were sacrificed by decapitation at the end of the 18-day period. The stomachs were removed and immediately investigated. There was no detection of peptic ulcers after visceral examination.

## Conclusions

The results indicated that neither the forced-exercise nor the anxiety-producing shock, either singly or in combination, was severe enough to induce peptic ulcers in adult male albino rats. Apparently, the environmental variables and experimental treatments used in this study do not act as stressors upon the gastrointestinal tract.

## Recommendations

Research is needed to determine the specific degree of physical exercise plus anxiety-producing electrical stress that can be imposed on adult male albino rats without inducing ulcers.

Further research is necessary to determine if any adaptive changes occur in the gastrointestinal tract as a result of physical training and anxiety-producing electrical stress of various intensities and durations.

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