A COMPARATIVE STUDY OF THE EFFECTS OF GONADECTOMY AND TAMOXIFEN TREATMENT ON ACID GASTRIC SECRETION IN ALBINO RATS

BY

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A THESIS
SUBMITTED TO THE
POSTGRADUATE SCHOOL
AHMADU BELLO UNIVERSITY, ZARIA
In partial fulfillment of the
requirements for the degree of

MASTER OF SCIENCE

DEPARTMENT OF HUMAN PHYSIOLOGY
FACULTY OF MEDICINE
AHMADU BELLO UNIVERSITY
ZARIA, NIGERIA

MARCH, 1995

DECLARATION

I hereby certify that I carried out the research in this thesis by myself in the Department of Human Physiology, Faculty of Medicine, Ahmadu Bello University, Zaria, under the supervision of Prof. M.A. Ali, Head, Department of Human Physiology, Dr. E.M. Sheriff, Head, Department of Human Anatomy, and Dr. A.B. Adelaiye, Assistant Dean, Faculty of Medicine.

Where use has been made of the published work of other investigators, this is acknowledged and the source of information appropriately referenced. No part of this thesis has been submitted or accepted elsewhere for a higher degree or diploma.



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DEDICATION

This work is dedicated to my parents, brothers and sisters for their wonderful love and support.

ACKNOWLEDGEMENTS

I wish to express my appreciation and profound gratitude to my supervisors, *Prof. M.A. Ali, Dr. E.M. Sheriff and Dr. A.B.Adelaiye,* for their guidance, constructive criticisms and invaluable assistance.

I also wish to express my gratitude to the entire staff of the Department of Human Physiology, most of whom were of assistance in many ways. The advice of the lecturers and the kind co-operation of the senior technologists in the department were largely instrumental to the completion of this research.

I am particularly indebted to the following people:

i. Mr. J.A. Anuka, of the Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmaceutical Sciences, for his invaluable contributions and suggestions, and especially for his love and concern for the success of this work.

ii. Dr. E. Amber and Dr. H. Zoaka, both of the Veterinary Teaching Hospital, for their help with the surgical procedures.

iii. Mr. J.L. Hamidu, whose friendship and moral assistance I enjoyed throughout the period of this work.

iv. Mr. S. Adebisi, of the Department of Human Anatomy, for his brotherly advice and assistance during the administration of the drugs.

Lastly, my thanks go to ICI, Pharmaceuticals, England, for their kind donation of a sample of tamoxifen.

ABSTRACT

The effects of gonadectomy and tamoxifen administration on basal and histamine-stimulated gastric acid secretion in male and females rats were studied. The effects on body and stomach weights were also studied. Gonadectomy was performed 30 days prior to gastric acid secretion estimation, and tamoxifen was administered subcutaneously for 30 days before gastric acid secretion estimation. Gastric acid output was determined by the continuous perfusion methoi of Ghosh and Schild (1958).

Both basal and histamine-stimu1ated gastric acid secretion in 14 castrated male rats were not significantly difference from those in 14 tamoxifen-treated nale rats ($P > 0.001$). Similarly, there was no significant difference between basal and histamine-stimulated gastric acid secretion in 14 ovariectomized rats, and 14 tamoxifen-treated female rats ($p > 0.001$). Basal and histamine-Stimulated gastric Acid outputs were significantly reduced in tamoxifen-treated male rats ($P < 0.001$), bolow the values obtained from 12 control male rats. This effect increased as the duration of treatment was increased. In female rats, basal and histamine-stimulated gastric acid secretion both Increased following tamoxifen administration, above the value for 12 control female rat3 ($P < 0.001$). This response also increased with increase in the duration of tamoxifen administration.

Castrated male rat3 and tamoxifen-treated male rats both gained significantly less weight than control male rats

(P<0.001). Ovariectomized rats gained significantly more weight than control female rats (P < 0.001). Tamoxifen-treated female rats gained no weight throughout the period of treatment. Stomach weights were not significantly different (P > 0.001) in either gonadectomized or tamoxifen-trsated male and female rats.

The effect of tamoxifen on gastric acid secretion in male rats is likely due to its antiandrogenic effect, while the result observed in female rats may be due to its antagonism of oestrogen. The results suggest that the susceptibility of males and females to peptic ulceration is not greater following tamoxifen administration than it is after castration or ovariectomy.

TABLE OF CONTENTS

DECLARATION ii

CERTIFICATION iii

DEDICATION iv

ACKNOWLEDGEMENTS v

ABSTRACT vii

CHAPTER ONE: INTRODUCTION 1

1.1 General Introduction 1
1.2. Breast Cancer and Tamoxifen 2
1.3. Statement of Research Problems 3
1.4 Gastric Secretion: Physiological Aspects . . . 5

1.4.1 Anatomical Consideration: 5
1.4.2 Control of Gastric Secretion 7

CHAPTER TWO: REVIEW OF LITERATURE 10

2.1. Sex Hormones and Gastric Function 10
2.2. Histamine and Gastric Acid Secretion 17
2.3. Tamoxifen 20

CHAPTER THREE: MATERIALS AND METHODS 24

3.1 MATERIALS 24

3.1.1 Choice of Experimental Animals 24
3.1.2 Experimental Animals 24
3.1.3 Materials employed for Perfusion of the Rat stomach 25

3.2 METHODS 27

3.2.1 Plan of the Experiments 27
3.2.2 Surgical Operations 29

3.2.2a. Bilateral Orchidectomy 29
3.2.2b. Bilateral Ovariectomy 29
3.2.2c. Sham Operations 30

3.2.3 Drug Administration 31
3.2.4 Determination of Gastric Acid Secretion by Continuous Perfusion Method 31
3.2.5 Determination of Body and Stomach Weights 33

CHAPTER FOUR: RESULTS 35

4.1.1 The effect of Histamine on basal gastric acid output in male (control) rats . . . 35
4.1.2 The effect of castration on basal and histamine-stimulated gastric acid output in male rats 35
4.1.3 The effect of tamoxifen administration (30 DAYS) on basal and histamine-stimulated gastric acid output in male rats 35
4.1.4 The effects of sham castration and vehicle (ETHYL OLEATE) administration on basal and histamine-stimulated gastric acid output in male rats 39
4.2.1 The effect of histamine on basal gastric acid output in female (control) rats . . 39
4.2.2 The effect of Ovariectomy on basal and histamine-stimulated gastric acid output in female rats 40
4.2.3 The effect of tamoxifen administration (30 DAYS) on basal and histamine-stimulated gastric acid output in female rats . . . 40
4.2.4 The effects of Sham Ovariectomy and Vehicle (ETHYL OLEATE) administration on basal and histamine-stimulated gastric acid output in female rats 44
4.3 The effects of tamoxifen administration (5, 10,15 DAYS) on basal and histamine-stimulated gastric acid output in male rats 46
4.4 The effects of tamoxifen administration (5, 10, 15 DAYS) on basal and histamine-stimulated gastric acid output in female rats . . . 46
4.5 The effects of castration and tamoxifen administration (30 DAYS) on body and stomach weights in male rats 47
4.6 The effects of ovariectomy and tamoxifen administration (30 DAYS) on body and stomach weights in female rats 49

CHAPTER FIVE: DISCUSSION 52

CONCLUSION 61

SUMMARY 63

REFERENCES 66

APPENDICES 71

LIST OF TABLES

Table 1a: The effect of Sham Castration and Vehicle (ethyl oleate) administration on basal and histamine-stimulated acid output in male rats. 45

Table 1b: The effect of Sham Ovariectomy and Vehicle (ethyl oleate) administration on basal and histamine-stimulated acid output in female rats. 45

Table 2a: The effect of different durations of Tamoxifen administration on basal and histamine-stimulated acid output in male rats. 48

Table 2b: The effect of different durations of Tamoxifen administration on basal and histamine-stimulated acid output in female rats. 48

Table 3a: Results of Body weight and Stomach weight studies in male rats.. 51

Table 3b: Results of Body weight and Stomach weight studies in female rats. 51

Appendix I: Tables of results for gastric acid output studies in male rats (control, castrated, tamoxifen-treated, sham-castrated, and vehicle-administered). 71

Appendix II: Tables of results for gastric acid output studies in female rats (control, ovariectomized, tamoxifen-treated, sham-castrated, and vehicle-administered).. . . . 77

Appendix III: Tables of results on the effects of different durations of tamoxifen administration on gastric acid output in male rats.. 83

Appendix IV: Tables of results on the effects of different durations of tamoxifen administration on gastric acid output in female rats.. 87

Appendix V: Tables of results for body weight and stomach weight studies in male rats. 91

Appendix VI: Tables of results for body weight and stomach weight studies in female rats. 97

LIST OF FIGURES

Figure 1. Chemical structure of Tamoxifen. 23

Figure 2. Hypothetical mechanism of action of tamoxiten. 23

Figure 3. The effect of histamine on basal gastric acid output in male (control) rats 36

Figure 4. Mean basal acid output in control, castrated, and tamoxiten-treated (30 DAYS) male rats. . . . 37

Figure 5. Mean histamine-stimulated acid output in control, castrated, and tamoxiten-treated (30 DAYS) male rats 38

Figure 6. The effect of histamine on basal gastric acid output in female (control) rats. 41

Figure 7. Mean basal acid output in control, ovariectomized, and tamoxiten-treated (30 DAYS) female rats. . . 42

Figure 8. Mean histamine-stimulated acid output in control, ovariectomatized, and tamoxiten-treated (30 DAYS) female rats. 43

LIST OF PLATES

PLATE 1: Photograph of prepared animal and perfusion apparatus ready for estimation of gastric acid output 34

PLATE 2: Photograph of animal during collection of gastric effluent 34

CHAPTER ONE

INTRODUCTION

1.1 General Introduction

The incidence of peptic ulcer disease is known to vary in different parts of the world (Langman, 1973; Tovey, 1974; Tovey, 1975). Several factors such as diet, culture, genetics, and socio-economic status are responsible for this variation. However, irrespective of the part of the world, it is generally agreed that sex has an effect on the frequency of occurrence of peptic ulcer. A higher frequency of occurrence of peptic ulcer in males has been reported by Truelove (1960), and this is in support of earlier findings by Doll (1952), and Clark (1953). On the basis of these and other reports, it was inferred that the sex hormones were responsible for the differences in occurrence of peptic ulceration in the two sexes.

One of the most important factors in the pathogenesis of peptic ulcer disease is the extent of gastric acid secretion in the stomach. The effects of the sex hormones on gastric acid secretion have therefore generated considerable interest over the past 60 years and continue to do so. The majority of early studies defining the effects of the sex hormones on gastric acid secretion were by estimations done during pregnancy (Artz, 1930; McCarthy, Evans and Dragstedt, 1954; Clark 1957). Later studies by Ghosh (1959), and Kaufmann and Spiro (1968), involved direct studies of the effects of the sex hormones on gastric acid secretion. These studies confirmed the earlier studies (Ojha and

Wood, 1950; MacDonald, 1956) which proposed that oestrogens reduce, and testosterone increases the level of gastric acid secretion.

The preventive effect of oestrogen against peptic ulceration in females is believed to depend on the extent of its action. It is therefore possible that factors which diminish oestrogen action could increase the susceptibility of the female to peptic ulceration.

1.2. Breast Cancer and Tamoxifen

Cancer of the breast is known to be the most widespread cause of death from cancer in women (Nicholson and Griffiths, 1980). The oestrogen-dependent nature of the disease has formed the basis for development of methods of treatment. Established methods include surgical ablation of the ovaries, the adrenal glands, and the hypophysis, all of which decrease plasma oestrogen concentration. These forms of endocrine therapy have shown low percentage effectiveness, and coupled with the surgical risk and trauma involved for the patient (Nicholson and Griffiths, 1980), it is not surprising that these operations are largely unacceptable.

The search for an effective, non-toxic method for breast cancer treatment has led to the emergence of certain compounds with antioestrogenic properties. These interfere with the ability of the receptor protein to bind with oestrogen. Recently, a compound known as tamoxifen has been introduced and

it has the ability to antagonize the biological effects of oestrogens. There is a reported low incidence of side effects during treatment with tamoxifen (Patterson and Baum, 1978). The efficacy of this compound and its increased acceptability in the management of breast cancer make it necessary to further investigate its other actions and effects.

With the introduction of this new form of treatment, it is necessary to study the effect of antioestrogenic action on gastric acid secretion especially as the beneficial effect of oestrogen on peptic ulcer has been shown. (Kaufmann and Spiro, 1968).

1.3. Statement of Research Problems

From the literature reviewed so far, no reports on the effects of oestrogens on gastric function have been found. Given the known effect of oestrogen on gastric secretion, it is possible to predict an effect of antioestrogens such as tamoxifen, on gastric function. Administration of antioestrogens would be expected to cause the opposite of the effect of oestrogen administration. Therefore, tamoxifen treatment should lead to an increase in gastric acid secretion. A finding such as this would certainly be of reward in assessing risk factors which could arise as a result of antioestrogen therapy.

A study of the effect of tamoxifen on gastric acid secretion could help establish the level of safety of the compound. It would therefore allow for an evaluation of the

different forms of breast cancer treatment, based on the degree to which these different forms place an individual to a high risk of peptic ulceration. Also, the results of this study would help in further elucidating the exact mechanism by which oestrogen affects gastric acid secretion. Adeniyi (1991) noted that there still is no consensus in the literature on how the hormone reduces gastric acid secretion levels. This is particularly important given the possibility of such a mechanism being non-genomic.

The effects of removal of the ovaries and the testes, on the levels of gastric acid secretion are well documented (Amure and Omole, 1970; Olowookorun, 1975; Adeniyi, 1991). These are in support of the majority of reports on the effects of exogenous sex hormones on gastric acid secretion. However, no reports have been found on the effects, if any, of tamoxifen on gastric acid secretion in either experimental animals or humans. Thus, a question that still remains unanswered is how the change in gastric acid secretion observed in gonadectomized animals compares with that expected following tamoxifen administration.

The present study is therefore designed to investigate the effects of tamoxifen on gastric acid secretion in both male and female rats, and to compare these findings with the effects of gonadectomy on gastric acid secretion.

A breakdown of the individual experimental objectives include the following studies:

a. The effect of orchidectomy on gastric acid secretion.

b. The effect of tamoxifen administration (30 days) on gastric acid secretion in male rats.

c. The effect of ovariectomy on gastric acid secretion.

d. The effect of tamoxifen administration (30 days) on gastric acid secretion in female rats.

e. The effect of different durations of tamoxifen administration (5, 10, 15 days respectively) on gastric acid secretion in male and female rats.

f. The effects of gonadectomy and tamoxifen administration on body and stomach weights in male and female rats.

1.4 Gastric Secretion: Physiological Aspects

1.4.1 Anatomical Consideration:

The differences in function of the different parts of the stomach are reflected histologically. There are three principle types of glands each lining a separate region of the stomach, the cardiac, oxyntic and pyloric. The cardiac gland area surrounds the gastro-oesophageal junction. It is made up of tubular coiled glands containing mucous cells and few parietal cells. These glands secrete mucosubstances and electrolytes. The oxyntic gland area occupies the fundus and the corpus of the stomach. It makes up about 80% of the gastric mucosa. The oxyntic glands are straight or slightly coiled tubules, arranged perpendicular to the mucosal surface. These gastric pits penetrate to about a quarter of the mucosal thickness and different secretory cells pour their juices into these pits.

These cells include (1) mucous neck cells; (2) parietal (oxyntic); (3) undifferentiated neck cells; (4) peptic (Chief) and (5) endocrine cells.

The mucous neck cells are few in number, being located in the upper segment of each oxyntic gland. The cytoplasm of these cells contains mucous granules which account for the mucus secreted. The parietal cells are more numerous and are mainly located in the upper and middle segments of the pit. They are triangular in shape and contain numerous mitochondria. The peptic cells are present most numerously in the lower half of the gland tubules. Some endocrine cells are present in the oxyntic gland area. These are scattered in the basement membrane and are responsible for secretion of substances like motilin, substance P and somatostatin.

The pyloric glands are located in the pyloric region of the stomach and also along the lesser curvature. The glands which are branched and coiled are made up of cells similar to the mucous neck cells. They secrete alkaline mucus and electrolytes. Argentaffin or Argyrophil cells are also found in the pyloric region. G cells can be found in the middle segment of the glands. These cells contain secretory granules in which gastrin is believed to be stored.

The histology of the stomach of the rat differs from that of the human. The forestomach of the rat is thin, translucent and non-glandular. It is lined with keratinized epithelium and cannot be compared to any part of the human stomach. The corpus

and the antrum of the rat stomach are however similar in histology and function to those of the human stomach. It should also be mentioned that, despite the difference between the anatomy of the rat stomach and that of the human, the mechanism of gastric acid secretion and its regulation remain basically the same in the two mammals.

1.4.2. Control of Gastric Secretion

Gastric secretion is usually divided into basal (unstimulated, interdigestive) and postprandial (stimulated, digestive) periods. The postprandial periods can be further subdivided into the cephalic, gastric and intestinal phases, according to the predominant influence. The division into phases is of limited application because all the phases overlap in time during the course of feeding.

The basal secretion of gastric acid varies considerably on individual basis. It shows a circadian rhythm with the highest output in the morning and the lowest output in the evening. Konturek (1979) has suggested that basal acid secretion is probably caused by tonic vagal stimulation and spontaneous releases of small amounts of gastrin. The abolition of basal acid secretion requires removal of both the vagi and the antrum. It is significant to note that vagotomy reduces basal acid output inspite of a rise in serum gastrin concentration. This implies that direct vagal activation of the parietal cells is the important determinant of basal acid secretion.

The cephalic phase refers to gastric secretion stimulated

by factors acting via the cranial nerves. The stimuli include thought, sight, smell, chewing and swallowing of food. This phase is mediated entirely by the vagal nerves. Impulses from the higher centres proceed via the vagi either directly to the parietal cells, stimulating acid secretion or to the G cells, causing gastrin release. The vagal effects in the cephalic phase are due to three mechanisms:

1. Direct stimulation of the parietal cells
2. Release of gastrin
3. Sensitization of the parietal cells to stimulation by gastrin, histamine, or other stimulants.

The gastric phase is that aspect of the secretory response which occurs due to the presence of food in the stomach. It is known that food in the stomach is the most potent stimulant of acid secretion and is capable of raising output to levels similar to those obtained with histamine or gastric stimulation. Distention of the oxyntic or pyloric area in the vagally innervated stomach during the gastric phase initiates both long (Vago-vagal) and short (intramural) reflexes with efferents to both the oxyntic glands and the G cells. These reflexes result in cholinergic activation of either the oxyntic glands or the G cells or both (Konturek, 1979). Food also stimulates gastric secretion by its chemical ingredients. The most potent of these stimulants are the products of protein digestion. Chemical stimulation combined with distension produces a higher rate of acid secretion than when any of the two occurs. The mechanism

involved in chemical stimulation of oxyntic glands is gastrin independent and atropine resistant (Konturek, 1979).

The intestinal phase of gastric secretion begins when food enters the small intestine. The mechanism involved during this phase have not yet been defined. Acid output during this phase is high and some of the gut hormones have been implicated (Konturek et al., 1976).

The observation that gastric acid secretion is limited after postprandial periods, forms the basis for the theory that gastric acid secretion depends on a balance between the stimulating and inhibitory influences. The inhibitory influences could be central, antral or intestinal in origin. Brooks (1976) showed that the appetite centre influences gastric secretion. The inhibition of appetite by emotional and environmental influences depresses the vagal reflex excitation of the cephalic phase. These support the theory that there is inhibition of gastric acid secretion from the higher centres. Gastric acid secretion has also been shown to be diminished by acidification of the antrum. One possible mechanism for this is a decrease in gastrin release. However, little is known about the physiological significance of this mechánism in man (Konturek, 1979).

CHAPTER TWO

REVIEW OF LITERATURE

2.1. Sex Hormones and Gastric Function

It is well known that gastric acid secretion is the fundamental factor enabling a gastric or duodenal ulcer to develop in a susceptible individual. By this, it implies that the difference between gastric acid secretion levels in the different sexes is largely responsible for the difference in their susceptibility to this disease. In an early study by Ojha and Venkatachalam (1951), the incidence of peptic ulcer disease was observed to be higher in males than in females. They also reported a relief from symptoms in peptic ulcer patients following the administration of stilboestrol. In measurements on cats given stilboestrol diproprionate for 6-15 days, they observed a significant reduction in gastric secretory response to histamine. These findings were in contrast to those reported by Barbhoo and Johnston (1966). In their study on the effects of oestrogens and progesterone on gastric acid secretion in duodenal ulcer patients, they noted that there was no significant change in acid or pepsin response to histamine after short term administration of oestrogens.

In 1968, Kaufmann and Spiro, investigated the effect of oestrogens on gastric secretory activity in peptic ulcer patients and normal monkeys. They reported a fall in acid secretion levels but this was not statistically significant. They concluded that there was no significant change in acid or

pepsin secretion following the administration of large doses of oestrogen in man or monkeys. In their studies on the healing of gastric ulcers following administration of oestrogens, they reported that all the gastric ulcers healed completely. Kaufmann and Spiro (1968) therefore suggested that the healing of gastric ulcers may be the result of a change in secretion levels even though there was no significant difference in the gastric secretion levels in their subjects after administration of oestrogen.

Landor and Wild (1970) studied the effect of naturally occurring oestrus on gastric secretion. They observed that periods of typical oestrus in mongrel bitches were invariably associated with depressed secretion of Hydrochloric acid from denervated gastric pouches. They also studied the gastric secretory responses in bitches with denervated gastric pouches following oophorectomy. This was to ascertain if the ovary exerts an influence on gastric secretion before and after oestrus. They reported that there was no such effect and that there was no significant difference between the secretory data obtained following oophorectomy and sham oophorectomy. Landor and Wild (1970) also investigated the effect of oral diethyl Stilboestrol on dogs with denervated pouches. They reported that the gastric secretory response was not constant. The secretions of all the dogs however rose significantly during the two weeks after oestrogen administration was stopped, when compared with the levels during the previous two weeks during which the dogs

were receiving diethyl stilboestrol daily. They suggested that although a definite and sustained reduction in acid output was not seen, the increases in secretion seen after administration was stopped indicates the possibility of some inhibitory oestrogenic effect.

Amure and Omole (1970) assessed the influence of the sex hormones on acid gastric secretion in rats of both sexes. They reported that bilateral castration of male rats significantly reduced gastric acid secretion. They attributed this inhibition following orchidectomy to a fall in testosterone blood concentration. However, following administration of testosterone to ovariectomized rats, there was no increase in gastric acid secretion. Amure and Omole (1970) also reported that ovariectomized rats treated with 17β oestradiol showed a statistically significant reduction in gastric acid secretion. They observed that only long term treatment with oestrogens was effective in significantly inhibiting gastric secretory activity in castrated male rats given histamine or gastrin. They therefore concluded that oestrogen has a significant and conclusive depressant effect on gastric acid secretion which could account for its beneficial effect on the healing of peptic ulcers in humans.

Based on reports of the influence of oestrogens on the secretory responsiveness of the stomach, Omole (1972) investigated the role of the oestrus cycle on the pattern of gastric secretion in the female rat. He observed that

ovariectomized or acyclic female rats, produced the highest mean basal acid secretion which significantly exceeded secretion in rats in the different phases of the oestrus cycle. The diestrus rats also secreted more than the proestrus or oestrus rats. He therefore suggested that the relatively lower levels of oestrogen in ovariectomized and diestrus rats may result in a reduction of the depressant effect of oestrogen on gastric acid secretion and thus may be responsible for the higher secretory responses observed in these rats. These results confirm earlier reports by Landor and Wild (1970), and Amure and Omole (1970).

Olowookorun (1975) studied the effect of gonadectomy on gastric acid secretion rates in male and female rats. He reported a significant decrease in gastric acid secretion in castrated rats used 28 days after gonadectomy. This result is in support of earlier suggestions that the male sex hormone may be the important factor responsible for the high gastric acid secretion in the anaesthetized male rat. (Amure and Omole, 1970). He suggested that the normal blood level of the male sex hormones may be necessary for adequate stimulation of the parietal cell directly or that the hormones might act synergistically with other substances in circulation to stimulate the parietal cells. Olowookorun (1975) also reported a significantly higher gastric acid secretion in ovariectomized rats when compared with normal female rats. This also confirms findings by Amure and Omole (1970), who reported that female sex hormones have an inhibitory effect on gastric acid secretion.

Csakvari et al (1980) performed an experiment to determine the role that female sex hormones play in the deviations in responses of rats of different sexes to histamine stimulation. They showed that ovariectomized rats had an increased sensitivity to histamine. This response was similar to that experienced with male animals. Csakvari et al (1980) also reported that gastric acid secretion in rats following histamine stimulation was higher in rats in diestrus than in those in oestrus. This is in support of earlier findings by Omole (1972), who reported a greater sensitivity of rats in dioestrus to gastrin than those in proestrus and oestrus. This is a confirmation that the basal and stimulated secretion of the female rat stomach are influenced by the hormonal changes which occur during the oestrus cycle.

It has long been believed that oestrogens cause a reduction in acid secretion during pregnancy (Lozzio et al, 1961). However, more recent reports by Takeuchi and Okabe (1[illegible], indicate that there is a marked gastric hypersecretion during pregnancy and lactation. They observed gastric acid hypersecretion during the middle and late stages of pregnancy as well as increased levels of mucosal histamine. They therefore concluded that the acid hypersecretion in pregnancy is mainly associated with vagal activity and increased histamine release.

Recently, Adeniyi (1991) investigated the influence of sex hormones on gastric acid secretion and parietal cell mass in the rat. He reported that normal male rats have a significantly

higher basal gastric acid secretion rate and parietal cell mass than normal female rats. He also reported a reduction in gastric acid secretion in castrated male rats and an increase in gastric acid secretion in ovariectomized rats when compared with normal female rats. These results are in agreement with earlier findings by Amure and Omole (1970), and Olowookorun (1975).

In his work, Adeniyi (1991) showed that ovariectomy caused an increase in the parietal cell mass and this he explained was responsible for the increased gastric acid secretion observed in ovariectomized rats. Castration of male rats resulted in a decrease in parietal cell mass and this accounts for the decrease in gastric acid secretion seen in these rats. Accordingly, Adeniyi (1991) concludes that the male sex hormone significantly increases, while the female sex hormone significantly reduces parietal cell mass.

The bulk of available related literature reviewed so far has been concerning the effects of the sex hormones on gastric function and the findings are well documented. However, the exact mechanism by which these sex hormones affect gastric function remains unknown. The parietal cell mass is a major determinant of the basal rate of gastric acid secretion. Parietal cells are unable to divide and so their continued renewal is dependent on differentiation from precursor cells. The parietal cell mass is affected by numerous factors. Gastrin causes an increase in the parietal cell mass while vagal denervation does not affect the number of parietal cells.

Pregnancy and lactation are accompanied by hyperplasia of the parietal cells (Konturek, 1979).This finding is noteworthy considering the increase in female sex hormone level during pregnancy. However, it is in agreement with the report by Takeuchi and Okabe (1984) that gastric acid secretion rate increases during pregnancy and lactation.

The sex hormones are known to have a marked effect on the physiological actions of the gastrointestinal tract. For this reason oestrogen and androgen receptors have been sought in these areas of the gastrointestinal tract known to be affected by sex steroids. Oestrogen receptors have been shown to be present in the skeletal muscle cells of the oesophagus of primates. (Winborn, Sheridan and McGill, 1983). In a more recent study, Winborn, Sheridan and McGill (1987), reported that neither androgen nor oestrogen receptors were observed within the nuclei of any luminal epithelial cells of the gastrointestinal tract wall; including the surface of the gastric pits and glands. However, they demonstrated the presence of sex steroid receptors in the nuclei of smooth muscle cells of the tunica muscularis of the stomach. They therefore, suggested that the sex steroids may directly alter only the contractile activity of the stomach and intestine. This report is consistent with earlier reports which have suggested that the sex hormones may influence the motility of the gastrointestinal tract. Bruce and Beshudi (1981) had reported that significant differences in contractile responses were observed between tissues from

oestrogen-treated and non-treated animals. This result indicates an excitatory influence of oestrogen on the contractile activity of gastric tissue. The absence of sex steroid receptors in the nuclei of luminal epithelial cells is significant, considering the effect of the sex hormones on gastric acid secretion.

2.2. Histamine and Gastric Acid Secretion

The role of histamine in the mechanism of gastric secretion continues to be an issue of extensive controversy dating as far back as the early part of this century when its powerful stimulatory effect on gastric secretion was observed. It is known to be present in the gastric mucosa in high concentration and the presence of histidine decarboxylase has also been shown in some species. This enzyme which catalyses the formation of histamine from histidine, increases in response to feeding and other stimuli known to cause gastrin and acetylcholine release in the gastric mucosa.

Histamine is one of the most potent stimulants of gastric acid secretion but its exact role in the mechanism of stimulation of the parietal cells has proved difficult to establish. Kahlson et al (1968) proposed the theory of histamine being the final common mediator for stimulation of gastric acid secretion. The discovery of H_2 receptor antagonists was considered evidence in support of this theory. Black et al (1972) showed that cimetidine not only inhibits histamine-stimulated gastric acid secretion but also inhibits gastric acid secretion induced by gastrin and cholinergic drugs. This finding

is in agreement with the earlier suggestion by Kahlson et al (1964) that on vagal stimulation, acetylcholine is released from nerve endings and this in turn causes histamine release from the gastric mucosa.

Subsequent reports have however, played down the role of histamine mediation in the mechanism of gastric acid secretion. It has been shown that insufficient amounts of histamine are released following gastrin injection, and these cannot be responsible for the responses observed. (Jonnson, 1971). Gastrin is a more powerful stimulant than histamine and this has led to the theory of multiple receptors on the parietal cells. Konturek (1979) has concluded that the inhibitory effect of H_2 blockers on all three modes of gastric acid stimulation can be best explained as being due to interaction among the receptors. He suggested that histamine receptor blockers may decrease the affinity of the two other receptors for their agonists. In other words, histamine is released in the gastric mucosa and sensitizes the parietal cells to the other stimuli.

Ohe (1983) reported that receptors for histamine, gastrin and muscarinic stimuli are located on the oxyntic cells and observed a strong interdependence between them. He, however, did not observe any change in the amount of intramucosal histamine during acid secretion stimulation by pentagastrin or bethanechol. This he concluded is evidence to indicate that endogenous histamine release is not involved in acid secretion stimulated by gastrin and muscarinic receptors.

The precise role of histamine in the mechanism of gastric acid secretion of the parietal cells still remains unresolved. Despite an earlier conclusion by Johnson (1971), that histamine does not play any physiological role in the stimulation of gastric acid secretion, Ohe (1983) believes histamine still plays an integral part in the mechanism of gastric acid secretion and suggests that such involvement is most certainly limited to the vicinity of the parietal cells.

It is known that the effect of histamine on gastric acid secretion is subject to influence by substances which have effects on the histamine receptors. In a recent study, Anuka et al (1991) investigated the effects of sex hormones on histamine-induced hypothermia. They reported that the sex hormones counteracted the hypothermia observed in chicks following administration of H_1- receptor and H_2-receptor agonists. They also reported a potentiation of the effects of these agonists by antioestrogens (Clomiphene and tamoxifen). As an explanation of these results, Anuka et al (1991) suggested that the results seen with the sex hormones may be largely due to a reduction in the H_1-receptor and H_2-receptor availability. Such a regulatory mechanism of H_1 and H_2 receptors by the sex hormones, would have implications for the other effects of histamine. These results are in agreement with the earlier reports on the effects of the sex hormones on histamine-stimulated gastric acid secretion Csakvari, et al. (1980). They observed an increased sensitivity of ovariectomized rats to histamine during gastric acid

secretion studies.

2.3. Tamoxifen

Tamoxifen is a citrate salt of the trans isomer of a triphenylethylene compound (Fig. 1). It is a white, odourless, crystalline powder and is only slightly soluble in water. It is a non-steroidal antioestrogen and probably acts by competitive inhibition of oestradiol at the oestrogen receptor. It is known to have a half-life of 7-14 hours in circulation and is mainly excreted by the liver.

Tamoxifen is currently considered the antioestrogen of choice in the treatment of post menopausal breast cancer. Harper and Walpole (1967b) first observed that it antagonized the uterotrophic effect of oestradiol when administered together. The extent of oestrogen antagonism provoked by tamoxifen, varies with animal species, and small differences in chemical structure and geometric conformation of tamoxifen derivatives, cause marked changes in their agonist and antagonist properties. Pasqualini, et al. (1988) have stated that tamoxifen is largely an oestrogen antagonist in the rat. This confirms an earlier report by Harper and Walpole (1967b). They stated that tamoxifen demonstrates all the normal characteristics of an antioestrogen in the rat by inhibiting the normal physiological responses of oestrogen target tissue to oestradiol.

Harper and Walpole (1967b) reported that the trans isomer of tamoxifen prevented implantation and also inhibited oestradiol-induced vaginal cornification. They observed that

tamoxifen suppresses the oestrus cycle but that normal cycles resume after treatment is stopped. Tamoxifen also inhibits ovulation in adults and pubescent rats. Harper and Walpole (1967b) attributed this to an antagonism by tamoxifen of the positive feedback effect of oestrogen on the hypothalamus. Tamoxifen has been reported to cause termination of pregnancy and also to delay parturition when administered at low doses (Fenwick, et al., 1977; Furr et al., 1979; Pasqualini, et al., 1988).

Some researchers have suggested that the effect of tamoxifen on breast tumour tissue could be due to its influence on either the hypothalamo-pituitary-ovarian or the hypothalamo-pituitary-adrenal axis (Nicholas and Griffiths, 1980). However, Nicholas and Griffiths (1980) also report that few convincing data exist concerning the effects of tamoxifen therapy on plasma hormone levels. In postmenopausal women with advanced breast cancer, tamoxifen therapy was without effect on plasma oestradiol levels (Wiang and Kennedy, 1977). Serum testosterone and androstenedione have been reported to be unaffected by tamoxifen therapy (Patterson, 1981).

The effects of tamoxifen in males differ markedly from those in females. Harper and Walpole (1967b) observed an antiandrogenic effect of tamoxifen in male rats. It reduced the weights of accessory sex organs, partially inhibited spermatogenesis and increased the weight of the adrenal glands. However, in humans, Comhaire (1976) showed that tamoxifen

therapy results in a rise in circulatory FSH and LH, with a secondary rise in plasma androgen.

Much attention has been focused on the antagonist property of tamoxifen because of its limited adverse side effects and clinical efficiency in the treatment of hormone-dependent breast cancer in postmenopausal women. Pasqualini, et al. (1988) have suggested three mechanisms by which tamoxifen could act as an antagonist of oestrogen (Fig. 2).

1. That tamoxifen could probably act through its metabolites. Tamoxifen is extensively metabolized and two of the major metabolites are N-desmethyltamoxifen and 4-hydroxytamoxifen, which have potent antagonist properties.
2. That tamoxifen could act by competitive binding with oestrogen for the same receptor binding site since oestrogens act by binding to receptors.
3. That tamoxifen could ultimately act by inhibiting oestrogen induction of specific proteins without binding with the oestrogen receptor.

With the amount of attention being focussed on the use of tamoxifen in the treatment of advanced breast cancer in place of other surgical forms of treatment, knowledge of its effect on gastric acid secretion would help establish the extent of its side effects. It could also be of value in further elucidating the mechanism by which oestrogen depresses gastric acid secretion.

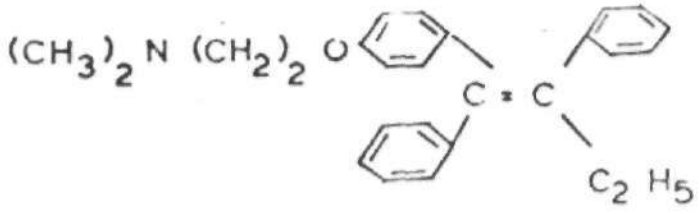


Figure 1: Chemical Structure of Tamoxifen.

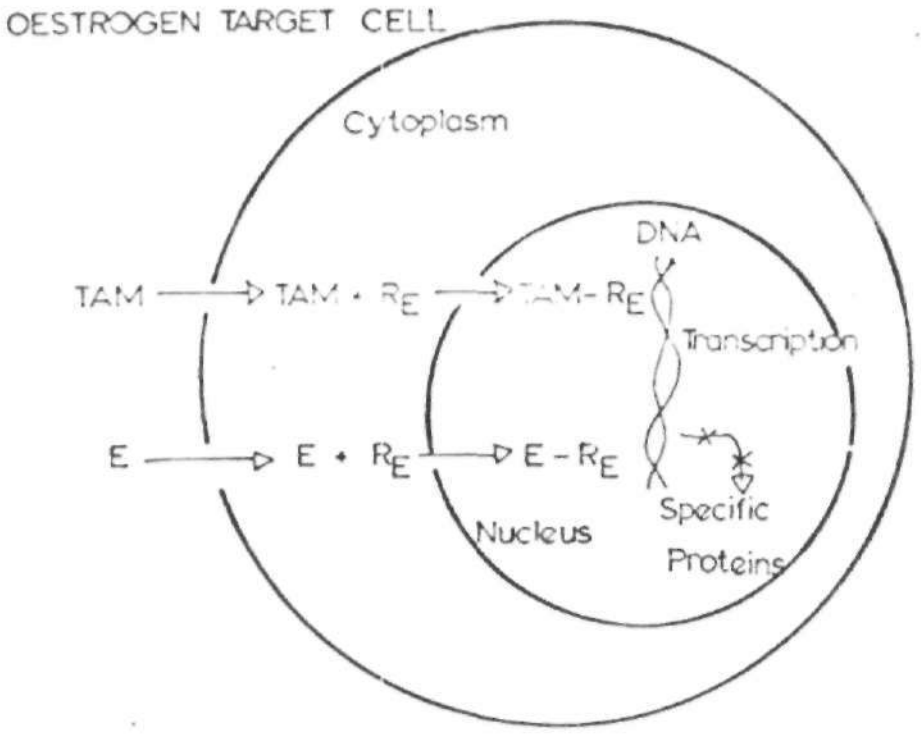


Figure 2: Hypothetical mechanism of action of tamoxifen.
TAM: tamoxifen; E: oestrogen; R_E: oestrogen receptor.
Modified from Pasqualini et el, 1988.

CHAPTER THREE

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Choice of Experimental Animals

Of all the animal species that are employed for experimental and research purposes, the albino rat remains a most suitable choice. Baker, Lindsey and Weisbroth (1979) stated that it is necessary to emphasize that the similarities between homeothermic mammals having the same food habits tend to be close, and that in some instances, using equivalent ages, the results obtained with one form can be very precisely transferred to another.

For this study, the albino rat was chosen for a number of reasons. Firstly, the high degree of adaptability to laboratory conditions as well as resistance to trauma make the rat ideal for the procedures involved in these experiments. Rats are smaller than most other experimental animals and this is advantageous since it allows for rearing large numbers under identical conditions. In terms of handling convenience and species homogeneity, the rat still remains the best choice of experimental animal. Another reason for choosing the rat is its availability and cost of maintenance. Rats are relatively cheaper to maintain than most other experimental animals.

3.1.2 Experimental Animals

Albino rats (Wistar Strain) of both sexes, weighing between

120-240g, were used for all the experiments in this study. The animals were separated according to sex and kept in different cages according to experimental group. All the rats were obtained from the Animal Breeding House of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University. They were housed in cages which were cleaned, washed and disinfected on a regular basis. They were also allowed 12 hours of photic and dark periods. All the animals were fed with chicken mash produced by Livestock Feeds (Nig) Ltd and supplemented with soybeans. This was at a rate of 2kg of soybeans to every 25kg of chicken mash. Feeding was ad libitum and all the rats had free access to drinking water prior to fasting for estimation of gastric acid secretion.

3.1.3 Materials Employed for Perfusion of the Rat stomach

A perfusion bottle was employed to perfuse the stomach of each rat in place of an automatic perfuser which was not available. The bottle with a capacity of 1 litre was suspended at about 50cm above the rat. The distal end of the perfusion tube was connected to the oro-oesophageal tube through which the perfusion fluid was passed into the stomach. A good part of the perfusion tube was placed in a thermostatically-controlled water bath and warmed to a temperature of 37 degrees centigrade in order to warm the perfusate to body temperature. The clamp attached to the perfusion tube was adjusted such that exactly 10.0 = 1.0 ml of the effluent were collected by gravity drainage

through the pyloric fistula at 10 minutes intervals. This was usually as clear as the perfusate and devoid of food particles.

In all the experiments, Normal (Isotonic) saline was used to perfuse the stomach. This was preferred to distilled water because its pH is 7.0 when freshly prepared. Also, absorption of large amounts of water can occur in the stomach during the long period of the experiments. The use of Isotonic Saline reduces water absorption along a concentration gradient.

3.2 METHODS

3.2.1 Plan of the Experiments

The major objective of this study was to compare the gastric acid secretion levels in two forms of breast cancer treatment using the rat as experimental animal. The rats used were therefore separated according to sex and divided into two sets. The first set of male and female rats was used to compare effects of gonadectomy and tamoxifen treatment on gastric acid secretion. This set was divided into two groups. Group 1 was made up of male rats and Group 2, female rats. Each of these two groups was further divided into five subgroups.

Subgroup (a). Twelve male and twelve female albino rats were used as controls to determine the basal and histamine-stimulated gastric acid outputs. These rats were kept together for 30 days from the start of the experiment before gastric acid secretion estimation was carried out. Body and stomach weights were also determined for all the rats.

Subgroup (b). Fourteen male and fourteen female albino rats were used to study the effect of gonadectomy on basal and histamine-stimulated gastric acid Outputs. The male rats were castrated and kept for 30 days after which gastric acid secretion estimation was carried out. Ovariectomies were performed on the female rats after which they were also

maintained for 30 days before gastric acid secretion determination. The effect of gonadectomy on body and stomach weights were also studied in both male and female rats.

Subgroup (c). Fourteen male and fourteen female rats were used to study the effect of tamoxifen treatment on the basal and histamine-stimulated gastric acid outputs. All the rats in this group were treated with tamoxifen daily for 30 days from the start of the experiment after which gastric acid secretion estimations were done. Body and stomach weights were also studied in all the rats.

Subgroup (d). Ten male and ten female rats were used to study the effect of sham gonadectomy on basal and histamine-stimulated gastric acid outputs. Sham castrations were carried out on the male rats while sham ovariectomies were performed on the female rats. Gastric acid output estimations were done 30 days after the operations. Body and stomach weights were determined for all the rats in this subgroup.

Subgroup (e). Nine male and nine female rats were used to study the effect of administration of Ethyl Oleate (solvent used as Vehicle) on basal and histamine-stimulated gastric acid output. Body and stomach weights were also determined for all the rats.

The second set of male and female rats were used to study the effect of different durations of tamoxifen treatment on basal and histamine-stimulated gastric acid secretion. This set was divided into two groups. Group 3 was made up of male rats

and Group 4, female rats. Each of these groups was divided into three subgroups.

Subgroup (a). Eight male and eight female rats were treated with tamoxifen daily for 5 days after which gastric acid secretion estimations were carried out.

Subgroup (b). Eight male and eight female rats were treated with tamoxifen daily for 10 days after which gastric acid secretion estimations were carried out.

Subgroup (c). Eight male and eight female rats were treated with tamoxifen daily for 15 days after which gastric acid secretion estimations were carried out.

3.2.2 Surgical Operations

3.2.2a. Bilateral Orchidectomy

The rat was first anaesthetized with Ketamine Hydrochloride at a dose of 40mg/Kg body weight. The hair over the scrotum was shaved and an incision was made through the skin of the scrotum and the tunic. Each testicle was then withdrawn and the ligament cut. The blood vessels and the spermatic cord were separated and then ligated. A few simple interrupted stitches using 5-0 silk sutures were placed in the skin to close the incision.

3.2.2b. Bilateral Ovariectomy

The rat was anaesthetized using Ketamine Hydrochloride at a dose of 40mg/kg body weight. The abdominal wall around the umbilicus was shaved clean of hair and cleaned with a piece of cotton wool soaked in antiseptic fluid. A midline incision was

made below the umbilicus. The horn of the uterus on one side was withdrawn as the corresponding lip of the incision was lifted with thumb forceps. Omentum and small intestine were first pushed forward and the uterine horn was lifted gently, bringing the ovary into view. The ovarian vessels were ligated and cut between. The ovarian pedicle was also ligated with plain catgut. The procedure was repeated with the second ovary. The abdomen was then closed with 5-0 silk sutures.

3.2.2c. Sham Operations

Each male rat in this subgroup was anaesthetized with Ketamine Hydrochloride at a dose of 40mg/kg body weight. The hair over the scrotum was plucked and an incision was made through the scrotum and the tunic. Each testicle was then brought into view before being replaced back into [illegible]. Two silk sutures were used to close the incision with simple interrupted stitches.

Each female rat was anaesthetized with Ketamine Hydrochloride at a dose of 40mg/kg body weight. The abdominal wall around the umbilicus was shaved of hair and wiped with a piece of cotton wool soaked in antiseptic fluid. A midline incision was made below the umbilicus into peritoneum. The contents of the peritoneum were pushed aside and each uterine horn was lifted gently, bringing the ovaries into view. These were pushed back into place and the abdomen was then closed with 5-0 silk sutures.

3.2.3 Drug Administration

The major drug used in this study was tamoxifen. It was obtained in the form of its citrate salt from ICI, England. Ethyl Oleate, which was used as the drug vehicle, was obtained from BDH, England. A dose of 25µg/100g body weight (Kosaki et al, 1977), of tamoxifen was administered daily to the appropriate rats dissolved in 0.1ml of Ethyl Oleate. Each rat was gently restrained and the drug injected subcutaneously through the skin over the back of the animal. 1ml syringes and fresh needles were used for administration in each case to reduce the risk of infection.

The same procedure was used for the vehicle administered rats. 0.1ml of Ethyl Oleate was injected daily also through the skin of the back of the rat. All the drugs used and the vehicle were stored in a refrigerator as specified by the manufacturers.

3.2.4 Determination of Gastric Acid Secretion by Continuous Perfusion Method

The continuous perfusion method employed in this study is an adaptation of the technique described by Ghosh and Schild (1958). Each rat was fasted overnight but allowed free access to water. The rat was weighed and anaesthetized with an intraperitoneal injection of 25% (wt/vol) Urethane Solution at a dose of 0.6ml/100g body weight. The trachea was then exposed and cannulated carefully with a rubber tubing of equivalent diameter, tying it firmly to prevent detachment. This cannula

was then exteriorized to allow for easy breathing. The trachea was aspirated with a syringe from time to time to prevent accumulation of mucus. The abdomen was opened through the linea alba and the pyloro-duodenal junction was exposed. A polyethylene tube was inserted through an incision in the duodenum into the stomach and secured firmly by a ligature around the pylorus. Care was taken to avoid tying up blood vessels.

A soft rubber catheter (external diameter, 2mm) was passed through the mouth into the oesophagus. A ligature was then placed around the oesophagus at the neck and care was taken to avoid including the vagus. The stomach was then washed with distilled water until the effluent was clear. The rat stomach was perfused with Normal saline and the effluent collected was assayed for titrable acid against 0.01M NaOH using Phenolphthalein as indicator.

During the surgical preparation of the animal, the equipment were switched on to get them ready for use. A good length of the perfusion tube was placed in a water bath to warm the perfusate to body temperature. After the rate of secretion had stabilized, basal acid secretion was measured for 1 hour after which the rat was injected with Histamine subcutaneously at a dose of 100mg/kg body weight. Gastric acid secretion was then determined every 10 minutes for 2 hours observing for peak acid output in each case.

3.2.5 Determination of Body and Stomach Weights

After the determination of basal and histamine-stimulated gastric acid secretion in the rats, the stomach of each rat was removed by cutting off the oesophagus at the cardiac sphincter, and the duodenum, at the duodeno-pyloric junction. It was opened along the greater curvature and the contents removed by gentle rinsing. The empty stomach was weighed on a Mettler balance, Type H30.

The rats in groups 1 and 2 were weighed at the start of the experiments. The weights at the end of 30 days, prior to gastric acid secretion estimations were also taken.

The results of the stomach weight measurements are presented as percentages of the total body weight after 30 days.

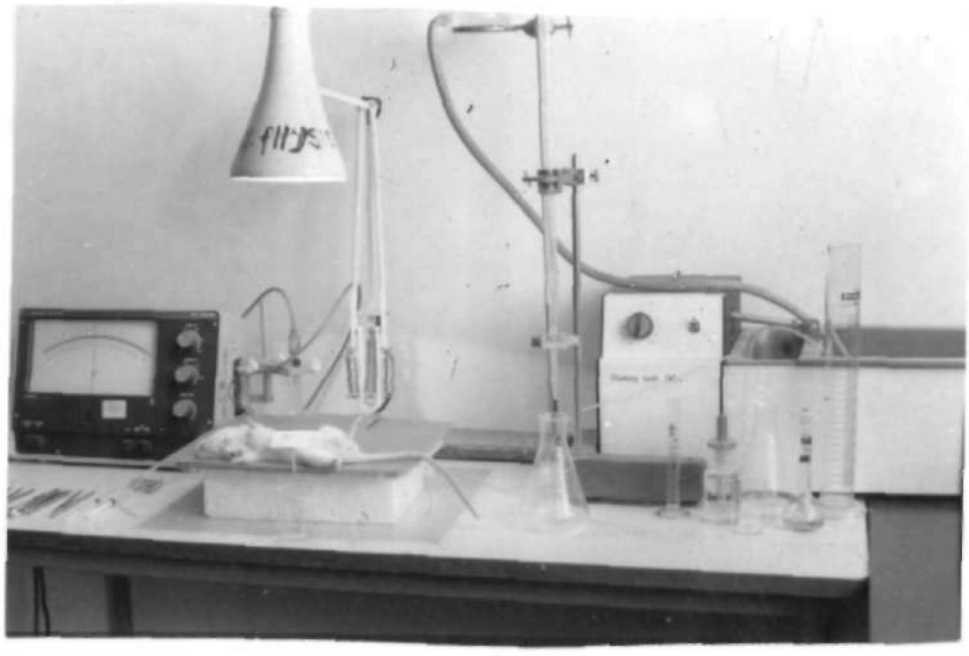


PLATE 1: Photograph of prepared animal and perfusion apparatus ready for estimation of gastric acid output.



PLATE 2: Photograph of animal during collection of gastric effluent.

CHAPTER FOUR

RESULTS

4.1.1 The effect of Histamine on basal gastric acid output in male (control) rats

The mean basal acid output was 2.58 + 0.03μmol/10min and the mean acid output over 2 hours following histamine administration was 13.80 + 0.16μmol/10min. The results are shown in Figure 3 and Appendix 1 (Table A).

4.1.2 The effect of castration on basal and histamine-stimulated gastric acid output in male rats

The mean basal acid output was 2.33 + 0.05μmol/10min and the mean acid output over 2 hours after histamine administration was 13.32 + 0.13μmol/10min.

There was a significant reduction in both the mean basal acid output ($P < 0.001$) and mean histamine - stimulated acid output ($P < 0.05$) below the values for control male rats. The results are shown in Figures 4 and 5, and Appendix 1 (Table B).

4.1.3 The effect of tamoxifen administration (30 DAYS) on basal and histamine-stimulated gastric acid output in male rats

The mean basal acid output was 2.42 + 0.05 μmol/10min and the mean histamine-stimulated acid output was 13.60 + 0.24 μmol/10min. There was also a significant difference between the mean basal acid output and that for the control male rats ($P < 0.02$) However, no significant difference was found between the

FIG-3: THE EFFECT OF HISTAMINE ON BASAL GASTRIC ACID OUTPUT IN MALE (CONTROL) RATS

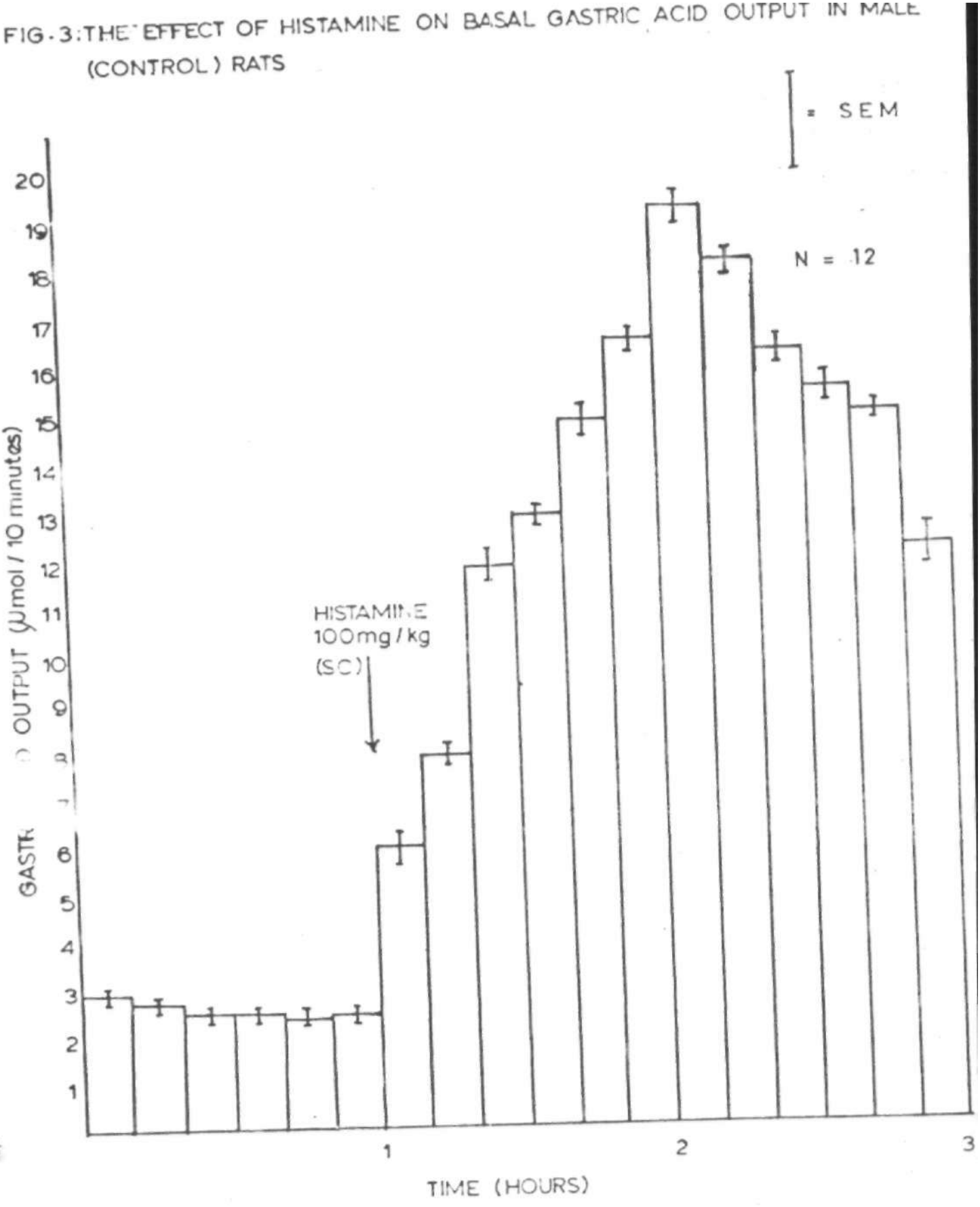
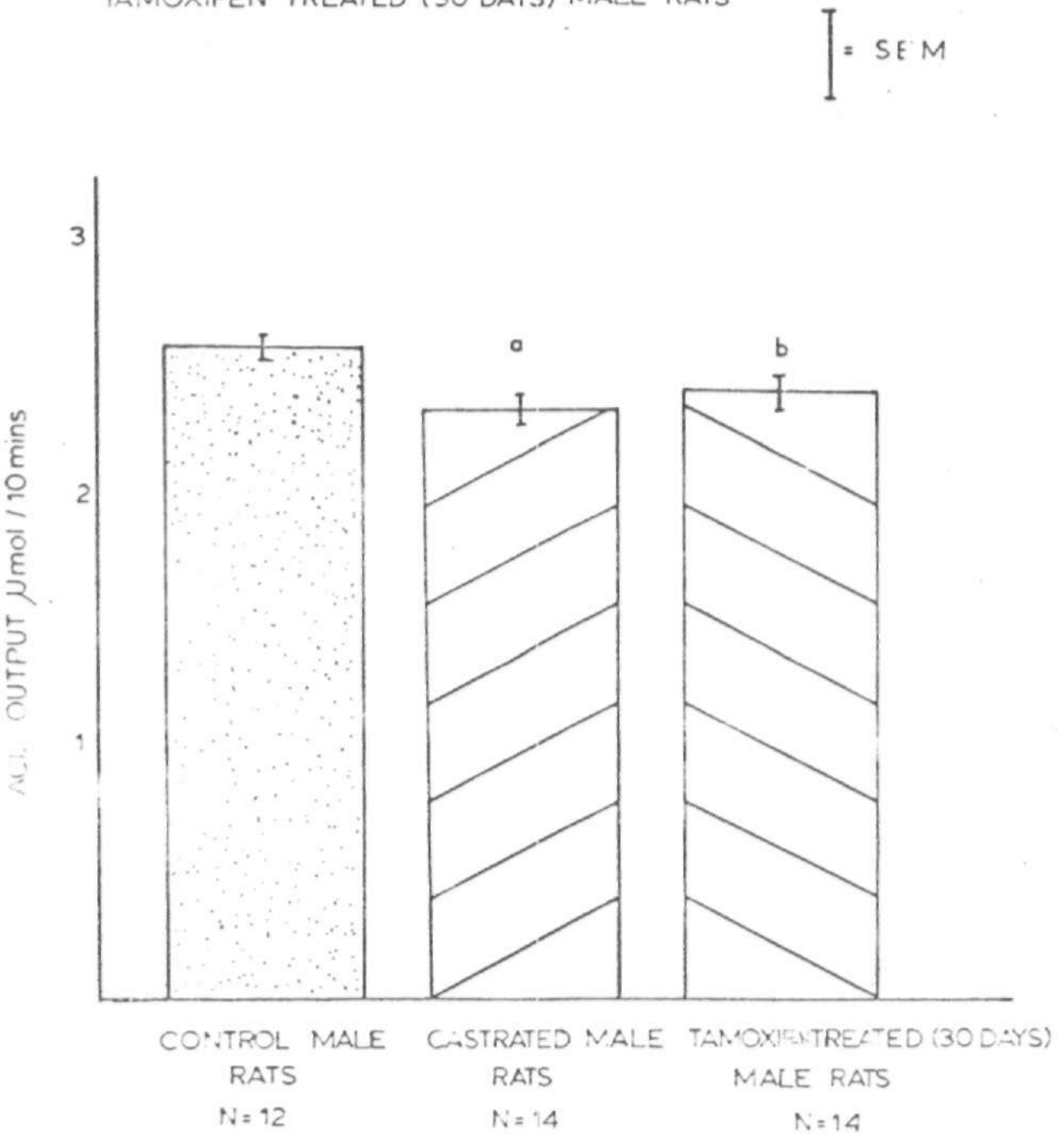


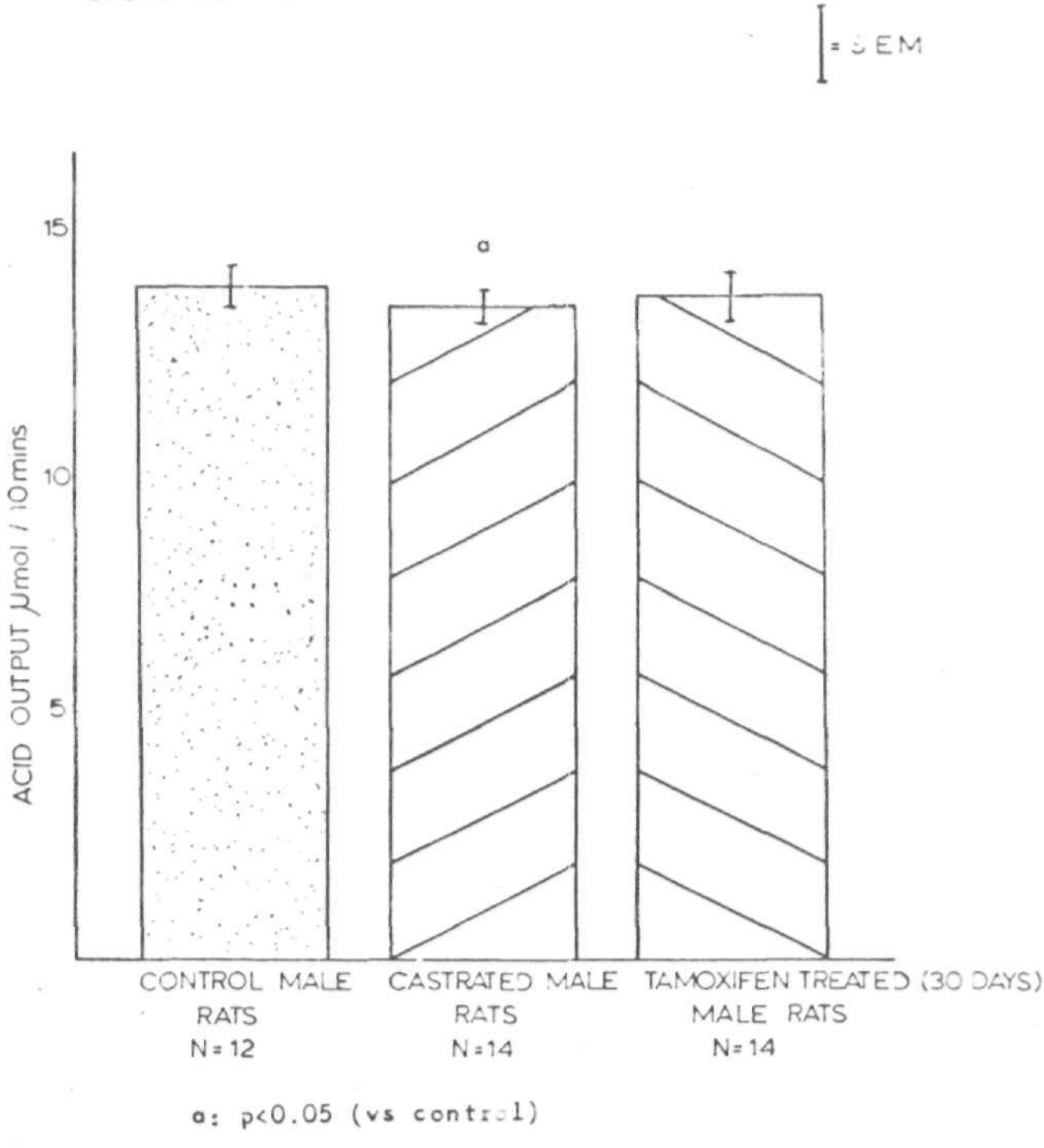
FIG 4 MEAN BASAL ACID OUTPUT IN CONTROL CASTRATED AND TAMOXIFEN TREATED (30 DAYS) MALE RATS



a: $p < 0.001$ (vs control)

b: $p < 0.02$ (vs control)

FIG. 5 MEAN HISTAMINE STIMULATED ACID OUTPUT IN CONTROL CASTRATED AND TAMOXIFEN TREATED (30 DAYS) MALE RATS



a: $p<0.05$ (vs control)

mean histamine- stimulated acid output and that for control male rats ($P > 0.001$).

There was no significant difference between both the mean basal acid output and mean histamine - stimulated acid output for tamoxifen-treated rats and those for the castrated male rats ($P > 0.001$). The results are shown in Figures 4 and 5, and Appendix 1 (Table C).

4.1.4 The effects of sham castration and vehicle (ETHYL OLEATE) administration on basal and histamine-stimulated gastric acid output in male rats

The mean basal acid output obtained in male rats after sham castration was 2.55 ± 0.05 µmol/10min and that obtained in male rats administered Ethyl Oleate was 2.53 ± 0.04 µmol/10minutes. Both means were not significantly different from that for control male rats ($P > 0.001$).

The mean histamine-stimulated acid output in male rats after sham castration was 13.88 ± 0.17 µmol/10min and that in male rats after Ethyl Oleate administration was 13.85 ± 0.14 µmol/10min. There was no significant difference between each of these means and that for control male rats ($P > 0.001$). The results are presented in Table 1a and Appendix 1 (Tables D and E).

4.2.1 The effect of histamine on basal gastric acid output in female (control) rats.

The mean basal acid output was 2.25 ± 0.04 μmol/10min and the mean acid output over 2 hours, following histamine administration was 12.48 ± 0.13 μmol/10min.

Both the mean basal acid output and mean histamine-stimulated acid output were significantly lower ($P < 0.001$) than those for control male rats. The results are shown in Figure 6 and Appendix II (Table A).

4.2.2 The effect of ovariectomy on basal and histamine stimulated gastric acid output in female rats

The mean basal acid output was 2.56 ± 0.06 μmol/10min while the mean histamine-stimulated acid output was 13.27 ± 0.05 μmol/10min.

Both the mean basal acid output and the mean histamine-stimulated acid output for the ovariectomized rats were significantly higher than those for the control female rats ($P < 0.001$). The results are presented in Figures 7 and 8 and Appendix II (Table B).

4.2.3 The effect of tamoxifen administration (30 DAYS) on basal and histamine-stimulated gastric acid output in female rats

The mean basal acid output was 2.45 ± 0.05 μmol/10min and the mean histamine-stimulated acid output was 13.11 ± 0.18 μmol/10min.

FIG. 6: THE EFFECT OF HISTAMINE ON BASAL GASTRIC ACID OUTPUT IN FEMALE (CONTROL) RATS

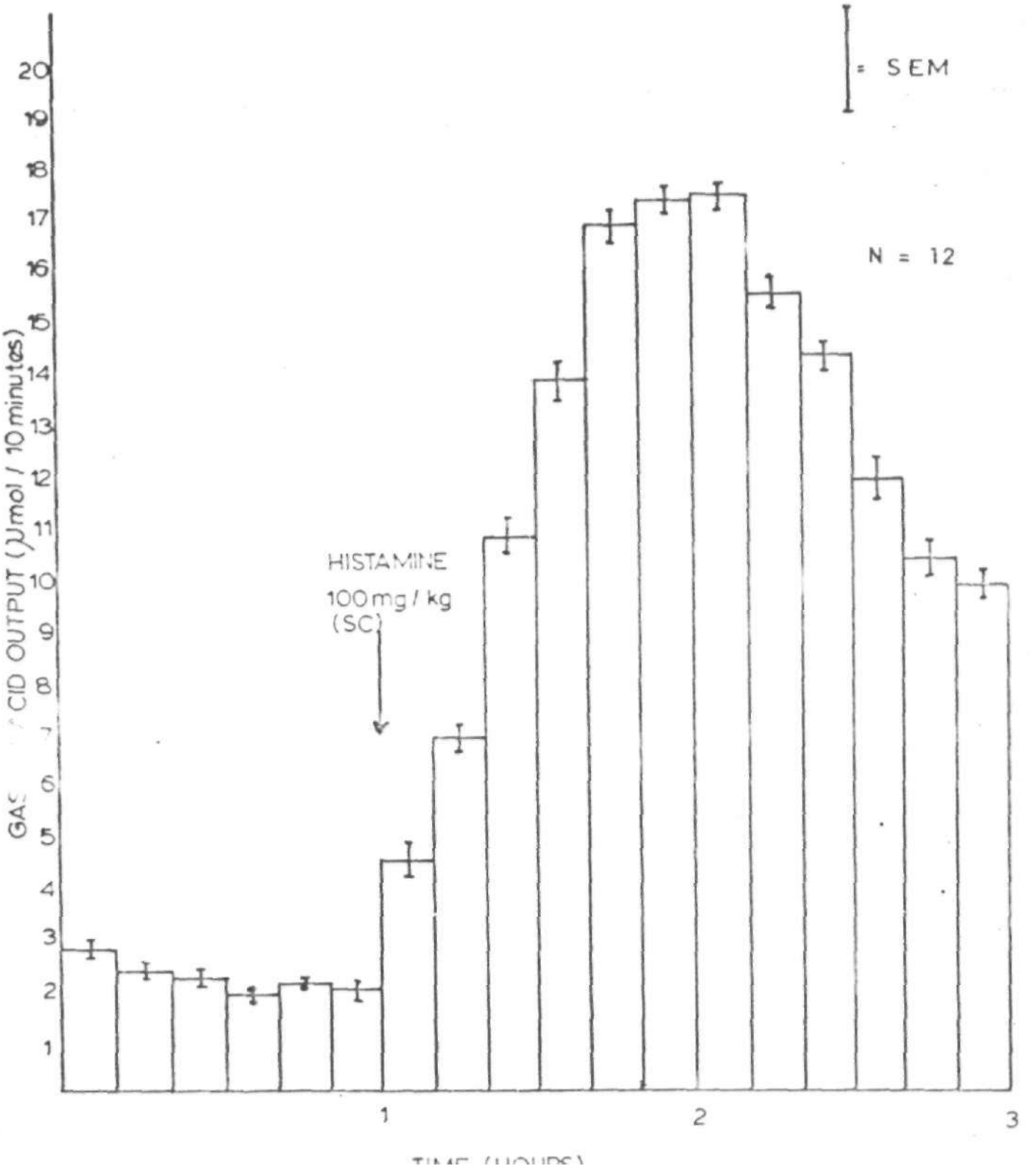
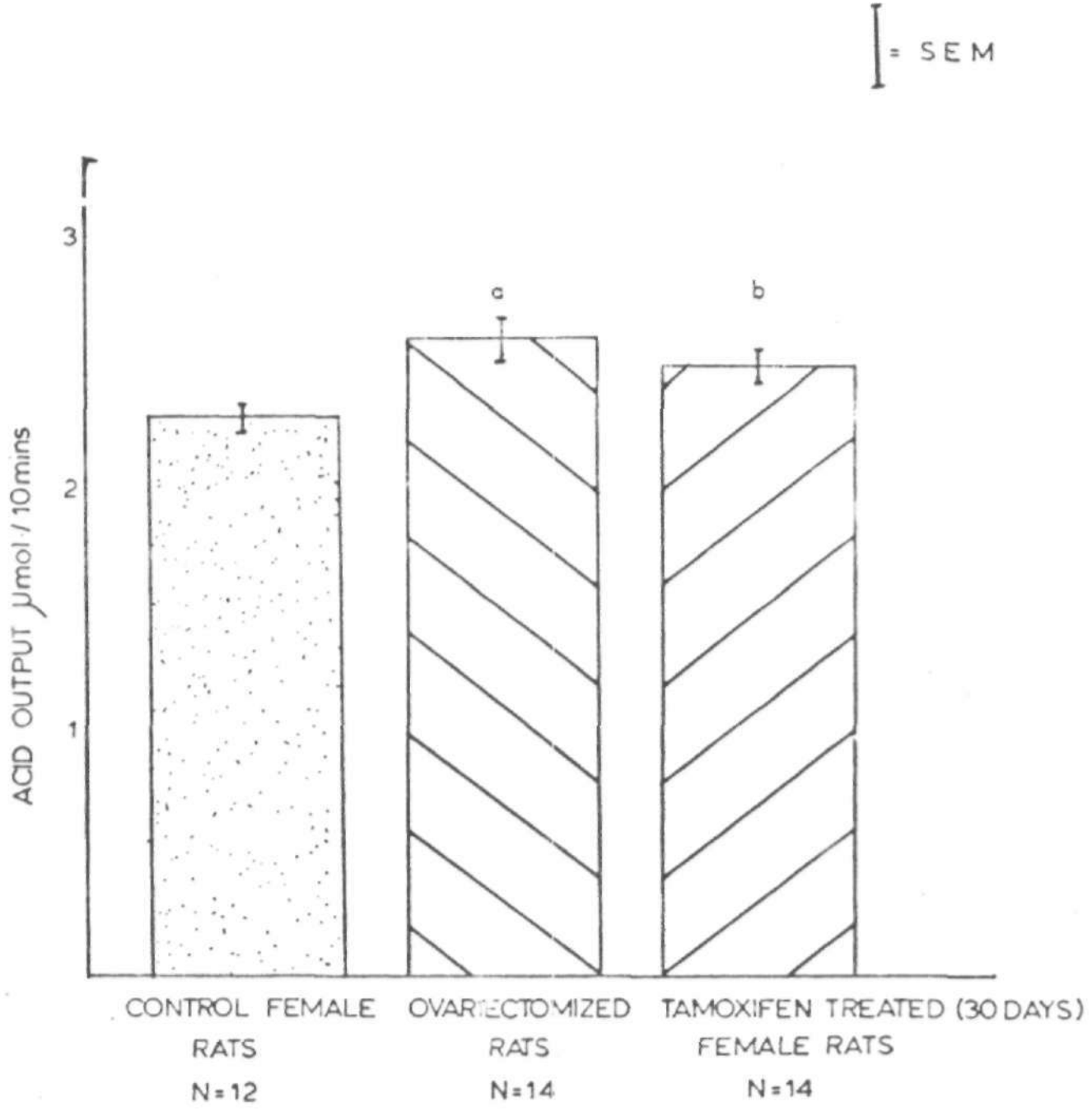


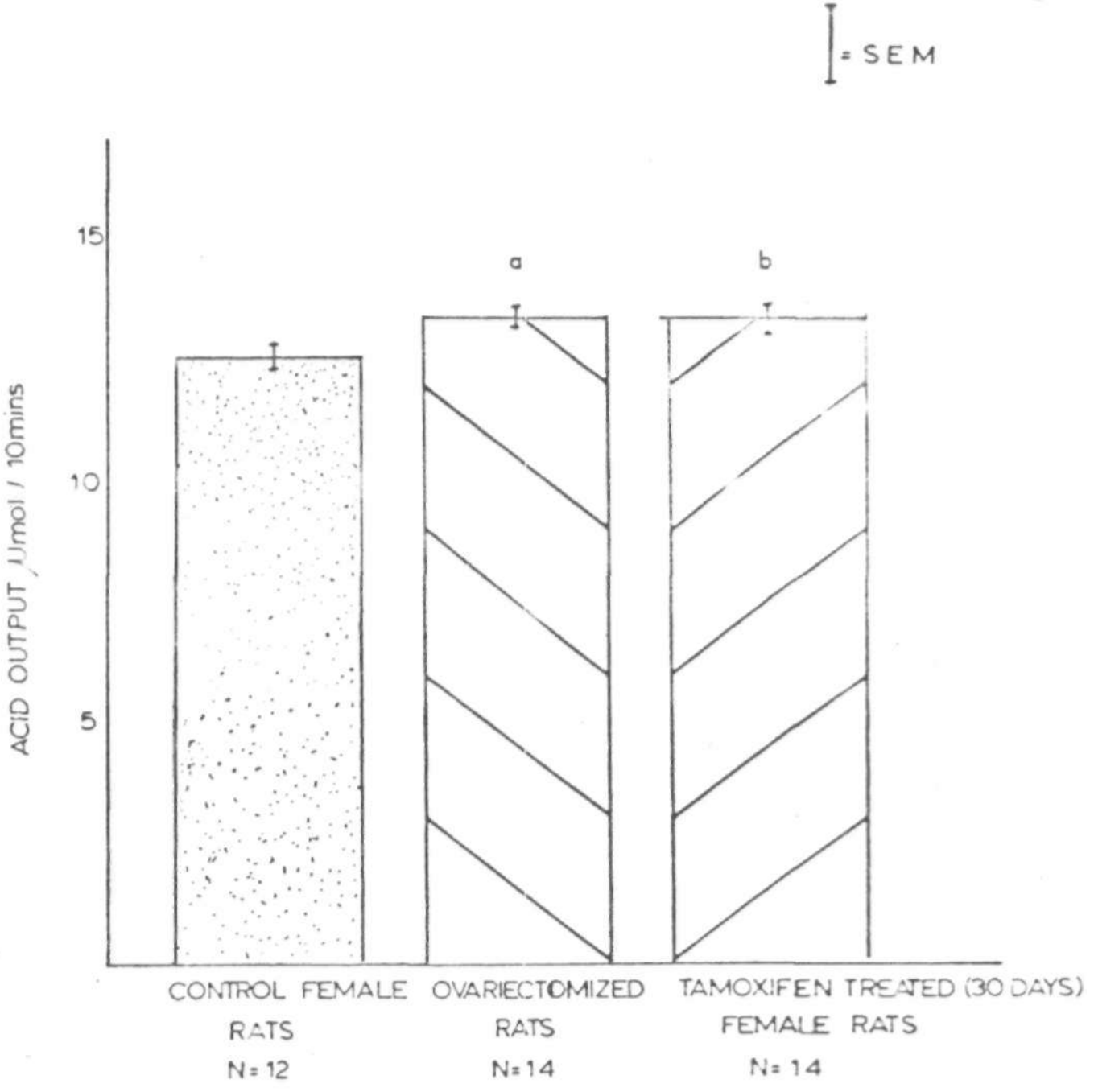
FIG 7 MEAN BASAL ACID OUTPUT IN CONTROL OVARIECTOMIZED AND TAMOXIFEN TREATED (30 DAYS) FEMALE RATS



a: $p<0.001$ (vs control)

b: $p<0.02$ (vs control)

FIG. 8 MEAN HISTAMINE STIMULATED ACID OUTPUT IN CONTROL OVARIECTOMIZED AND TAMOXIFEN TREATED (30 DAYS) FEMALE RATS



a: $p < 0.001$ (vs control)

b: $p < 0.02$ (vs control)

Both the mean basal acid output and the mean histamine-stimulated acid output for tamoxifen-treated female rats were significantly ($P < 0.02$) higher than those for control female rats. There was no significant difference ($P > 0.001$) between both the mean basal acid output and the mean histamine-stimulated acid output for ovariectomized rats and those for tamoxifen-treated female rats.

The results are shown in figures 7 and 8 and Appendix II (Table C).

4.2.4 The effects of sham ovariectomy and Vehicle (ETHYL OLEATE) administration on basal and histamine-stimulated gastric acid output in female rats

The mean basal acid output obtained in female rats after sham ovariectomy was 2.24 ± 0.05 µmol/ 10min and that obtained in female rats administered Ethyl Oleate was 2.27 ± 0.05 µmol/10min. Both means were not significantly different ($P > 0.001$) from that for control female rats.

The mean histamine-stimulated acid output in female rats after sham ovariectomy was 12.42 ± 0.17 µmol/10min. and that in female rats after Ethyl Oleate administration was 12.50 ± 0.15 µmol/10min. There was no significant difference ($P > 0.001$) between each of these means and that for control female rats. The results are presented in Table 1a and 1b and Appendix II (Tables D and E).

Table 1a: The effect of Sham Castration and Vehicle (ethyl oleate) administration on basal and histamine-stimulated acid output in male rats.

Group	Basal acid output (μmol/10 minutes)	Histamine-stimulated acid output (μmol/10 minutes)
Control (12)	2.58 +- 0.03	13.80 +- 0.16
Sham castration (10)	2.55 +- 0.05	13.88 +- 0.17
Vehicle administration (9)	2.53 +- 0.04	13.85 +- 0.14

Table 1b. The effect of Sham Ovariectomy and Vehicle (ethyl oleate) administration on basal and histamine-stimulated acid output in female rats.

Group	Basal acid output (μmol/10 minutes)	Histamine-stimulated acid output (μmol/10 minutes)
Control (12)	2.25 +- 0.04	12.48 +- 0.13
Sham Ovariectomy (10)	2.24 +- 0.05	12.42 +- 0.17
Vehicle administration (9)	2.27 +- 0.05	12.50 +- 0.15

Note: Values are mean + or - standard error of the mean. The number of observations are given in parentheses.

4.3 The effects of tamoxifen administration (5, 10, 15 DAYS) on basal and histamine-stimulated gastric acid output in male rats

The mean basal acid output in male rats after 5 days of tamoxifen administration was 2.52 ± 0.04 μmol/ 10min, and the mean histamine-stimulated acid output for the same rats was 13.78 ± 0.25 μmol/ 10min.

The mean basal acid output in male rats administered tamoxifen for 10 days was 2.51 ± 0.04 μmol/ 10min. The mean histamine - stimulated acid output for the same rats was 13.75 ± 0.22 μmol/ 10min.

The mean basal acid output in male rats after 15 days of tamoxifen administration was 2.46 ± 0.06 μmol/ 10min and the mean histamine-stimulated acid output for this group of rats was 13.72 ± 0.48 μmol/ 10min.

There was no significant difference ($P > 0.001$) between th the mean basal acid output and mean histamine-stimulated ... output f.r each of these groups and those for control male rats. However, both the basal and histamine-stimulated acid outputs were observed to decrease non-significantly, with increase in duration of administration. The results are shown in Table 2a and Appendix III.

4.4 The effects of tamoxifen administration (5, 10, 15 DAYS) on basal and histamine-stimulated gastric acid output in female rats

The mean basal acid output in female rats after 5 days of tamoxifen administration was 2.33 ± 0.07 μmol/ 10min and the mean histamine-stimulated acid output for the same group of rats was 12.78 ± 0.20 μmol/ 10min.

The mean basal acid output in female rats after 10 days of tamoxifen administration was 2.36 ± 0.04 μmol/ 10min and the mean histamine - stimulated acid output for the same rats was 12.83 ± 0.14 μmol/ 10min.

The mean basal acid output in female rats after 15 days of tamoxifen administration was 2.38 ± 0.03 μmol/ 10min and the mean histamine - stimulated acid output for the same group was 12.89 ± 0.15 μmol/ 10min.

There was no significant difference ($P > 0.001$) between both the mean basal acid output and mean histamine-stimulated acid output for each of these groups and those for control female rats. However, non-significant increases in both the mean basal acid output and mean histamine - stimulated acid output were observed with increase in duration of administration. The results are shown in Table 2b and Appendix IV.

4.5 The effects of castration and tamoxifen administration (30 DAYS) on body and stomach weights in male rats

The mean change in body weight of control male rats was 41.7 ± 2.24g. This mean was significantly ($P < 0.01$) greater than that obtained from castrated male rats. The mean change in body weight of castrated male rats was 30.6 ± 2.99g.

Table 2a: The effect of different durations of Tamoxifen administration on basal and histamine-stimulated acid output in male rats.

Duration of administration (Days)	Basal acid output (μmol/10 minutes)	Histamine-stimulated acid output (μmols/10 minutes)
- (Control; 12)	2.58 +- 0.03	13.80 +- 0.16
5 (8)	2.52 +- 0.04	13.78 +- 0.25
10 (8)	2.51 +- 0.08	13.75 +- 0.22
15 (8)	2.46 +- 0.06	13.72 +- 0.48

Table 2b: The effect of different durations of Tamoxifen administration on basal and histamine-stimulated acid output in female rats.

Duration of administration (Days)	Basal acid output (μmol/10 minutes)	Histamine-stimulated acid output (μmols/10 minutes)
- (Control; 12)	2.25 +- 0.04	13.48 +- 0.13
5 (8)	2.33 +- 0.07	12.78 +- 0.14
10 (8)	2.36 +- 0.04	12.83 +- 0.14
15 (8)	2.38 +- 0.03	12.89 +- 0.15

Note: Values are mean + or - standard error of the mean. The number of observations are given in parentheses.

The mean change in body weight for tamoxifen treated male rats was 21.8 ± 3.85g. This value was significantly lower ($P < 0.001$) than that for control male rats, but not significantly different ($P > 0.001$) from the value for castrated male rats.

The mean stomach weights (percentage of body weight) for control male rats was 0.81 ± 0.05%. The mean value for the castrated male rats and the tamoxifen-treated male rats, were 0.74 ± 0.05% and 0.79 ± 0.06% respectively. There was no significant difference ($P > 0.001$) between the mean stomach weight for each of these groups and that for control male rats.

The mean change in body weight for sham castrated male rats (41.6 ± 2.10g) and that for the vehicle administered male rats (42.4 ± 2.39g), were not significantly different ($P > 0.001$) from that for control male rats. Similarly, mean stomach weight (percentage of body weight) for sham castrated male rats (0.80 ± 0.04%) and that for vehicle administered male rats (0.74 ± 0.05%), were not significantly different ($P > 0.001$) from that for control male rats. The results are presented in Table 3a and Appendix V.

4.6 The effects of ovariectomy and tamoxifen administration (30 DAYS) on body and stomach weights in female rats

The mean change in body weight of control female rats was 10.3 ± 1.24g. This mean was significantly less ($P < 0.001$) than that for ovariectomized rats. The mean change in body weight for ovariectomized rats was 38.7 ± 2.44g. The mean change

in body weight for tamoxifen administered female rats was - 1.3 ± 3.08g and this value was significantly less ($P < 0.001$) than those for control female rats and ovariectomized rats.

The mean stomach weight (percentage of body weight) for control female rats was 0.86 ± 0.11%. The mean values for the ovariectomized rats and the tamoxifen treated female rats were 0.83 ± 0.05% and 0.86 + 0.07% respectively. The mean stomach weight for each of these groups was not significantly different ($P > 0.001$) from that for control female rats.

The mean change in body weight for sham ovariectomized rats (9.9 ± 1.14g) and that for the vehicle administered female rats (10.5 ± 0.09g) were not significantly ($P > 0.001$) different from that for control female rats. Similarly, the mean stomach weight (percentage of body weight) for sham ovariectomized rats (0.85 ± 0.13%) and that for the vehicle administered female rats (0.77 ± 0.06%) were not significantly ($P > 0.001$) different from that for control female rats. The results are presented in Table 3b and Appendix VI.

Table 3a: Results of Body weight and Stomach weight studies in male rats.

Group	Change in Body weight (gm)	Weight of Stomach as a percentage of final Body weight (%)
Control (12)	41.7 +- 2.24	0.81 +- 0.05
Castrated (14)	30.6 +- 2.99a	0.74 +- 0.05
Tamoxifen-treated (14)	21.8 +- 3.85a	0.79 +- 0.06
Sham Castrated (10)	41.6 +- 2.10	0.80 +- 0.04
Vehicle administered (9)	42.4 +- 2.39	0.74 +- 0.05

a: P<0.001 vs Control

Table 3b: Results of Body weight and Stomach weight studies in female rats.

Group	Change in Body weight (gm)	Weight of Stomach as a percentage of final Body weight (%)
Control (12)	10.3 +- 1.24	0.86 +- 0.11
Ovariectomized (14)	38.7 +- 2.44a	0.83 +- 0.05
Tamoxifen-treated (14)	-1.3 +- 3.08a,b	0.86 +- 0.07
Sham-Ovariectomized (10)	9.9 +- 1.14	0.85 +- 0.13
Vehicle administered (9)	10.5 +- 0.90	0.77 +- 0.06

a:P < 0.001 vs Control
b:P < 0.001 vs Ovariectomized rats

Note: Values are mean + or - standard error of the mean.
The number of observations are given in parentheses.

CHAPTER FIVE

DISCUSSION

The results of gastric acid secretion studies on normal control rats revealed slight variations between rats. These slight differences in both the basal and histamine-stimulated acid outputs in the different rats may be as a result of individual variations, operative handling, and possibly weight.

The anaesthetic, urethane, which was used in all the experiments has been shown to depress gastric acid secretion (Robert, et al., 1989). The values obtained from the animals in this experiments may therefore be slightly lower than in the conscious animal.

The gastric acid secretory response to histamine in the control rats in this study, (Figs. 3 and 6), confirm the findings of Ghosh and Schild (1953). In most cases, peak acid output was reached after 60 minutes; but recovery of the gastric acid output to its basal level was never over in less than one hour.

A comparison of the effects of orchidectomy and tamoxifen administration on gastric acid secretion in male rats reveals very little difference. Gastric acid output measurements 30 days after bilateral castration in male rats showed that, both the basal and histamine-stimulated gastric acid outputs were significantly reduced below those of control male rats (Figs. 4 and 5). This result is consistent with those of Olowookorun (1975) and Adeniyi (1991). This difference has been attributed

to the stimulatory effect of the male sex hormones on gastric acid secretion. Adeniyi (1991) demonstrated in his work that castrated male rats have decreased parietal cell mass. The effect of the male sex hormones on gastric acid secretion can therefore be attributed to their effect on parietal cell mass. The effect of administration of tamoxifen on the basal acid secretion was a significant reduction below that obtained with control male rats (Fig. 4). This result is similar to that obtained with castrated male rats and reflects an antiandrogenic effect of tamoxifen. Harper and Walpole (1967b) first reported of the antiandrogenic effect of tamoxifen. This fact was later confirmed by [illegible] et al., (1981) who found that tamoxifen inhibits testosterone formation by the Leydig cells. This antiandrogenic property of tamoxifen would therefore most likely be responsible for the dampening of the stimulatory effect of the male sex hormones on gastric acid secretion. This effect of tamoxifen on the basal acid output in male rats may therefore be due to an indirect effect on the parietal cell mass. However, no significant difference was found between stomach weights of tamoxifen-treated male rats and control male rats (Table 3a). The effect of tamoxifen administration on histamine-stimulated acid output in male rats was not significantly different from the results obtained with control male rats (Fig 5). This result may be due to an effect of tamoxifen on the action of histamine. Tamoxifen has been shown to potentiate the effects of histamine by possibly regulating the histamine receptors (Anuka, 1991). It

appears that the inhibitory effect of tamoxifen on parietal cell number and function in male rats may probably just be nullified by its effect on histamine.

The effect of ovariectomy on basal and histamine-stimulated gastric acid secretion was not different from the effect of tamoxifen administration on basal and histamine-stimulated gastric acid secretion. Gastric acid output estimation 30 days after ovariectomy showed significant increases in both the basal acid output and the histamine-stimulated acid output above those for control female rats (Fig 7). This result confirms earlier findings by Amure and Omole (1970) and more recently, Adeniyi (1991). This increase in basal acid output observed in ovariectomized animals is caused by an absence of the inhibitory effect of oestrogen on gastric secretory activity. This effect of oestrogen on gastric acid secretion has also been demonstrated with castrated male rats administered oestrogen for long durations (Amure and Omole, 1970). Adeniyi (1991) has contended that this effect of oestrogen may be due to its inhibitory effect on parietal cell function and number. Therefore, it seems likely that the significantly higher acid output observed in ovariectomized animals is as a result of an increase in the parietal cell mass. Ovariectomy was also found to cause an increase in the histamine -stimulated acid output above that of control female rats (Fig 7). An increase in the parietal cell mass would lead to an increase in the acid output following histamine administration. Oestrogen has been shown to

reduce the sensitivity of tissues to histamine, possibly by regulating the histamine receptor availability (Csakvari et al, 1981; Anuka, 1991). This suggests that ovariectomy would help potentiate the effects of histamine, thus causing a higher histamine-stimulated acid output than in control female rats.

The studies on the effect of tamoxifen administration on basal and histamine-stimulated gastric acid secretion showed that both results were significantly higher than for control female rats (Figs. 6 and 7). This findings was not different from that obtained with ovariectomized rats. However, the increase in basal and histamine-stimulated acid output for tamoxifen treated female rats was not as significant as that for ovariectomized rats. Tamoxifen is known to be an antagonist of oestrogen in the rat. Therefore, the result obtained indicates that the drug caused an increase in gastric acid secretion by antagonizing the inhibitory effect of oestrogen on gastric secretory activity. Like oestrogen, tamoxifen is believed to act by binding with the oestrogen receptor before being translocated into the nucleus. However, no oestrogen receptors have been located on the parietal cells of the stomach (Winborn, Sheridan and McGill, 1987), and so it seems unlikely that either oestrogen or tamoxifen acts directly on the stomach to affect gastric acid secretion. It is possible though, that oestrogen might act via its receptors located outside the gastro-intestinal tract to influence yet unidentified agents which may directly affect parietal cell activity.

The results of the comparisons between the effects of gonadectomy and tamoxifen administration on gastric acid secretion show that the effects seen with tamoxifen-treated male rats were not as significantly different from the control as those seen with castrated male rats. Similarly, the results obtained with tamoxifen treated female rats were not as significantly higher than the control as those obtained with ovariectomized rats. This suggests that tamoxifen administration to females in place of ovariectomy would not place them greater risk of peptic ulceration. Also, tamoxifen administration to males would probably help reduce their susceptibility to peptic ulceration.

Studies on the effects of different durations of tamoxifen administration on basal acid secretion in male rats gave results which were not significantly different from those for control male rats (Table 2a). There was, however, decrease in basal acid output with increase in duration of administration. The histamine-stimulated acid secretion for each duration of tamoxifen administration, was not significantly different from the control value and a decrease was observed as the duration of administration increased. These results appear to be caused by a steady rise in the plasma tamoxifen concentration. Nicholson and Griffiths (1980) stated that on continued daily administration, basal plasma tamoxifen concentration rises steadily within the first 40 days of treatment. Such an increase in plasma concentration of tamoxifen would enhance its effects

hence the results observed in these experiments.

The effects of different durations of tamoxifen administration on basal and histamine-stimulated acid secretion in female rats are shown in Table 2b. The acid output for all durations of tamoxifen administration in this group were not significantly different from those of control female rats. There was however, increase in both acid outputs with increase in duration of administration. This result also suggests a gradual increase in the plasma concentration of tamoxifen with continued administration.

The results of the studies on the effects of castration on body and stomach weights in male rats are shown in Table 3a. Castrated male rats had significantly lower body weights than control male rats, 30 days after surgery. This may be due to the effect of castration on protein anabolism which is vital to growth. No significant difference was observed between stomach weight of castrated male rats and those of control animals. This implies that the growth of the stomach is not directly affected by the male sex hormones. This is, however, contrary to the findings of Adeniyi (1991), who reported that castrated male rats had significantly lower stomach weights than normal male rats.

Daily administration of tamoxifen to male rats resulted in significantly lower body weights than control male rats. This effect may be attributed to the antiandrogenic property of tamoxifen in the male rat. It is possible that tamoxifen

inhibits protein anabolism in the male rat thereby inducing the observed decrease in weight gain. There was no significant difference between the stomach weights for tamoxifen treated male rats and those for control male rats (Table 3a). This absence of any change in stomach weight in male rats treated with tamoxifen, further suggests that androgens may not have direct effects on the stomach as such. It is also likely that an inhibitory effect of tamoxifen on the parietal cell mass may not be sufficient to significantly alter stomach weight.

The effects of ovariectomy on body and stomach weight are shown in Table 3b. Ovariectomized female rats had significantly greater body weights than control female rats. This result is in agreement with earlier reports (Wade, 1976; Mueller and Hsiao, 1980). Oestrogens are known to decrease body weight and this has been reported to result indirectly from oestrogenic modulation of food intake (Wade, 1976). The increase in body weight after ovariectomy has been shown to be accompanied by an increase in food intake. However, there are suggestions that the increase in body weight in ovariectomized animals is largely independent of the increase in food intake (Mueller and Hsiao, 1980). Mueller and Hsiao (1980) have proposed that oestrogens may alter metabolic processes by action on peripheral tissues or by action on brain areas regulating metabolic processes. Such mechanisms would allow for increase in body weight after ovariectomy without alterations in food intake.

The mean body weight of female rats administered tamoxifen

was significantly less than those for control female rats (Table 3b). Tamoxifen did not antagonize the response to oestrogen in terms of body weight but rather induced a non-significant loss of body weight in female rats. This result could be attributed to an inhibition of food intake. This argument is supported by the report of Bowman et al (1983), in which they stated that tamoxifen acts as an oestrogen agonist in terms of regulation of body weight and food intake. They suggested that the mechanism by which tamoxifen inhibits food intake and growth may be by modulation via the oestrogen receptor system of the hypothalamus.

The stomach weights of ovariectomized and tamoxifen-treated female rats were not significantly different from those of control female rats. (Table 3b). These findings suggest that the stomach is not directly affected in terms of weight by the sex hormones and also by their antagonists. This is more so given the absence of sex hormone receptors in most parts of the stomach.

The effects of sham gonadectomy on gastric acid secretion and weight in both male and female rats, were not significantly different from those of control male and female rats (Tables 1a, 1b, 3a and 3b). This indicates that the animals all recovered from the operational shock and the other effects of surgery before the gastric acid secretion and weight measurements were carried out.

This also implies that the results obtained with gonadectomy were certainly due to alterations in the sex hormone levels.

The results of vehicle (Ethyl Oleate) administration on gastric acid secretion and weight in male and female rats were not significantly different from those of control rats (Table 1a and 1b). This confirms the inert nature of the vehicle and proves that all the differences observed between control and tamoxifen-administered rats were not due to the vehicle used.

CONCLUSIONS

Based on the analysis of the results obtained in this study, the following conclusions have been drawn:

1. There is no difference between the effects of ovariectomy and tamoxifen-treatment on gastric acid secretion in female rats. Similarly, the effect of castration on gastric acid secretion is not significantly different from that of tamoxifen treatment in male rats.

2. Long-term administration of tamoxifen increases gastric acid secretion levels in female rats, while long-term administration of tamoxifen in male rats decreases gastric acid secretion levels.

3. Gastric acid secretion in male rats decreases in response to increase in the duration of tamoxifen administration. Increase in the duration of tamoxifen treatment in female rats causes an increase in gastric acid secretion.

4. Castration of male rats causes a decrease in weight gain when compared with control rats. Long-term administration of tamoxifen in male rats causes a decrease in weight gain. Castration and tamoxifen treatment in male rats have no effect on stomach weight.

5. Ovariectomy causes an increase in weight gain in female rats when compared with control. Long-term tamoxifen administration decreases weight gain in female rats. Ovariectomized and tamoxifen-treated female rats do not have different stomach weight values compared with control female rats.

6. Finally, tamoxifen treatment may therefore not increase the susceptibility of either males or females to peptic ulcer disease above the levels expected following castration or ovariectomy.

SUMMARY

1. One hundred and sixty six male and female albino rats were employed to study the effect of tamoxifen on gastric acid secretion and to compare the results obtained with the effects of gonadectomy on gastric acid secretion.

2. The effects of different durations (5, 10 and 15 days) of tamoxifen administration on basal and histamine-stimulated acid output were studied in male and female rats.

3. The effects of tamoxifen administration and gonadectomy on body and stomach weights were also studied in male and female rats.

4. Gastric acid secretion was estimated by a continuous perfusion method with the effluent assayed for titrable acid after 10 minutes intervals.

5. Basal gastric acid output over 1 hour and histamine-stimulated gastric acid output over 2 hours were determined for all the rats used.

6. Computed results show that the basal and histamine-stimulated acid outputs in castrated male rats were less than acid output values for control male rats, but were not

different from acid output values for tamoxifen treated male rats.

7. The basal and histamine-stimulated acid outputs in ovariectomized rats were greater than the acid output values for control female rats; but these were not different from acid output values for tamoxifen-treated female rats.

8. The results of gastric acid secretion studies showed that tamoxifen-treated male rats had lower basal and histamine-stimulated acid outputs than control male rats, and tamoxifen-treated female rats had higher basal and histamine-stimulated acid outputs than control female rats.

9. The magnitude of the effects of tamoxifen administration on gastric acid secretion in male and female rats was observed to increase in response to increase in the duration of administration.

10. The results of the body weight studies showed that castrated and tamoxifen-treated male rats both gained less weight than control male rats.

11. The control female rats gained less weight than ovariectomized rats, but gained more weight than the

tamoxifen-treated female rats.

12. It was suggested that the effect of oestrogen on gastric acid secretion may be mediated by receptors located outside the gastrointestinal tract.

13. It was concluded that the susceptibility of males or females to peptic ulceration is not greater following tamoxifen administration than it is after castration or ovariectomy.

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APPENDIX I

Tables of Results for Gastric Acid Output studies in male rats (Control, Castrated, Tamoxifen-treated, Sham-castrated, and Vehicle-administered).

Table A: The effect of Histamine on basal gastric acid output in male (Control) rats.

	EXPT I	EXPT II	EXPT III	EXPT IV	EXPT V	EXPT VI	EXPT VII	EXPT VIII	EXPT IX
1	3.00	3.50	2.50	3.00	3.00	4.00	3.00	2.00	3.00
2	2.50	3.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00
3	2.50	2.00	3.00	2.50	2.50	3.00	2.00	2.50	3.00
4	2.50	2.00	2.50	2.50	2.50	2.50	2.00	3.50	2.50
5	2.00	2.50	2.00	2.50	2.00	2.00	3.50	2.00	2.50
6	2.50	2.50	2.50	3.00	2.00	2.00	3.50	2.00	2.50
MEAN +- SEM	2.50+-0.12	2.58+-0.22	2.58+-0.14	2.50+-0.14	2.50+-0.17	2.75+-0.28	2.67+-0.28	2.50+-0.24	2.75+-0.10
HISTAMINE									
1	6.50	5.00	6.50	5.00	7.50	6.00	5.50	6.50	4.50
2	7.00	7.00	8.00	7.00	8.00	8.00	7.50	8.00	8.00
3	12.00	11.00	12.50	12.50	13.50	10.50	11.00	11.50	10.50
4	12.50	13.00	13.00	12.00	13.00	12.00	12.00	13.00	14.00
5	15.50	14.00	15.50	13.50	16.50	13.00	14.50	15.00	14.50
6	16.00	16.00	16.50	15.00	17.50	16.00	15.50	17.00	16.50
7	19.50	17.50	20.00	18.00	20.00	18.00	19.00	19.00	19.00
8	17.50	18.00	18.00	17.00	18.50	17.50	17.00	18.50	20.00
9	16.50	15.00	16.50	15.50	17.50	15.00	15.50	16.50	16.50
10	14.50	14.50	16.50	14.00	17.00	15.00	14.00	15.50	15.00
11	16.00	15.00	14.50	15.00	15.50	14.00	15.50	15.50	14.00
12	12.00	12.00	13.50	13.00	14.00	12.00	12.00	13.00	12.50
MEAN +- SEM	13.79+-1.10	13.17+-1.09	14.25+-1.08	13.12+-1.05	14.88+-1.08	13.08+-1.00	13.25+-1.07	14.08+-1.07	13.75+-1.22

Note: All values are in micro Mol./10 minutes.

Table A: (continued)

EXPT X	EXPT XI	EXPT XII	Mean +- S.E.M.
2.50	2.50	2.50	2.88+-0.15
2.50	3.00	2.50	2.71+-0.11
2.50	2.50	2.50	2.54+-0.09
2.50	3.00	2.00	2.50+-0.12
2.50	3.00	2.50	2.42+-0.13
2.00	2.00	3.00	2.46+-0.14
2.42+-0.08	2.67+-0.15	2.50+-0.12	
5.50	6.00	7.50	6.00+-0.26
9.00	9.50	8.00	7.92+-0.21
11.50	13.00	12.50	11.33+-0.27
13.00	13.50	13.00	12.83+-0.17
14.50	16.00	15.00	14.79+-0.28
17.00	17.50	16.50	16.42+-0.21
20.50	20.00	20.00	19.21+-0.27
18.50	19.00	17.00	18.04+-0.25
15.50	17.50	16.50	16.17+-0.24
16.50	16.50	16.00	15.42+-0.29
14.00	15.00	14.50	14.88+-0.19
10.00	11.50	9.50	12.08+-0.36
13.79+-1.18	14.58+-1.13	13.83+-1.07	

Table 8: The effect of castration on basal and histamine-stimulated gastric acid output in male rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT.
	2.00	3.00	2.00	3.00	3.00	2.50	2.00	3.50	2.5
	2.50	2.50	2.00	3.00	2.50	2.00	3.00	2.00	2.5
	3.50	3.00	3.00	2.00	2.50	2.00	2.50	2.50	2.0
	2.50	2.00	3.00	2.00	3.00	2.00	2.50	2.50	1.5
	2.00	1.50	2.00	2.00	2.50	2.00	2.50	2.00	2.5
	2.00	1.50	1.00	2.50	2.50	1.50	3.00	2.00	1.5
MEAN+-S.E.M.	2.42+-0.22	2.25+-0.26	2.17+-0.28	2.42+-0.18	2.67+-0.10	2.00+-0.12	2.58+-0.14	2.42+-0.22	2.08+-
HISTAMINE									
	4.50	3.50	4.50	5.50	5.00	3.50	7.50	6.50	3.0
	7.00	6.00	6.00	8.00	7.00	7.50	8.00	7.00	7.5
	13.00	12.00	10.00	14.00	10.00	10.50	10.50	9.50	12.0
	17.00	16.00	15.00	18.00	12.50	14.00	13.00	12.50	14.5
	18.00	17.50	16.50	19.50	14.50	19.50	15.50	14.00	17.0
	19.50	18.00	18.00	20.00	17.00	16.50	17.00	16.00	19.0
	16.50	15.50	18.00	17.50	19.00	18.00	19.00	18.00	20.5
	16.00	15.00	16.00	17.00	20.00	17.00	17.00	17.00	17.0
	15.00	11.00	14.50	13.00	19.00	16.50	16.00	14.00	16.0
	12.00	14.00	14.00	16.00	16.00	13.50	14.50	13.50	14.5
	12.00	11.00	12.00	13.50	12.00	11.00	12.00	12.00	12.0
	10.00	9.00	10.00	10.50	10.00	10.00	10.00	10.00	12.0
MEAN+-S.E.M.	13.38+-1.25	12.37+-1.30	12.89+-1.23	14.38+-1.26	13.50+-1.36	13.12+-1.32	13.33+-1.04	12.50+-1.02	13.75+-

Note: All values are in micro Mol./10 minutes.

Table B: (continued)

EXPT. X	EXPT. XI	EXPT. XII	EXPT. XIII	EXPT. XIV
2.00	3.00	2.00	2.00	2.50
2.50	2.00	2.00	2.50	2.50
2.50	2.50	3.00	2.00	2.50
2.50	2.50	3.00	2.00	2.50
2.00	2.50	2.00	2.50	2.00
2.50	3.00	2.00	1.50	2.00
2.33+-0.10	2.58+-0.14	2.33+-0.19	2.08+-0.14	2.33+-0.10
6.00	4.00	4.00	3.50	4.50
11.00	7.50	8.00	6.00	5.50
14.00	11.00	14.50	10.50	11.00
15.50	14.00	15.00	13.00	13.00
18.00	16.50	16.00	17.00	14.50
17.00	18.00	17.50	18.00	17.50
16.50	17.00	19.00	18.50	16.00
15.00	19.00	16.50	14.00	19.50
15.00	17.00	15.00	16.50	18.00
14.00	15.50	12.50	15.50	16.00
11.50	12.50	12.00	11.00	12.50
9.50	11.50	12.00	10.00	9.00
13.58+-0.96	13.60+-1.26	13.50+-1.16	13.46+-1.44	13.10+-1.33

Table C: The effect of Tamoxifen administration (30 DAYS) on basal and histamine-stimulated gastric acid output in rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT
	3.00	2.50	2.00	3.00	2.50	3.00	2.50	2.00	2.
	4.00	2.00	1.50	2.00	2.00	2.50	3.50	2.00	3.
	2.50	2.50	2.50	3.00	2.50	2.50	2.50	2.50	3.
	2.00	2.50	2.50	2.50	2.00	2.50	2.50	2.50	2.
	2.00	2.50	2.00	2.50	2.50	2.00	2.00	3.00	2.
	2.00	2.50	2.50	2.00	2.50	2.00	2.00	2.00	2.
MEAN+-S.E.M.	2.58+-0.30	2.42+-0.08	2.17+-0.15	2.50+-0.17	2.33+-0.10	2.50+-0.12	2.50+-0.20	2.33+-0.15	2.67+
HISTAMINE									
	4.50	4.00	3.50	7.50	6.00	5.00	3.00	5.50	4.
	8.50	9.00	10.00	10.00	12.00	10.00	5.50	7.00	6.
	11.00	13.50	12.00	12.50	13.50	13.00	10.00	11.50	8.
	15.50	15.50	19.00	13.00	14.00	16.00	13.00	12.50	12.
	16.50	17.00	20.00	13.00	16.50	16.50	16.50	13.00	13.
	18.00	16.00	19.50	14.50	18.00	17.00	18.00	15.00	14.
	20.50	19.00	21.00	15.00	16.50	18.50	19.50	15.50	17.
	18.00	21.00	19.00	16.50	14.50	17.50	17.00	18.00	20.
	17.00	17.00	14.00	14.00	14.00	15.00	15.00	17.50	18.
	15.00	13.50	12.00	13.00	13.50	13.50	14.00	15.50	19.
	14.50	13.00	10.00	12.50	13.50	12.50	13.00	14.00	12.
	12.00	11.00	7.50	10.50	10.00	10.50	11.00	12.50	14.
MEAN+-S.E.M	14.25+-1.25	14.13+-1.28	13.88+-1.58	12.67+-0.67	13.50+-0.88	13.75+-1.07	12.95+-1.37	13.13+-1.05	13.29+

Note: All values are in micro Mol./10 minutes

Table C: (continued)

EXPT. X	EXPT. XI	EXPT. XII	EPT. XIII	EXPT. XIV
2.00	2.50	2.00	2.50	2.00
2.00	2.50	2.00	2.50	3.00
2.50	2.00	2.00	3.00	3.00
2.50	2.50	2.00	3.00	2.00
2.00	2.50	2.00	3.00	2.00
2.00	2.50	2.50	2.50	2.50
2.17+-0.11	2.42+-0.08	2.08+-0.08	2.75+-0.10	2.42+-0.18
6.00	7.00	5.00	5.50	6.00
11.00	12.50	10.50	7.50	10.00
15.00	15.50	13.00	13.00	12.00
16.00	16.50	14.00	16.00	13.50
16.50	18.00	16.50	17.00	15.00
17.50	18.00	16.50	18.00	16.50
18.00	22.00	20.00	18.00	13.50
21.00	18.50	17.00	16.50	13.00
17.00	18.50	16.00	14.00	11.00
14.00	15.00	13.50	13.00	10.50
13.00	13.50	11.50	12.50	10.00
11.00	11.50	9.50	11.50	8.00
14.66+-1.10	15.54+-1.10	13.58+-1.12	13.54+-1.10	11.57+-0.12

Table D: The effect of sham castration on basal and histamine-stimulated gastric acid output in male rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT
1	2.50	2.50	3.00	3.00	2.50	3.50	2.00	2.50	3.
2	2.50	2.50	2.50	3.00	2.50	2.50	2.50	3.00	3.
3	3.00	2.50	3.00	3.00	2.50	2.50	2.00	3.00	2.
4	2.00	2.50	2.50	2.00	2.00	2.00	2.50	3.00	2.
5	2.50	2.00	2.50	3.00	2.50	2.00	2.50	2.00	3.
6	2.50	2.50	2.50	2.00	2.00	2.50	2.50	2.50	2.
MEAN+-S.E.M.	2.50+-0.12	2.42+-0.08	2.67+-0.10	2.83+-0.15	2.33+-0.10	2.50+-0.20	2.33+-0.10	2.67+-0.15	2.75
HISTAMINE									
1	5.50	6.50	5.50	6.00	4.00	6.00	5.00	6.50	6.
2	8.00	8.00	11.00	8.50	6.50	7.50	6.50	8.00	8.
3	11.50	13.00	13.00	12.00	8.50	11.00	11.00	11.50	12.
4	13.00	13.50	14.00	13.50	13.50	13.50	13.50	12.00	13.
5	14.50	15.50	15.50	15.50	14.00	14.50	15.00	14.50	17.
6	16.00	17.00	17.00	17.00	15.00	16.00	18.50	16.50	19.
7	19.50	20.00	19.50	18.50	19.00	19.00	18.00	21.00	20.
8	17.00	18.50	17.00	17.50	22.00	18.00	19.00	18.00	21.
9	15.50	16.50	16.00	15.50	23.50	17.50	16.50	16.50	19.
10	15.00	16.00	15.50	14.00	18.00	16.50	14.00	16.50	18.
11	14.50	16.00	13.50	13.00	12.00	14.00	14.00	15.00	15.
12	12.00	13.00	12.00	11.50	9.50	12.00	10.00	12.50	11.
MEAN+-S.E.M.	13.50+-1.07	14.46+-1.10	14.13+-1.00	13.46+-1.03	13.79+-1.68	13.80+-1.13	13.41+-1.26	14.04+-1.15	15.08

All values are in micro Mol/10 minutes

Table D: (continued)

EXPT. X
2.50
3.00
2.00
3.00
2.50
2.00
2.50+-0.17
3.50
6.50
10.00
11.50
15.00
17.50
18.00
19.50
16.50
16.50
12.50
10.50
13.12+-1.36

Table E: The effect of vehicle (ETHYL OLEATE) administration on basal and histamine-stimulated gastric acid output in male rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT.
1	2.50	2.50	3.00	2.50	2.50	3.50	2.00	3.00	3.00
2	2.50	3.00	3.00	2.50	2.50	2.50	2.50	2.50	3.00
3	3.00	2.50	2.50	3.00	2.50	2.00	2.50	3.00	3.00
4	2.00	2.50	2.50	2.50	2.50	2.00	2.00	2.50	3.00
5	2.50	2.50	2.50	3.00	2.50	2.50	2.50	2.00	2.00
6	2.50	2.50	2.00	3.00	2.00	1.50	3.00	2.50	2.00
MEAN+-S.E.M.	2.50+-0.12	2.58+-0.08	2.50+-0.14	2.75+-0.10	2.42+-0.08	2.33+-0.26	2.42+-0.14	2.58+-0.14	2.67+-0
HISTAMINE									
1	5.00	6.00	4.50	6.50	4.50	4.00	6.50	6.00	4.50
2	8.00	9.00	7.00	7.50	8.00	10.00	8.00	9.50	6.00
3	10.50	11.00	11.00	9.00	13.00	14.00	12.50	13.00	10.00
4	12.00	13.50	13.00	14.00	13.50	15.00	13.50	14.50	14.00
5	13.50	14.50	16.50	15.50	15.00	15.50	14.00	15.00	16.50
6	16.50	17.00	15.00	16.50	18.00	16.50	16.00	16.50	17.50
7	18.00	19.00	18.50	19.00	19.00	19.00	18.50	19.50	18.00
8	18.50	20.00	19.50	17.00	16.50	17.50	18.50	18.50	20.00
9	15.00	16.00	19.50	16.50	15.00	16.00	16.00	17.00	18.50
10	14.50	15.50	17.50	15.50	13.00	15.00	16.00	15.50	15.00
11	14.00	15.00	15.00	15.00	12.50	13.50	15.50	16.00	13.00
12	11.50	12.50	10.00	12.00	12.00	12.50	13.50	13.50	11.50
MEAN+-S.E.M.	13.08+-1.10	14.08+-1.11	14.17+-1.40	13.67+-1.11	13.33+-1.12	14.04+-1.09	14.00+-1.02	14.54+-1.04	13.71+-1

All values are in micro Mol./10 minutes

APPENDIX II

Tables of Results for Gastric Acid Output studies in female rats (Control, Ovariectomized, tamoxifen-treated, sham-castrated, and vehicle-administered)

Table 8: The effect of histamine on basal gastric acid output in female (control) rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT.
1	3.00	2.50	3.00	2.00	3.00	3.00	3.00	3.00	4.0
2	2.50	2.50	2.00	2.00	3.00	2.00	3.00	3.00	2.0
3	2.00	2.50	2.00	2.00	3.00	3.00	2.50	2.50	2.0
4	2.00	2.00	2.00	1.50	2.00	2.00	2.00	2.50	1.5
5	2.00	2.00	2.00	2.00	2.50	2.00	1.50	2.00	2.0
6	2.00	2.00	1.50	2.50	2.00	2.00	1.50	1.50	2.0
MEAN+-S.E.M.	2.25+-0.16	2.25+-0.10	2.08+-0.18	2.00+-0.12	2.58+-0.18	2.33+-0.19	2.25+-0.26	2.42+-0.41	2.25+-
HISTAMINE									
1	5.00	4.50	4.00	3.00	5.00	6.00	6.50	3.50	3.5
2	6.00	6.50	6.00	7.00	7.00	7.50	7.50	6.50	5.5
3	11.00	10.00	10.00	10.00	11.50	11.50	12.50	10.50	9.0
4	14.50	15.00	14.50	15.50	13.00	13.00	14.00	12.00	14.0
5	17.00	16.50	16.00	16.00	17.50	16.50	18.00	16.00	16.5
6	17.50	17.50	17.50	18.50	17.00	17.00	18.50	16.50	17.0
7	17.50	17.00	16.50	16.50	18.00	17.50	19.00	17.00	17.5
8	15.00	15.50	15.00	16.00	15.50	16.00	16.50	14.50	15.5
9	15.00	14.00	14.00	14.00	14.00	15.00	15.00	13.00	15.0
10	12.00	12.50	12.00	13.00	11.00	11.50	12.00	10.00	13.5
11	10.50	10.00	9.50	10.50	10.00	10.50	11.00	9.00	11.0
12	10.00	10.00	10.00	11.00	9.50	10.50	10.50	8.50	10.0
MEAN+-S.E.M.	12.58+-1.17	12.42+-1.17	12.08+-1.18	12.33+-1.24	12.40+-1.15	12.70+-1.04	13.42+-1.15	11.40+-1.16	12.33+-

Note: All values are in micro Mol./10 minutes.

Table A: (continued)

EXPT. X	EXPT. XI	EXPT. XII	MEAN+-S.E.M.
2.00	3.00	2.00	2.79+-0.16
2.50	2.00	2.00	2.38+-0.12
2.00	2.00	1.50	2.25+-0.13
2.00	2.00	1.50	1.92+-0.08
2.00	2.50	3.00	2.13+-0.10
2.00	2.00	3.50	2.04+-0.15
2.08+-0.08	**2.25+-0.16**	**2.25+-0.31**	
4.00	5.50	4.00	4.54+-0.[illegible]
7.00	8.00	8.50	6.92+-0.[illegible]
10.00	12.00	11.50	10.79+-0.[illegible]
14.00	14.00	13.00	13.82+-0.[illegible]
16.50	19.00	16.50	16.83+-0.[illegible]
18.00	16.50	16.50	17.38+-0.[illegible]
18.00	16.50	18.00	17.42+-0.[illegible]
16.00	14.00	17.00	15.54+-0.[illegible]
15.00	13.00	15.00	14.38+-0.[illegible]
14.00	10.00	11.50	11.92+-0.[illegible]
12.00	11.00	9.50	10.42+-0.[illegible]
9.50	10.00	9.50	9.92+-0.[illegible]
12.83+-1.23	12.50+-1.06	12.54+-1.17	

Table 8: The effect of Ovariectomy on basal and histamine-stimulated gastric acid ouput in female rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT.
1	4.00	2.50	2.50	3.50	3.00	2.50	2.50	3.00	3.5
2	4.00	2.50	2.50	3.50	2.00	3.00	2.00	3.00	3.0
3	3.00	2.00	3.00	3.00	2.00	3.50	2.50	3.00	2.5
4	2.00	2.00	3.00	2.50	2.00	2.50	2.00	2.50	3.0
5	2.00	2.00	2.50	2.50	2.00	2.50	2.00	2.50	2.5
6	2.50	2.50	3.00	2.00	2.50	2.50	2.00	2.00	2.0
MEAN+-S.E.M.	2.92+-0.34	2.25+-0.10	2.75+-0.10	2.[illegible]+-0.23	2.0[illegible]+-0.00	2.75+-0.16	2.17+-0.10	2.67+-0.15	2.75+-
HISTAMINE									
1	4.50	5.50	6.00	3.50	5.00	4.50	6.00	4.00	5.0
2	5.50	6.50	7.00	5.50	6.00	5.00	8.50	8.00	9.5
3	10.00	11.50	8.50	9.50	9.50	10.50	13.50	11.00	13.5
4	12.50	13.50	13.50	11.00	12.50	13.50	14.50	11.50	14.0
5	15.50	15.00	16.00	15.00	16.00	16.50	15.00	14.50	14.5
6	18.00	17.00	18.50	17.50	18.00	18.00	16.00	17.50	16.0
7	16.00	15.50	18.50	17.00	16.50	17.50	17.00	17.00	18.5
8	19.00	20.00	16.50	18.50	18.50	20.00	17.00	20.00	17.0
9	18.50	17.50	17.00	19.00	17.50	18.50	14.50	15.50	15.0
10	15.50	14.50	16.00	16.00	16.50	15.00	14.00	15.00	14.5
11	12.50	11.50	13.50	14.00	13.00	11.00	13.50	13.50	13.0
12	10.00	11.00	10.50	9.00	10.00	11.50	11.00	11.50	11.5
MEAN+-S.E.M.	13.12+-1.34	13.25+-1.19	13.46+-1.23	13.04+-1.43	13.29+-1.29	13.46+-1.41	13.30+-0.92	13.25+-1.21	13.50+-

Note: All values are in micro Mol./ 10 minutes

Table B: (continued)

EXPT. X	EXPT. XI	EXPT. XII	EXPT. XIII	EXPT. XIV
3.00	2.00	3.00	2.50	3.00
3.00	2.50	2.50	2.50	2.00
2.50	2.00	3.00	3.00	2.00
2.50	2.50	2.00	2.50	2.50
2.50	3.00	2.00	2.50	2.50
2.00	3.00	2.50	2.50	3.00
2.58+-0.14	2.50+-0.17	2.50+-1.17	2.58+-0.08	2.50+-0.17
3.50	4.00	6.50	4.00	6.50
8.50	8.50	7.50	8.50	7.50
12.50	13.50	12.50	14.00	13.00
13.00	13.00	14.50	14.50	15.00
13.50	14.50	16.00	16.00	16.50
15.50	16.00	18.00	17.00	15.50
18.50	19.00	19.00	18.00	18.00
16.50	16.00	16.50	16.50	17.00
15.50	16.00	14.50	16.00	16.00
14.00	13.50	13.50	13.00	14.50
12.50	11.50	10.50	12.00	10.50
12.50	10.50	10.50	12.50	9.00
13.01+-1.08	13.00+-1.11	13.29+-1.09	13.50+-1.10	13.25+-1.08

Table 6: The effect of tamoxifen administration (20 mg/kg) on basal and histamine-stimulated gastric acid output in female rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT.VIII	EXPT. IX
1	2.00	2.50	2.50	3.00	2.50	3.00	2.50	3.50	3.00
2	3.00	2.50	2.50	3.50	2.00	2.50	2.50	2.50	2.00
3	2.50	2.00	2.50	2.50	2.00	3.00	2.50	2.00	3.00
4	2.50	3.00	2.50	2.50	2.50	3.00	2.50	2.00	2.00
5	2.50	3.00	2.00	2.00	1.50	2.00	2.00	2.00	3.00
6	2.00	2.00	2.00	2.50	1.50	2.50	2.50	3.00	3.00
MEAN+-S.E.M.	2.42+-0.14	2.50+-0.17	2.33+-0.10	2.75+-0.19	2.00+-0.17	2.67+-0.15	2.42+-0.08	2.50+-0.24	2.67+-0
HISTAMINE									
1	5.00	4.00	5.50	5.00	4.50	6.50	5.50	7.50	4.50
2	7.50	6.50	7.00	6.50	7.00	11.50	8.00	8.50	9.00
3	9.00	8.00	9.00	10.00	11.50	14.50	10.50	12.00	13.00
4	12.50	11.50	10.50	12.50	12.50	15.00	14.00	14.00	19.00
5	15.00	14.00	14.50	13.50	13.00	16.50	15.50	15.50	22.00
6	17.50	16.00	16.00	15.00	15.00	18.00	17.00	17.50	21.50
7	20.00	19.00	17.00	20.00	17.00	18.50	18.00	19.00	20.50
8	18.50	17.50	20.00	18.50	15.50	16.00	16.50	16.00	17.00
9	15.00	14.00	17.50	15.00	13.50	15.00	14.00	15.50	15.00
10	14.00	13.50	13.00	13.50	13.50	14.50	13.50	14.50	11.00
11	12.00	11.50	12.00	12.00	12.00	12.50	11.00	14.00	9.00
12	11.50	10.50	11.50	11.00	10.50	11.00	10.00	11.50	7.00
MEAN+-S.E.M.	13.14+-1.24	12.17+-1.23	12.79+-1.21	13.[illegible]+-1.31	12.13+-0.97	14.12+-0.92	12.80+-1.06	13.79+-0.95	14.04+-1

Note: All values are in micro Mol./10 minutes.

Table C: (continued)

EXPT.X	EXPT. XI	EXPT. XII	EXPT. XIII	EXPT. XIV
2.50	3.00	3.50	2.50	3.00
3.00	3.00	2.50	3.50	2.50
2.50	2.50	2.50	2.50	3.00
2.00	2.00	2.50	2.00	2.00
1.50	2.50	2.00	2.00	2.00
1.50	2.00	2.50	2.00	2.50
2.17+-0.23	2.50+-0.17	2.58+-0.18	2.42+-0.22	2.50+-0.17
3.50	6.50	6.50	5.50	6.00
5.50	9.50	9.00	8.50	8.00
13.50	11.50	12.50	13.00	12.00
14.00	13.50	13.00	14.00	13.50
16.50	15.00	15.00	16.50	15.00
17.00	16.00	17.50	17.50	17.00
19.50	15.50	15.50	17.00	18.00
17.00	14.00	14.50	15.50	17.50
16.00	15.00	13.50	14.50	15.00
13.50	12.50	12.00	14.50	13.50
14.00	11.00	10.50	11.50	14.00
11.00	9.50	9.00	9.50	11.00
13.42+-1.31	12.45+-0.81	12.38+-0.89	13.13+-1.03	13.4.+-1.03

Table D: The effect of Sham Ovariectomy on basal and histamine-stimulated gastric acid output in female rats.

	EXPT. I	EXPT. II	EXPT.III	EXPT. IV	EXPT. V	EXPT. VI	EXPT.VII	EXPT.VIII	EXPT.
1	3.50	2.00	2.00	2.50	3.00	2.50	2.50	2.50	2.0
2	2.00	2.50	1.50	3.00	2.00	2.50	2.50	1.50	2.5
3	2.00	2.50	2.00	2.50	2.00	2.00	2.00	2.00	2.5
4	2.00	2.50	2.50	2.50	2.00	2.00	2.00	2.00	2.5
5	1.50	2.00	2.00	2.00	2.50	2.50	2.50	2.00	2.5
6	2.00	2.00	2.00	2.50	2.00	2.50	3.00	2.00	1.5
MEAN+-S.E.M.	2.17+-0.26	2.25+-0.10	2.00+-0.12	2.50+-0.12	2.25+-0.16	2.33+-0.09	2.41+-0.14	2.00+-0.12	2.25+-
HISTAMINE									
1	5.50	5.50	4.00	5.50	4.50	4.00	6.00	4.00	6.0
2	8.50	8.50	6.00	6.00	6.50	7.00	8.00	8.50	9.0
3	10.00	12.50	9.50	9.00	10.50	10.50	10.00	14.00	12.0
4	13.00	14.00	12.00	10.50	13.00	11.00	11.00	15.00	12.5
5	14.50	15.50	14.50	13.50	15.00	13.00	13.00	16.00	14.0
6	16.50	19.00	15.00	15.50	16.50	14.00	14.50	17.00	15.5
7	15.00	17.00	16.00	18.00	20.00	14.00	16.50	17.50	13.0
8	13.50	14.50	19.00	14.50	17.50	16.50	16.00	16.00	13.0
9	12.50	13.00	16.00	17.00	15.00	17.00	14.50	16.00	12.0
10	12.00	11.50	13.50	15.50	14.50	15.00	13.50	13.00	11.5
11	10.00	10.00	12.00	12.50	12.00	13.00	13.00	12.50	11.0
12	9.50	9.50	11.00	9.50	11.50	10.00	11.00	12.00	10.0
MEAN+-S.E.M.	11.70+-0.85	12.50+-1.08	12.38+-1.19	12.67+-1.26	13.04+-1.23	12.08+-1.06	12.25+-0.89	13.45+-1.10	11.63+-

Note: All values are in micro Mol./10 minutes.

Table D: (continued)

EXPT. X
4.00
2.00
2.00
2.00
2.00
2.00
2.33+-0.30
4.50
7.00
11.50
12.00
13.50
14.50
16.00
18.00
15.00
14.00
13.50
11.00
^12.54+-0.28

Table E: The effect of vehicle (ETHYL OLEATE) administration on basal and histamine-stimulated gastric acid output in female rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII	EXPT.
1	2.00	2.50	2.00	2.50	2.50	2.50	2.50	2.50	3.0
2	2.00	2.50	3.00	2.50	2.00	1.50	2.00	2.50	2.0
3	2.50	2.50	2.00	3.00	2.00	2.00	2.50	2.50	2.5
4	2.00	2.50	2.50	3.00	2.00	2.00	2.50	3.00	2.5
5	2.50	2.00	2.00	1.50	2.00	2.50	1.50	2.50	2.0
6	2.50	3.00	2.00	2.00	2.00	1.50	2.50	2.00	1.5
MEAN+-S.E.M.	2.25+-0.10	2.50+-0.12	2.25+-0.16	2.42+-0.22	2.08+-0.08	2.00+-0.17	2.25+-0.16	2.50+-0.12	2.25+-
HISTAMINE									
1	6.00	7.00	4.50	5.00	3.00	6.50	4.00	4.50	4.0
2	9.50	7.00	9.50	7.50	5.50	7.00	6.50	6.00	7.5
3	11.50	11.50	13.00	11.50	7.50	12.00	11.00	10.50	9.0
4	13.00	13.50	12.00	13.50	11.50	13.50	12.00	11.50	11.5
5	16.50	15.50	13.50	15.00	12.00	16.00	15.00	12.00	14.5
6	20.00	16.00	15.50	17.50	13.00	17.00	17.50	14.00	18.0
7	16.00	16.00	16.50	18.00	16.00	18.00	20.00	14.50	18.5
8	13.50	18.00	13.00	17.00	19.00	15.50	17.00	17.00	15.5
9	13.00	18.50	12.50	15.00	17.50	15.00	15.50	16.50	15.0
10	11.00	15.50	11.00	12.00	15.00	11.50	14.50	14.50	13.0
11	10.50	11.50	10.00	9.50	14.50	11.00	12.50	13.00	12.5
12	9.50	11.00	9.50	8.50	10.00	10.50	11.00	11.50	11.0
MEAN+-S.E.M.	12.50+-1.03	13.25+-1.16	11.17+-0.87	12.50+-1.17	12.04+-1.34	12.79+-1.03	13.04+-1.27	12.13+-1.05	12.50+-

Note: All values are in micro Mol./10 minutes

APPENDIX III

Tables of Results on the effects of different durations of tamoxifen administration on Gastric Acid output in male rats.

Table A: The effect of tamoxifen administration (5 mg/kg) on basal and histamine-stimulated gastric output in male rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII
1	4.00	2.50	2.50	3.00	3.00	2.50	3.50	3.00
2	2.00	2.50	2.50	2.00	3.50	2.50	2.50	2.50
3	2.00	1.50	3.00	3.00	2.50	2.50	3.00	3.00
4	2.00	3.00	2.50	2.00	2.50	3.00	2.00	2.50
5	2.50	2.50	2.50	3.00	2.50	2.00	2.50	2.50
6	2.50	2.00	2.00	3.00	1.50	1.50	2.50	2.00
MEAN+-S.E.M.	2.50+-0.20	2.33+-0.19	2.50+-0.12	2.67+-0.19	2.58+-0.25	2.33+-0.19	2.67+-0.19	2.58+-0.14
HISTAMINE								
1	3.50	4.00	4.50	5.50	5.00	4.00	6.00	5.50
2	8.50	8.00	7.50	8.50	8.00	7.00	9.00	6.00
3	13.00	11.50	14.00	11.50	10.50	9.50	10.50	13.00
4	17.50	14.50	18.50	14.50	11.50	10.50	13.50	14.00
5	19.50	16.50	20.00	17.50	17.00	14.00	16.00	15.50
6	19.50	17.50	21.00	17.50	17.00	17.00	19.00	20.00
7	19.00	18.00	19.50	20.50	16.50	17.50	19.00	17.00
8	17.00	17.00	17.50	21.00	17.00	16.00	18.50	17.50
9	15.50	14.50	14.50	16.50	16.00	17.00	19.00	16.00
10	10.00	13.00	12.00	18.00	16.50	15.50	17.50	14.00
11	9.00	12.00	9.50	17.50	15.50	14.50	16.50	12.50
12	6.50	9.50	8.00	17.50	15.00	14.00	16.00	10.50
MEAN+-S.E.M.	13.21+-1.54	13.00+-1.18	13.88+-1.54	14.79+-1.25	14.04+-1.20	13.04+-1.20	15.04+-1.21	13.46+-1.22

Note: All values are in micro Mol./10 minutes.

Table 8: The effect of tamoxifen administration (10 DAYS) on basal and histamine-stimulated gastric acid output in male rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII
1	2.50	3.50	3.00	3.50	3.00	2.50	3.00	2.50
2	2.00	2.50	3.50	2.50	3.00	3.00	3.00	2.50
3	2.00	2.50	3.50	3.00	2.50	3.00	2.50	2.00
4	2.00	2.50	2.00	2.50	2.50	3.00	2.50	2.50
5	2.50	2.00	1.50	2.50	2.00	2.50	2.00	2.00
6	1.50	2.00	1.50	2.00	3.00	2.50	2.00	2.50
MEAN+-S.E.M.	2.08+-0.14	2.50+-0.20	2.50+-0.35	2.75+-0.16	2.67+-0.15	2.75+-0.10	2.50+-0.17	2.33+-0.10
HISTAMINE								
1	5.00	6.50	4.00	5.00	4.00	3.00	4.50	4.00
2	8.00	9.50	9.50	9.00	8.00	9.00	9.00	10.50
3	10.50	12.00	14.50	10.00	10.50	9.50	12.50	14.50
4	11.50	13.00	18.50	13.00	12.50	13.50	15.00	19.50
5	15.00	14.50	21.50	14.50	14.00	13.50	17.50	21.00
6	18.00	16.50	20.50	17.00	17.00	17.50	18.50	22.00
7	18.00	16.00	19.50	19.00	19.50	18.50	19.00	20.50
8	17.00	14.50	17.00	21.00	20.00	21.00	17.50	19.50
9	18.00	15.00	15.00	16.50	15.50	14.50	15.50	14.50
10	16.50	12.50	11.50	14.00	15.00	16.00	14.00	13.00
11	15.00	11.50	10.00	15.50	14.50	13.50	12.00	10.50
12	15.00	9.00	7.50	11.50	12.50	10.50	10.50	9.00
MEAN+-S.E.M.	13.96+-1.10	12.54+-0.84	14.08+-1.55	13.83+-1.24	13.58+-1.26	13.33+-1.34	13.79+-1.20	14.88+-1.58

Note: All values are in micro Mol./10 minutes.

Table C: The effect of tamoxifen administration (15 DAYS) on basal and histamine-stimulated gastric acid output in male rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII
1	2.50	3.00	2.00	2.00	3.00	3.00	3.00	4.00
2	2.50	2.50	2.50	2.00	3.00	2.50	2.00	2.00
3	2.50	2.50	2.50	3.00	3.00	2.50	2.00	2.00
4	2.00	2.50	2.50	2.50	2.50	2.00	3.00	2.00
5	2.50	2.00	2.50	2.00	2.00	2.00	3.00	2.00
6	2.00	2.50	2.50	2.00	2.00	2.00	3.00	2.50
MEAN+-S.E.M.	2.33+-0.10	2.50+-0.12	2.42+-0.13	2.33+-0.16	2.58+-0.18	2.33+-0.15	2.83+-0.15	2.42+-0.30
HISTAMINE								
1	4.00	5.00	4.50	5.50	7.00	5.00	6.50	5.50
2	10.00	9.00	7.50	8.00	12.00	10.00	9.00	8.50
3	13.50	9.50	15.00	13.00	16.00	14.00	11.50	13.00
4	15.50	13.50	17.50	17.00	17.00	15.00	12.00	16.00
5	17.50	14.00	16.50	20.00	17.50	16.50	12.00	16.50
6	18.00	17.00	19.00	22.50	18.50	16.50	13.50	17.50
7	19.50	15.50	21.50	21.00	19.00	17.00	14.50	18.50
8	17.50	13.00	19.00	18.50	22.00	20.00	15.00	18.00
9	15.00	12.50	18.00	13.00	18.00	16.00	13.00	15.00
10	13.50	12.00	15.50	12.50	15.00	12.50	12.00	13.50
11	12.00	11.00	16.00	10.00	14.00	13.00	11.00	12.50
12	11.00	8.50	13.00	7.00	12.00	10.00	10.00	10.50
MEAN+-S.E.M.	13.92+-1.19	11.17+-0.92	15.25+-1.35	14.00+-1.59	15.67+-1.10	13.33+-1.14	11.67+-0.66	13.75+-1.11

Note: All values are in micro Mol./10 minutes.

APPENDIX IV

Tables of Results on the effects of different durations of tamoxifen administration on Lactic Acid output in [illegible]

Table 8: The effect of tamoxifen administration (5 mg/kg) on basal and histamine-stimulated gastric acid output in f rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII
1	2.50	2.50	2.00	3.00	2.50	3.50	3.00	3.50
2	2.50	2.00	2.50	2.50	2.00	3.00	2.50	3.00
3	2.50	2.50	3.00	2.50	2.50	3.00	2.50	2.00
4	2.50	1.50	2.00	1.50	2.00	2.50	2.00	2.00
5	2.00	1.50	2.50	2.00	2.50	2.00	2.00	2.50
6	2.00	2.00	2.50	1.50	2.50	2.00	1.50	2.00
MEAN+-S.E.M.	2.33+-0.10	2.00+-0.17	2.42+-0.14	2.17+-0.23	2.33+-0.10	2.67+-0.23	2.25+-0.20	2.50+-0.24
HISTAMINE								
1	4.00	5.00	6.00	3.00	4.50	3.50	4.00	3.00
2	8.50	8.00	11.00	5.50	6.00	5.50	6.50	7.50
3	9.00	11.00	12.00	7.50	7.50	9.00	13.00	14.00
4	11.50	15.50	15.50	11.50	11.00	12.00	17.00	17.00
5	13.50	15.00	17.00	12.00	12.50	13.00	19.50	19.00
6	16.00	16.00	20.00	13.00	14.50	16.00	22.00	20.50
7	18.00	16.00	18.50	17.00	18.00	18.00	20.00	22.00
8	19.00	15.50	17.00	20.00	21.00	21.00	17.00	17.50
9	15.50	12.50	14.50	21.50	19.50	18.50	12.00	12.00
10	14.00	10.00	13.00	17.00	17.00	15.00	10.50	9.00
11	13.50	8.50	11.50	13.00	13.50	13.00	8.00	8.50
12	11.50	8.00	11.00	6.50	8.00	9.00	6.00	7.00
MEAN+-S.E.M.	12.83+-1.18	11.76+-1.07	13.86+-1.10	12.29+-1.63	12.75+-1.52	12.71+-1.44	12.96+-1.69	13.08+-1.70

All values are in micro Mol./10 minutes.

Table 8. The effect of **tamoxifen administration** (10 DAYS) **on basal and histamine-stimulated gastric acid output in** female rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII
1	2.00	2.50	3.00	3.00	2.00	3.00	2.50	3.00
2	2.00	2.50	2.00	2.50	3.00	2.00	2.50	3.00
3	2.00	2.00	2.50	2.00	2.00	2.50	2.00	2.50
4	2.50	2.00	2.00	2.50	3.00	2.50	2.00	1.50
5	3.00	2.00	2.00	2.00	2.00	2.50	2.50	2.50
6	2.50	2.00	2.00	2.50	2.00	3.00	2.50	2.50
MEAN+-S.E.M.	2.33+-0.15	2.17+-0.10	2.25+-0.16	2.42+-0.14	2.33+-0.19	2.50+-0.14	2.33+-0.10	2.50+-0.20
HISTAMINE								
1	4.00	6.50	4.50	4.50	5.50	5.50	3.50	3.50
2	7.00	9.00	7.00	6.00	7.50	6.50	6.00	5.00
3	11.50	10.50	9.50	10.50	10.50	11.00	10.00	8.50
4	14.00	13.50	13.00	13.00	12.00	14.00	15.50	12.50
5	16.00	15.00	14.50	14.00	14.50	15.50	16.00	14.50
6	18.00	16.00	16.00	17.00	16.00	16.50	18.00	17.00
7	18.50	20.00	17.50	18.50	16.50	17.50	19.00	19.00
8	17.50	17.00	19.00	19.50	17.00	18.00	16.50	20.50
9	14.50	16.00	15.00	15.00	13.00	17.50	14.50	16.00
10	13.00	14.00	14.50	14.50	12.00	14.50	13.00	13.50
11	11.50	12.50	12.00	12.50	10.50	11.50	12.00	10.50
12	9.00	10.00	11.00	11.00	9.50	11.00	10.50	9.00
MEAN+-S.E.M.	12.87+-1.25	13.33+-1.06	12.79+-1.18	13.00+-1.26	12.04+-1.51	13.25+-1.17	12.88+-1.31	12.46+-1.48

All values are in micro Mol./10 minutes.

Table C: The effect of tamoxifen administration (5 mg/kg) on basal and histamine-stimulated gastric acid output in female rats.

	EXPT. I	EXPT. II	EXPT. III	EXPT. IV	EXPT. V	EXPT. VI	EXPT. VII	EXPT. VIII
1	2.50	3.00	3.00	2.50	4.00	3.00	2.00	2.50
2	2.50	2.00	2.00	3.00	3.00	2.00	2.50	2.50
3	2.50	3.00	2.50	3.00	2.00	3.00	2.50	3.00
4	2.00	2.00	2.50	3.50	1.50	2.00	2.50	2.00
5	2.00	2.00	2.50	1.50	2.50	2.00	2.50	2.00
6	2.00	2.50	2.00	1.50	2.50	2.00	2.50	2.00
MEAN+-S.E.M.	2.25+-0.10	2.42+-0.18	2.42+-0.14	2.50+-0.31	2.40+-0.22	2.33+-0.19	2.42+-0.08	2.33+-0.15
HISTAMINE								
1	4.50	3.50	4.00	6.00	4.00	4.50	5.00	5.00
2	6.50	8.00	8.50	7.00	6.00	7.00	6.50	6.00
3	10.00	9.50	9.50	10.50	10.00	11.00	10.50	9.50
4	13.50	13.00	11.00	11.00	12.50	12.50	12.50	10.00
5	14.00	14.00	14.50	14.00	15.50	13.00	13.50	12.00
6	17.50	16.50	16.00	18.50	18.00	16.50	16.50	17.50
7	19.50	17.00	18.50	19.00	19.50	16.00	18.50	18.00
8	18.00	19.50	20.00	20.50	18.00	15.00	19.00	20.50
9	15.50	15.00	16.00	19.00	16.00	14.50	17.00	17.00
10	14.00	13.50	13.00	16.00	15.50	13.50	14.00	15.00
11	12.50	13.00	12.00	13.00	12.50	11.50	12.50	12.00
12	11.00	11.00	11.50	10.50	10.50	10.00	9.50	9.50
MEAN+-S.E.M.	13.04+-1.25	12.79+-1.20	12.80+-1.23	13.67+-1.36	13.15+-1.35	12.08+-0.99	12.92+-1.24	12.67+-1.37

All values are in micro Mol./10 minutes.

APPENDIX V

Tables of Results for Body weight
and Stomach weight studies in male rats.

Table A: Body weight and stomach weight of male (control) rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight (%)
1	198.2	221.7	23.5	2.00	0.90
2	230.6	278.0	47.4	1.92	0.69
3	205.1	240.4	35.3	1.66	0.81
4	202.7	253.7	51.0	3.04	1.20
5	192.0	233.3	41.3	1.52	0.65
6	198.6	247.7	49.1	1.71	0.69
7	219.8	257.4	37.6	1.80	0.70
8	179.2	221.0	41.8	1.59	0.72
9	193.0	228.0	35.0	1.32	0.58
10	205.1	244.9	39.8	2.23	0.91
11	212.4	261.5	49.1	2.48	0.95
12	216.1	265.0	48.9	2.36	0.89
MEAN+-S.E.M.	204.4+-3.34	246.1+-4.97	41.7+-2.24	1.97+-0.13	0.81+-0.05

Table 8: The effect of castration on body weight and stomach weight in male rats.

	Initial body weight, (gm)	Final body weight after 30 days (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	192.8	222.6	29.8	1.42	0.64
2	229.0	260.8	31.8	1.54	0.59
3	218.9	253.8	34.9	2.26	0.86
4	206.2	239.8	33.6	1.83	0.76
5	200.4	246.5	46.1	1.49	0.61
6	214.8	238.4	23.6	1.48	0.62
7	189.5	220.9	31.4	2.05	0.93
8	205.7	240.0	34.3	1.99	0.83
9	199.3	239.8	40.5	1.06	0.44
10	192.6	229.8	37.2	1.88	0.82
11	184.3	200.4	16.1	1.30	0.65
12	231.2	231.7	0.5	2.60	1.12
13	210.0	236.4	26.4	1.49	0.63
14	193.4	236.0	42.6	2.05	0.87
MEAN+-S.E.M.	204.94+-3.74	235.54+-3.80	30.6+-2.99	1.75+-0.11	0.74+-0.05

Table C: The effect of tamoxifen administration (30 DAYS) on body weight and stomach weight in male rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	199.1	201.7	2.6	1.13	0.56
2	220.5	245.0	24.5	1.27	0.52
3	219.4	232.7	13.3	1.65	0.71
4	224.0	258.0	34.0	1.75	0.68
5	197.4	213.3	15.9	2.01	0.94
6	196.8	208.0	11.2	2.02	0.97
7	216.8	224.9	8.1	1.93	0.86
8	238.2	257.0	18.8	2.70	1.05
9	203.4	220.4	17.0	2.34	1.06
10	220.5	227.7	7.2	2.73	1.20
11	207.7	241.5	33.8	2.17	0.90
12	199.0	237.4	38.4	1.07	0.45
13	210.8	233.7	22.9	1.65	0.71
14	209.4	261.4	52.0	1.28	0.49
MEAN+-S.E.M.	211.2+-3.19	233.1+-4.79	21.8+-3.85	1.84+-0.14	0.79+-0.06

Table D: The effect of sham castration on body weight and stomach weight in male rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	218.8	262.7	43.9	2.50	0.95
2	160.1	205.9	45.8	1.32	0.64
3	154.5	193.6	39.1	1.[illegible]	0.87
4	171.3	206.3	35.0	1.41	0.68
5	211.2	260.6	49.4	1.[illegible]	0.72
6	159.7	190.2	30.5	1.37	0.70
7	[illegible]5.5	255.[illegible]	29.3	2.[illegible]	0.90
8	145.6	193.2	47.6	1.25	0.65
9	168.4	219.4	51.0	1.62	0.74
10	172.5	209.6	37.1	1.99	0.95
MEAN+-S.E.M.	178.14+-8.73	220.34+-8.51	41.64+-2.10	1.784+-0.14	0.804+-0.04

Table E: The effect of vehicle (ETHYL OLEATE) administration on body and stomach weight in male rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	213.4	261.5	48.1	1.46	0.56
2	209.4	240.3	30.9	1.67	0.70
3	196.2	235.7	39.5	1.44	0.61
4	213.8	269.1	55.3	1.45	0.54
5	232.5	272.5	40.0	2.50	0.92
6	198.2	269.3	71.1	1.89	0.70
7	200.8	242.0	41.0	1.81	0.75
8	154.2	199.6	45.4	1.50	0.71
MEAN+-S.E.M.	202.14+-6.24	247.54+-8.71	42.44+-[illegible]	1.69+-0.15	0.74+-0.05

APPENDIX VI

Tables of Results for Body weight
and Stomach weight studies in female rats.

Table A: Body weight and stomach weight of female (control) rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	203.4	213.5	10.1	1.24	0.58
2	120.5	130.9	10.4	0.90	0.69
3	196.8	209.1	12.3	2.97	1.42
4	119.4	129.1	9.7	2.34	1.81
5	207.7	214.2	6.5	1.50	0.70
6	140.5	149.2	8.7	1.21	0.81
7	203.4	220.9	17.5	1.15	0.52
8	138.2	145.2	7.0	0.78	0.54
9	199.1	208.6	9.5	1.42	0.68
10	160.5	180.4	20.1	1.34	0.74
11	172.4	179.5	7.1	1.53	0.85
12	178.5	183.4	4.9	1.74	0.95
MEAN+-S.E.M.	170.04+-9.25	180.34+-9.45	10.34+-1.24	1.514-0.17	0.86+-0.11

Table 8: The effect of ovariectomy on body weight and stomach weight in female rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of body weight, (%)
1	162.1	182.4	20.3	1.77	0.97
2	137.5	187.8	50.3	1.54	0.82
3	176.8	201.7	24.5	1.17	0.58
4	151.3	192.6	41.3	1.14	0.59
5	134.0	160.3	26.3	1.03	0.64
6	145.4	196.2	50.8	2.35	1.20
7	163.2	204.5	41.3	2.25	1.10
8	139.2	178.3	39.1	1.69	0.95
9	168.2	211.9	43.7	1.92	0.90
10	151.7	187.0	35.3	1.46	0.78
11	143.5	193.4	49.9	1.37	0.71
12	153.6	191.1	37.5	1.32	0.69
13	189.5	249.1	59.6	1.99	0.80
14	170.4	210.9	40.5	1.81	0.86
MEAN+-S.E.M.	157.6+-5.12	196.3+-5.25	38.74+-2.44	1.63+-0.11	0.83+-0.05

Table C: The effect of tamoxifen administration (30 DAYS) on body weight and stomach weight in female rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	208.5	[illegible]	-14.5	1.63	[illegible]84
2	186.8	194.5	7.7	1.19	0.61
3	170.1	164.8	-5.3	1.57	0.95
4	167.6	174.9	7.3	2.45	1.40
5	186.3	183.8	-2.5	2.43	1.32
6	181.5	173.7	-7.8	1.85	1.07
7	150.5	173.1	22.6	0.94	0.54
8	171.0	166.5	-4.5	1.15	0.69
9	164.0	171.7	7.7	1.44	0.84
10	177.9	189.3	11.4	1.70	0.90
11	156.8	150.4	-6.4	0.93	0.54
12	179.9	172.8	-7.1	1.10	0.61
13	169.8	168.8	-1.0	1.32	0.78
14	180.4	151.4	-29.0	1.50	0.98
MEAN+-S.E.M.	175.3+-3.72	174.5+-3.24	-1.3+-3.08	1.52+-0.12	0.86+-0.07

Table D: The effect of Sham Ovariectomy on body weight and stomach weight in female rats.

	Initial body weight, (gm)	Final body weight after 30 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	176.8	186.7	10.9	1.78	0.95
2	169.4	173.5	4.1	1.28	0.74
3	177.5	184.5	7.0	0.96	0.52
4	150.7	165.4	14.7	1.16	0.70
5	153.2	162.9	9.7	2.62	1.61
6	188.4	200.7	12.3	1.10	0.55
7	179.5	196.0	16.5	1.22	0.62
8	170.1	177.6	7.5	2.91	1.64
9	182.5	191.0	8.5	1.11	0.58
10	168.4	175.5	7.1	1.04	0.60
MEAN+-S.E.M.	171.7+-3.63	181.64+-3.62	9.94+-1.14	1.52+-0.21	0.85+-0.13

Table 5: The effect of Volunteer (ORAL OLIVE) administration on body and stomach weights in female rats.

	Initial body weight, (gm)	Final body weight after 21 days, (gm)	Change in body weight, (gm)	Weight of stomach, (gm)	Weight of stomach as % of final body weight, (%)
1	192.6	203.3	10.7	1.38	0.68
2	171.4	180.7	9.3	1.07	0.59
3	156.8	165.3	8.5	1.17	0.71
4	149.5	157.6	8.1	1.26	0.80
5	167.7	182.2	14.5	0.91	0.50
6	184.3	195.0	10.7	1.85	0.95
7	170.4	177.9	7.5	1.51	0.85
8	170.6	185.0	14.4	2.04	1.10
MEAN+-S.E.M.	170.44-4.51	180.94-4.06	10.54-0.90	1.404-0.13	0.774-0.06

APPENDIX VII

CALCULATION OF GASTRIC ACID OUTPUT.

From the theory of acid-base titration (Boyce and Palmer, 1975)

$$M_A . V_A = M_B . V_B$$

where M_A = Molarity of Acid
V_A = Volume of Acid
M_B = Molarity of base
V_B = Volume of base

Acid Output = $M_B \times V_B$ per time,

Example:

If M_B = 0.01M NaOH
V_B = 0.60 ml

mMol = 0.01 x 0.60
= 0.006 mMol

If sample was collected after 10 minutes interval

Acid Output = 0.006 mMol/10 minutes.
= 6.0 micro mol /10 minutes.

In terms of mMol/L,

$$M_A(\text{mMol/L}) = (M_B . V_B \times 1000)/V_A$$

If the volume of acid = 1.20ml

$$\text{mMol/L} = (0.006 \times 1000)/1.20 = 60/12$$

Concentration (mMol/L) = 5 mMol/L.

APPENDIX VIII

STATISTICAL FORMULAE

In all cases where comparison between two sets of data were required, the student's t test was employed since inspite of the small sample sizes, the samples were randomly selected. In comparisons of the basal acid output, or histamine-stimulated acid output, between two different groups, an unpaired simple t test was employed. Statistical comparisons between the stomach weight and body weight in the control and the various experimental groups were also performed using the unpaired simple t test.

The formula for the unpaired sample t test is given as (Hill, 1977):-

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{s^2/n_1 + s^2/n_2}}$$

where $\bar{x}_1$ = mean value of samples in one group
$\bar{x}_2$ = mean value of samples in second group

s = standard deviation.

$$s^2 = \frac{\sum(x_1 - \bar{x}_1)^2 + \sum(x_2 - \bar{x}_2)^2}{n_1 + n_2 - 2}$$

The degrees of freedom, $df = n_1 + n_2 - 2$

where n_1 = number of samples in one group

n_2 = number of samples in the second group.

APPENDIX IX

LIST OF MATERIALS USED

1. Beakers (10ml, 25ml, 100ml)
2. Burettes (25ml)
3. Measuring Cylinders (10ml, 100ml)
4. Pipettes (10ml, 25ml)
5. Volumetric Flasks (25ml, 50ml, 250ml, 1000ml)
6. Dissecting Kit and Board.
7. Heating Lamp.
8. Handgloves.
9. Water Bath (Thermostatically Controlled)
10. Thermometer.
11. Antiseptic Fluid
12. Hypodermic Syringes (1ml, 5ml) and Needles (18,22 ganges)
13. Cotton Wool
14. Sutures (silk, catgut)
15. Cannulae (Tracheal, Pyloric)
16. Oro-Oesophageal tube.
17. pH Meter (PW 9418/30) Philips, England.
18. Mettler Balance (H80) Mettler Instruments, West Germany.