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# THE INVESTIGATION OF EXERCISE-INDUCED ANAPHYLACTIC SUBJECTS IN RELATION TO NON-EXERCISE-INDUCED ANAPYLACTIC SUBJECTS OF TYPE A AND TYPE B BEHAVIOR PATTERN

by

YVONNE BRANDEJS

A THESIS
SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES
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Whatever you can do, or dream you can
begin it. Boldness has genius, power
and magic in it.

– Goethe

DEDICATION

To my brother Peter from whom I have taken the example of diligence and dedication in continuing my studies.

## ABSTRACT

The purpose of this study was to measure plasma norepinephrine and epinephrine immediatly before exercise and at self-perceived exhaustion effort in three exercise-induced anaphylactic subjects and 16 normal healthy subjects; 8 of Type A and 8 of Type B behavior pattern. Other parameters measured in the study were: heart rate, lactate concentration, neutrophil leukocytes and platelets.

All subjects took the Jenkins Activity Survey to determine what percentile ranking on the Type A or B scale they were. All subjects underwent a modified treadmill test to self-perceived exhaustion effort; the subject determined herself when she was exhausted and terminated the test. The the subjects with exercise-induced anaphylaxis were tested twice on the treadmill.

Statistical analysis was done using Carlson's Full Rank multivariate analysis of variance within which three univariate analysis of variance were included. The multivariate analysis of variance was not significant ($p<0.05$) but the univariate analysis of variance revealed statistical significance. The univariate analysis were performed under these following hypothesis: 1) group differences, 2) repeated differences, 3) interaction effects. No significant ($p<0.05$) differences were observed for group differences in any of the variables, but a statistical significance ($p<0.0001$) was observed for all variables for repeated differences and a significant ($p<0.05$) difference was observed for interaction effects for heart rate and plasma epinephrine.

This study revealed that the subjects with exercise-induced anaphylaxis had significantly lower plasma epinephrine but comperable levels of plasma norepinehrine at self-perceived exhaustion as the Type A or B subjects and that the Type B subjects had a lower heart rate at rest than did the Type A or exercise-induced anaphylactic subjects.

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Finally, I wish to express my warm thanks to my family, but most of all to my mother who supported and encouraged me throughout this study.

## PREFACE

I have chosen this unusual topic for my thesis because I have exercise-induced anaphylaxis.

My concern in the first chapter is to describe this reaction and compare it to two similar reactions. Thus far, studies in this area have only described the symptomatology and the triggering mechanism of this reaction have been established. Clinically, it has been difficult to examine since it occurs only during exercise, but not every time exercise is performed. It cannot be induced at will. It resembles an allergic reaction but no immunologic factors have been identified.

In chapter two, I have defined anaphylaxis, discussed three existing theories on exercise anaphylaxis and tried to develop my own theory on the triggering mechanism of this reaction.

My basis for the hypothesis is the mast cell exoplasmosis, factors affecting it and sympathetic stimulation occuring in exercise.

The hypothesis I have developed is only one possibility; many others are feasible and should be tested in the future.

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# Chapter I
## INTRODUCTION

With the current popularity of fitness, jogging has become one of the primary ways of developing and maintaining cardiovascular efficiency. As the number of participants in cardiovascular activities such as road racing and marathons increase, more exercise-related reactions are discovered.

The three most common reactions from exercise are: syncope( the failure of venous return); hyperthermia (an abnormally high core temperature); and exercise-induced anaphylaxis, a newly discovered reaction. The main problem at road races and marathons is that some of the symptoms of one reaction may manifest themselves in the other two. Thus, when an athlete collapses, it is difficult to accurately diagnose the initial reaction and therefore to determine the appropriate treatment. The most common symptoms in all three are: sudden collapse, nausea and a substantial decrease in blood pressure.

The most frequent reaction following strenuous exercise is the failure of venous return which results in syncope. Syncope is derived from the Greek word meaning to cut short (Engel, 1950). Clinically syncope is a loss or near loss of consciousness due to a reversible disturbance in the cerebral blood flow. It is related to transient ischemia or redistribution of blood perfusion to the brain (Hickler and Howe, 1979).

During dynamic muscular work the leg muscles contract rhythmically, enhancing venous return against gravity by the pumping action of the musculature, maintaining cardiac output. When the exercise is stopped the pumping action of the muscles ceases; as a result the blood temporarily remains in the dilated vascular bed, which decreases the venous return to the heart and becomes a predisposition to syncope

(Astrand, 1977). Loss of consciousness occurs when the systolic arterial blood pressure falls below 80 mmHg (Engel, 1950; Hickler and Howe, 1979). Other clinical signs prior to syncope include visual blurring, decreased auditory acuity, lightheadness, giddiness, general weakness, tachycardia, pallor, hyperventilation, increased gastrointestinal peristalic activity and nausea (Hickler and Howe, 1979).

A second exercise-related reaction secondary to syncope during running is hyperthermia which is caused by an excess of heat in the body (Cloves and O'Donnell, 1974). During exercise in hot weather, a runner's body temperature increases due to heat produced by metabolic work and solar radiation. If exercise is performed at 70% to 75% of maximum oxygen consumption, the heat production may range from 900 to 1500 kcal/hr. An additional 100 to 150 kcal/hr may be gained from radiant exposure (Hanson, 1979). Cooling by sweat evaporation is influenced by the relative humidity and wind velocity. While jogging the average runner may loose 1.5 to 2.5 l of water each hour of jogging. Fluid intake by most runners seldom replaces more than 50% of this loss (Hanson, 1979).

Runners who are not acclimatized to the heat may not be able to initiate and maintain adequate sweat losses and water. Consequently, during exercise they attain high core temperatures and low blood volume which result in hyperthermia and hypovolemia respectively (Costill, 1977).

Three types of injuries can result from hyperthermia: 1) heat cramps which are caused by acute electrolyte loss and are characterized by fatigue and muscular cramps in the lower limbs; 2) heat exhaustion or heat prostration, which results from hypovolemia and is characterized by progressive lassitude and inability to work; these symptoms are followed by severe headache, vomiting, tachycardia, hypotension and syncope; 3) heat stroke or heat pyrexia, which becomes a life-threatening emergency and is characterized by severe nervous disturbance, hyperpyrexia, hot and dry ashen skin, cessation of sweating, severe hypotension and syncope.

The last and least understood exercise-related reaction is becoming increasingly apparent owing to the popularity of fitness. The symptoms are identical to those of anaphylactic shock triggered by immunologic stimuli such as Hymenoptera stings (Siegal, 1980) and allergies to certain foods, drugs or pollen . Although this exercise-induced anaphylaxis is most often caused by running, it can also be triggered by other demanding cardiovascular activities . Siegal (1980) observed this reaction in both novice and well-trained athletes and Sheffer and Austen (1980) documented cases in which the episodes varied from a single occurence to several attacks a year, for up to 16 years. The types of exercises preceding the attacks ranged from mild tennis warm-ups and dancing to strenuous activities such as sprinting in track events, jogging or running (from 1 km to a marathon distance), and during basketball, soccer and tennis. The attacks may be recurrent and induced by only one activity such as jogging, but they may not necessarily occur with each exercise episode.

The attacks usually begin during or immediately following the exercise. The subject experiences intense pruritus, which begins in some localized part of the body and then becomes generalized; this is commonly known as urticaria. Subsequent symptoms of urticaria include small hives and cutanous angioedema expecially of the face (eyelids and lips in particular), but in some cases choking or laryngeal edema with respiratory distress, syncope, gastrointestinal colic, and headaches may follow. However, urticaria is the initial manifestation and the hallmark of this syndrome (Sheffer and Austen, 1980).

Sheffer and Austen (1980) divide the symptomatology of an attack into four stages: prodromal, early, fully established and post-exertional. The first stage is characterized by a feeling of fatigue, generalized warmth and pruritus. Second stage a sensation of burning skin and urticarial eruptions that become confluent and are followed by

angioedema. The features of the third stage as described by Sheffer and Austen (1980) are collapse, transient periods of syncope, choking, stridor, gastrointestinal colic, nausea and vomiting. The blood pressure and heart rate during syncope experienced by the author of this thesis have been 70/0 and 50/50 mmHg and 180 and 150 beats per minute respectively. The symptoms of the third stage can last from 30 minutes up to 4 hours. The fourth stage of the attack is characterized by persistant headaches lasting 24 to 48 hours, (Sheffer and Austen, 1980). The author of this thesis has also experienced fourth stage symptoms, such as uncontrollable shivering (hypothermia-oral body temperature of 34 C) and peripheral vasodilation, which is evidenced by nailbed cyanosis.

Sheffer and Austen (1980) have performed routine hematologic studies on the complement activity, immunoglobulin classes and blood chemistries and found all the values to be within the normal range. The sérum IgE concentrations were not elevated in any of their patients.

This reaction can distinguished from syncope and hyperthermia by the initial symptoms of severe pruritus and facial angioedema (Table I). It appears that syncope and hyperthermia most often occur during in jogging (i.e. road races and marathons), while exercise-induced anaphylaxis can occur sporadically and during various activities. This suggests that some thus far unidentifiable variable(s) may be present in such instances. If it is present, it is not activated to the same extent in each attack.

Since this syndrome has been discovered only recently, there are very few theories on the potential triggering mechanisms . Both Siegal (1980) and Sheffer and Austen (1980) have attempted to identify some possible mechanisms, but because of the variety and diversity of symptoms none have been experimentally substantiated.

TABLE I

DOMINANT SYMPTOMS OF THE THREE EXERCISE REACTIONS

| VARIABLE | SYNCOPE | HYPERTHERMIA | EXERCISE-INDUCED ANAPHYLAXIS |
|---|---|---|---|
| DOMINANT SYMPTOMS | visual blurring<br>giddiness<br>dizziness<br>nausea | cramps,<br>lassitude<br>disorientation<br>headache<br>vomiting | itchiness<br>facial swelling<br>abdominal cramps<br>nausea<br>vomiting |
| MENTAL STATUS | unconscious if upright conscious if supine | altered mental state or unconscious | unconscious if upright conscious if supine |
| RECTAL TEMP (C ) | 37-39 | 40-42 | 37-34 |
| SKIN COLOUR SWEATING | pale, vasodilation | pale, vasodilation | red skin, white wheals vasodilatation |
| BLOOD PRESSURE | systolic low | systolic and diastolic low | systolic and diastolic low |
| HEART RATE (beats/min) | 100-140 | 120-160 | 120-180 |

## 1.1 DEFINITION OF TERMS

ANAPHYLAXIS: unusual or exaggerated allergic reaction of an organism to foreign protein or other substances.

ANGIOEDEMA: characterized by the sudden appearance of temporary edematous areas of the skin or mucous membranes and occasionally of the viscera, which is often associated with dermographia, urticaria and erythema.

BASOPHIL: granular leukocyte with an irregularly shaped, relatively pale-staining nucleus that is partially constricted into two lobes, and with cytoplasm containing coarse bluish black granules of variable size.

BRADYCARDIA: slowness of the heart beat, as evidenced by slowing of the pulse rate to less than 60 beats per minuts.

CARDIAC OUTPUT: amount of blood ejected by the heart in the circulatory system usually expressed as litres per minute.

EUTHERMIA: characterized by proper temperature, promoting warmth.

HOMOCYTOTROPIC: having an affinity for cells from the same species.

HYPERSENSITIVITY: state of altered reactivity in which the body reacts with an exaggerated response to a foreign agent.

HYPERTHERMIA: abnormally high body temperature.

HYPOVOLEMIA: abnormally decreased volume of circulating fluid (plasma) in the body.

HYMENOPTERA STINGS: stings caused by an order of insects usually having two pairs of well developed membranous wings, such as bees, wasps and ants.

INOTROPIC: affecting the force or energy of muscular contractions.

LEUKOCYTOSIS: an increase in the number of leukocytes in in the blood, resulting from various causes.

MAST CELL: connective tissue cell whose specific physiologic function remains unknown; capable of elaborating basophilic metachromatic cytoplasmic granules that contain histamine, heparin and, in certain species such as the rat and mouse, serotonin.

NEUTROPHILIA: increased number of neutrophils in the blood.

NEUTROPENIA: A decrease in the number of neutrophil leukocytes.

NORMOVOLEMIA: normal blood volume.

PROSTRATION: extreme exhaustion or powerlessness due to heat.

PRURITUS: itching.

PYREXIA: abnormal elevation of body temperature; fever.

REAGIN ANTIBODY: antibody of a specailized immunoglobulin class (IgE) that binds to tissue cells of the same species from which it is derived and interacts with an antigen to induce the release of histamine and other vasoactive amines.

STRIDOR: a harsh, high-pitched respiratory sound, such as the inspiratory sound often heard in acute laryngeal obstruction.

TACHYCARDIA: excessive rapidity in the action of the heart; usually applied to a heart rate above 100 beats per minute.

THROMBOCYTOSIS: increased number of platelets in the peripheral blood.

THROMBOCYTOPENIA: decrease in number of blood platelets.

URTICARIA: vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated patches (wheals) that are redder or paler than surrounding skin and often attended by severe itching.

## Chapter II
## REVIEW OF LITERATURE

Exercise-induced anaphylaxis is an exertional clinical syndrome (Siegal, 1980) that has distinct urticarial symptoms of pruritus and angioedema. These symptoms differentiate it from other exercise induced reactions such as syncope due to failure of venous return and hyperthermia. Theories about the mechanism of action of such anaphylaxis have not been satisfactorily substantiated.

The classical term anaphylaxis was first coined by Poiter and Richet in 1902 (as described by Richter in1980), and was derived from the Greek word "ana" meaning backward and "phylaxis" meaning protection. Anaphylaxis was first seen in experiments with dogs: although they tolerated initial injections of an extract made from sea anemones and mussels, they mainfested adverse reactions to later injections of the same extract (Richter, 1980). Two prerequisites are necessary for this classical anaphylactic syndrome. One, the individual must not only be exposed to the toxin, but also reexposed to it, and two, there must be a latent period of sensitization. Anaphylaxis is not dependent on the accumulation of a substance but rather the reintroduction of a minute dose (Orange and Donsky, 1978).

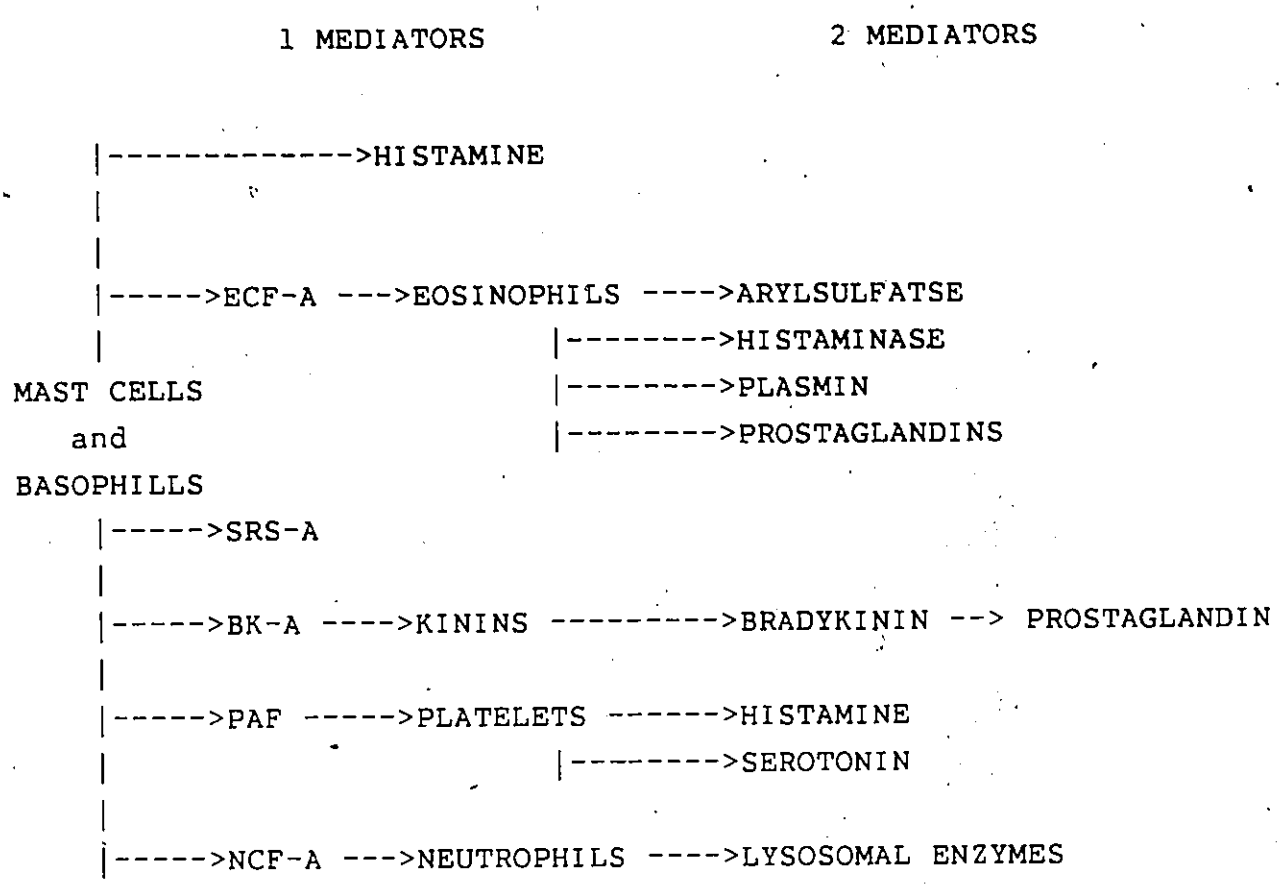
This type of anaphylaxis is also considered an immediate hypersensitivity reaction referred to as a Type I reaction. It is usually mediated by IgE antibodies that form specifically in response to an allergen (Richter, 1980; Broder, 1979; Orange and Donsky, 1978; Austen, 1976). When these specific antibodies, usually referred to as reagins or homocytotropic antibodies, form they bind to mast cells and basophils. Subsequent interaction of the cell- fixed antibody and the specific allergen results in the liberation of chemical mediators (Table II) such as histamine, eosinophil

chemotactic factor of anaphylaxis (ECF-A), slow reacting substance of anaphylaxis (SRS-A), platelet activating factor (PAF), basophil- derived kallikrein of anaphylaxis (BK-A), and neutrophil chemotactic factor of anaphylaxis (NCF-A) (Austen, 1974; Orange and Donsky, 1978; Broder, 1979), (see Table II for mediator release). These mediators act on various tissues or organs and cause the following life-threatening clinical manifestations, (Austen, 1971; Richter, 1980):

1. Respiratory distress due to bronchial obstruction or laryngeal edema or both.
2. Primary vascular collapse with or without antecedent respiratory difficulty resulting in hypoxia.
3. Gastrointestinal maifestations such as diarrhea, nausea, vomiting and abdominal pain.

TABLE II

RELATIONSHIP AND CHARACTERISTICS OF THESE MEDIATORS




(Orange and Donsky, 1978)

HISTAMINE: Histamine is a low-molecular weight primary amine that has an imidazole ring. In all mammals it is stored preformed in mast cells and basophils, but in humans it is also found in the epidermis, gastrointestinal tract and central nervous system. Histamine has several effects on a variety of tissues: it induces urticarial wheals, which are white, elevated circumscribed swellings that result from increased capillary permeability. It causes severe pruritus and erythema (localized hyperemia due to arterial dilation). Also histamine affects the heart; it stimulates arterio-venous conduction and induces arhrythmias. It causes contraction of various smooth muscles in the ilium, bronchi and uterus as well of the tracheal muscle, and it increases the vascular permeability of general and microvasculature. Increased gastric secretion has also been found to be induced by histamine. It is a possible activator of vagal nerves and triggers vagal cholinergic bronchoconstriction. Histamine apparently also is able to increase chemotaxis of eosinophils (Orange and Donsky, 1978).

EOSINOPHILIC CHEMOTACTIC FACTOR OF ANAPHYLAXIS (ECF-A): This substance is a mixture of tetrapeptides and exists in a preformed state in tissue mast cells or peripheral blood basophils. Its importance is in its chemotactic activity toward neutrophils and eosinophils, which contain arylsulfatase b (which inactivates SRS-A) and histaminase (which inactivates PAF). The main function of ECF-A is to attract eosinophils to a site of allergic inflammation (Orange and Donsky, 1978) and to maintain homeostasis against immunologic damage (Broder, 1979). The eosinophils attracted to the allergic site contain phospholipases that when released during inflammation, cleave phospholipids of the cell membrane to form arachidonic acid, which is further metabolized to produce prostaglandins (Broder, 1979). Although many diverse prostaglandins exist PGE1, PGF1 and PGF2 increase peristolic activity and induce diarrhea and vomiting (Levine, 1973;Hedquist, 1974). Prostaglandins have also been shown to act synergistically

with bradykinin to produce pain and a sensation of "burning skin" (Orange and Donsky, 1978).

SLOW-REACTING SUBSTANCE OF ANAPHYLAXIS (SRS-A): This substance appears to be a low-molecular weight acidic sulfate ester. It is distinguishable from histamine because it takes several minutes (histamine takes several seconds) to produce a maximal contraction. SRS-A is not preformed in cells, but is produced after an allergen-IgE antibody reaction of various tissues such as the lung and nasal polyps and peripheral leukocytes. Its activity is not blocked by antihistamines; in the presence of antihistamines SRS-A causes contraction of the duodenal tissue and bronchioles. It acts synergistically with histamine to contract smooth muscle cells and blood vessels (Orange and assocaites, 1976; Plaut and Lichenstein, 1978). Also, SRS-A has been shown to increase vascular permeability (Orange and Donsky, 1978).

BASOPHIL-DERIVED KALLIKREIN OF ANAPHYLAXIS (BK-A): This substance is an arginine-type esterase that has been isolated from lung and blood leukocytes in humans. It is a preformed compound found in mast cells and cleaves kininogens with serum alpha globulins to produce bradykinin. Bradykinin increases vasodilation by increasing vascular permeability of peripheral arteries, thereby producing hypotension and potentiating the effects of histamine. Bradykinin also increases smooth muscle contractions however, its unique feature is that induces pain by stimulating the nerve terminals (Plaut and Lichtenstein, 1978).

PLATELET ACTIVATING FACTOR (PAF): The structure of this compound has not yet been determined but it is known to be formed from a precursor in sensitized lung or peripheral basophils by IgE-dependant mechanims. It is distinguished from SRS-A by its resistance to treatment by eosinophil-arylsulfatase, but it is inactivated by phospholipase. Its primary function is to aggregate and degranulate platelets to release histamine and serotonin. Serotonin is a vasoactive amine like histamine and induces contraction of smooth

muscle cells, bronchoconstriction and vasoconstriction and increases capillary permeability. In humans 90% of serotonin is stored in the mucosa of the gastrointestinal tract and 10 % is in the central nervous system and platelets (Plaut and Lichtenstein, 1978).

NEUTROPHILIC CHEMOTACTIC FACTOR (NCF): The basic structure of this substance has not yet been isolated but it has been shown to be generated by the mast cell after IgE-antigen interaction. It attracts neutrophils, which then release lysosomal enzymes during tissue injury (Plaut and Lichtenstein, 1978). Movat (1972) reported that neutrophils release a protein that causes mast cells to release histamine. Although neutrophils are not prominent cells in hypersensitivity reactions, they have been measured in modest numbers during anaphylaxis (Broder, 1979).

The mediator release described above occurs not only during IgE antibody-antigen reactions but also during non-IgE antibody-antigen anaphylactic reactions (cutaneous anaphylaxis and cytotoxic or complement mediated histamine release, Broder, 1979). Some of the features of the classical anaphylactic reaction are pertinent to two of the three present theories that attempt to describe anaphylaxis in exercise.

The most common theory of classic anaphylaxis (Type I hypersensitivity reaction), is one in which the mast cells and basophils are coated with the specific IgE reagin antibodies for a particular allergen and when these allergens form complexes with the reagin antibodies the mast cell membrane becomes activated.

Certain foods can become allergens and are known to produce Type I hypersensitivity. Maulitz (1979) presented a study of a runner in whom hypersensitivity to shellfish (shrimp and oysters) developed 5 to 24 hours before the exercise related event (10 km race); this resulted in an allergic reaction of post-exercise urticaria and almost com-

plete airway closure. The runner abstained from eating shellfish for 30 days, during which time he participated in 30 separate runs; no allergic episodes occurred. After the 30 days the runner challenged himself by eating 100 g of smoked oysters 24 hours before a 10-km run. Again, hypersensitivity developed immediately after the run.

Based on Maulitz (1979) results, Siegal (1980) speculated that exercise may induce a "delayed" Type I hypersensitivity reaction in an appropriately sensitized person after he or she has been exposed to an allergic agent. Various foods, pollens or drugs may serve as allergic primers for the exercise related reactions.

The second theory on exercise-induced anaphylaxis is based on the same mechanism that provokes cold urticarias; patients experience the same generalized symptoms as in exercise-induced anaphylaxis but to a lesser degree; that is, their symptoms rarely progress beyond angioedema. The mechanism in cold urticaria is mediated by the IgE sensitized antibodies, which are attached to the mast cell and activate the cell, as in the IgE-antigen complex. However no antigen has yet been linked to this syndrome. Hynie (1980) postulated that in cold urticaria the IgE antibody's light and heavy chains are distorted by the cold, thereby affecting the cell membrane in the same manner as antigen-antibody complex. Siegal (1980) felt that the same sequence occurs in exercise-induced anaphylaxis however, the mechanism by which exercise triggers the reaction is unknown.

The third theory on exercise-induced anaphylaxis does not involve immunopathology; it is based on exercise-induced hyperhistaminemia. Mathews and Pan (1970) found an increase in plasma histamine concentration during exercise in a patient in whom prominent pruritus and urticaria developed after every exercise session. They concluded that the hyperhistaminemia was due to increased histamine release with exertion from quantitatively normal stores of the amine in the mast cells or basophils and in the skin. They be-

lieved that there may be other sources of histamine, for example the wall of the gastrointestinal tract or in the microvasculature. Schayer (1970) presented evidence that all mammals have an inducible form of histidine decarboxylase which promotes the formation of histamine in the microcirculation. Beaven (1976) found that histamine accumulated in the vessels of the microcirculation in a warm environmental temeperature of (37 C), and stated that inducible histamine can also form after exercise.

It is pertinent to the development of the hypothesis of this thesis to discuss the mast cell degranulation, the receptors affecting the mast cell and the receptor stimulants involved in the exoplasmosis of histamine.

In the first stage of mast cell degranulation the membrane's receptors are activated by chemical or physical stimulants or by an IgE antibody. This causes fusion of the perigranular membrane of the histamine containing granules and the cell membrane, which leads to the formation of "pores" within the mast cell membrane. This allows the "naked" granules to come into contact with the cytoplasm (Stanworth, 1972). In the second stage the levels of cyclic AMP decrease due to the action of the alpha-adrenorecepotor stimulants, (Jack 1978), and potassium mediated cyclic GMP increase occur (Ball and associates, 1972). In and third stage the membrane ATP'ase activity is increased. Stanworth (1972) postulated that a specific activation is caused by calcium ions, or by some physical dearrangement of the cell membrane. The increased ATP'ase activity causes contraction of the cellular microtubules, which aggregate and transport the histamine granules to the periphery of the cell, where they are exposed to the extracellular cations, particularly sodium. Sodium is exchanged for the COO-HI group of the heparin-protein complex in the granule and rest of the granule's contents are expulsed from the cell (Uvnas, 1972; Stanworth, 1972).

Calcium ions appear to be necessary in two stages of this mechanism (Middleton, 1974; Ranadive, 1979). Calcium is needed in the first stage, at the site of interaction of the stimulus and the cell membrane and at the end of stage three at the end of the release process, when calcium requiring enzymes (ATP'ase) may be essential for the translocation of the granules to the periphery (Ranadive and Ruben, 1973) and for the contraction of the microtubules during the granule translocation (Uvnas, 1972).

A mast cell has several receptors on its surface. These receptors can be defined as macromolecular cell constituents with which drug molecules interact to produce an effect on a cell, tissue or organ (Middleton, 1974). Receptors have affinities for agonists and antagonists, which cause conformational changes in the cell membrane (Beaven 1976) and perturbations of the receptor substances (Rang and Ritter, 1970). The sympathetic divisions of the autonomic nervous system are intimately involved in the modulation of the Type I allergic reaction (Broder, 1979) in which mast cell and basophil histamine are released. The sympathetic effect on many tissues is influenced by both the alpha and beta adrenergic receptors, which serve different and sometimes opposite functions (Goodman and Gilman, 1975; Middleton, 1974).

The alpha receptors are classified by their relative potency series; the potency of phenylephrine is higher than that of norepinephrine which is higher than epinephrine which is higher than isoproterenol. The beta receptors contrast this potency series; the potency of isoproterenol the highest, epinephrine and phenylephrine the lowest and norepinephrine in between (Middleton, 1974; Beaven, 1976). The mast cell and basophil activation, and subsequent release of histamine is modulated by the sympathetic pathways in which the cyclic AMP is lowered (Broder, 1979). Ball and colleagues, 1972) found that infusion of catecholamines into humans with adrenergic blockers favour a pure 'alpha-agonistic' effect.

As shown by Beaven (1976), Plaut and Lichtenstein (1978) and Coffey and Middleton (1973) in slices of lung and blood leukocytes in humans, beta-adrenergic agents such as epinephhine and isoproterenol (Austen, 1971; Ash and Schild, 1966) prostaglandin A, E1,E2, F2 and exogenous histamine (Beaven, 1976; Middleton, 1974) cholera endotoxin and methylxanthines, can elevate adenyl cyclase which elevates cyclic AMP and the increased level of cyclic AMP inhibits the release of the chemical mediators from the mast cell (Plaut and Lichtenstein, 1978).

Alpha-adrenergic agents such as norepinephrine have been shown to decrease the cyclic AMP levels in mast cells in rats; reaction is magnified in the presence ofthe beta blocker propranolol (McIntire 1973; Coffey and Middleton, 1973; Beaven, 1976; Butcher and coworkers, 1976) McIntire, (1973) and Coffey and Middleton (1973) suggested that alpha-adrenergic receptor stimulation may modulate histamine release from mast cells and basophils.

Further experimentation by Coffey and Middleton (1973) showed that the ATP'ase activity in the mast cells in rats was clearly increased by norepinephrine and epinephrine, particularly by norepinephrine in combination with propranolol. Middleton (1974) suggested that the experiments by himself and Coffey (1973) showed that alpha-adrenergic receptor stimulation modulates histamine release. Swamy and Triggle (1972) proposed a hypothetical model for the activation of the alpha adrenergic receptors. The critical sites can be described as the norepinephrine (alpha agonist) recognition sites (defined as the alpha-adrenergic receptor), which are obligatorily linked with calcium mobilization sites such that the activation of the former results in the availability of calcium for the contraction and in the two stages of mast cell histamine release mentioned by Ranadive and Ruben (1973).

In summary, norepinephrine through alpha receptor stimulation decreases cyclic AMP and increases ATP'ase activity within the mast cells. Norepinephrine also increases

the availability of calcium ions necessary at the site of interaction with the stimulus and the cell membrane and for the microtubule contraction and granule translocation.

Exercise causes an increase in both norepinephrine and epinephrine in the blood (Pierce and colleagues, 1976; Howley, 1976; Manhem coworkers, 1978; Christensen and associates, 1979). The norepinephrine levels rise gradually as the intensity of exercise increases and become disproportionately elevated at high workloads ( >80% VO2) ( Davies colleagues, 1974). However, epinephrine rises slowly and is not significantly elevated at submaximal workloads, only at maximal and supramaximal workloads (Cousineau, 1977; Christensen and associates, 1979).

Kotchen and colleagues (1971) studied six healthy subjects who had just completed an 8-week training program. The exercise consisted of 40%, 70% and 100% VO2 maximum workload on a bicycle ergometer. Plasma norepinephrine and epinephrine levels were obtained at rest and immediately following each exercise session. They found that the norepinephrine concentrations became significantly greater after each sucessive workload; The epinephrine levels were elevated significantly only after maximum workload. These investigators found that the sympathetic nervous system is stimulated by exercise and that degree of stimulation depends on the intensity of the exercise.

Haggendal and coworkers (1970) were not only interested in observing the increase in arterial plasma concentrations of norepinephrine but also in investigating the levels during exercise to see if they differed significantly between physically fit and unfit individuals exercising at identical workloads. Three untrained and two trained subjects exercised at two submaximal workloads and one maximal/ supramaximal workload on a bicycle ergometer. Their results confirmed their hypothesis which indicated that norepinephrine is directly related to the relative workloads of the individual; this relationship extends even to workloads re-

quiring maximum oxygen consumption. When the norepinephrine levels of trained versus untrained individuals were compared at the same absolute workloads, the norepinphrine values were much lower in the trained subjects. Haggendal and co-workers' explanation for the direct relationship between the norepinephrine concentration and workload is based on the theory that the norepinephrine release is from nerve terminals of the adrenergic neurons and is correlated to an increased sympathetic impulse flow. The absence of detectable levels of epinephrine in the blood indicated that the adrenal glands did not contribute significantly to the catecholamine blood levels; this also confirms the release of norepinephrine from the nerve terminals of the peripheral sympathetic neurons as the major source of plasma norepinephrine.

Watson and associates (1980) measured the increase in plasma norepinephrine levels after bicycle exercise. The workload was constant (85%) for each individual's heart rate maximum, and the exercise was performed to exhaustion. The plasma norepinephrine levels increased in every subject. The increase between the end of exercise and the maximum concentration of plasma norepinephrine (138 seconds) was significant. Although Watson and associates (1980) discussed several possibilities to account for the increase, they believed that it was due to pooling of blood in the vasodilated lower limbs. Together with the fall in blood pressure at the end of exercise, which reduced stimulation of the low pressure cardiopulmonary and high pressure sinoaortic receptors, a reflex increase in sympathetic vasoconstrictor activity will occur, thereby augmenting the already elevated plasma norepinephrine levels.

Watson and associates (1980) felt that exercise-induced asthma resulted from an abnormal inbalance between the alpha and beta receptor tones and they suggested that the alpha receptors were stimulated to a greater extent by the high plasma norepinephrine levels observed when exercise

was stopped. Such an effect is also possible in exercise-induced anaphylaxis since the second- and third- stage symptoms described by Sheffer and Austen (1980) also occur when exercise is stopped. Elmadjian and colleagues (1958) measured the excreted levels of norepinephrine in hockey players immediately before and after a hockey game. Among, the players who participated in the game; the norepinephrine levels increased five times after the game; among players who did not participate the levels were only twice as high as before the game. In one player who was involved in a fight during the game the norepinephrine levels increased eight times after the game.

Simpson and associates (1974) compared the plasma norepinephrine levels of men who showed predominantly Type A behavior characteristics and Type B behavior characteristics at rest and during exercise respectively. Significant differences were found at rest, but the men with the Type A characteristics had much higher levels during exercise.

Type A behaviour has been defined by Jenkins and colleagues, (1979) as follows:

> " That behavior pattern considered to be an overt behavioral syndrome or style of living characterized by EXTREMES of competitivness (sometimes stringently repressed), haste, impatience, restlessness, hyperalertness, explosivness of speech, tenseness of facial muscles and feelings of being under the pressure of time and under the challenge of responsibility. Persons having this pattern are often so deeply committed to their vocation or profession that other aspects of their lives are relatively neglected. Not all aspects of this syndrome or pattern need be presented for a person to be classified as possessing it. The pattern is neither a

> personality trait nor a standard reaction of a characterologically predisposed person to a situation that challenges him or her. Different kinds of situations evoke maximal reactions from different persons."

Those who display the Type B behaviour pattern contrast those with the Type A behaviour pattern. They are relaxed, unhurried, mellow, and satisfied . They may also be interested in progress and achievement; however, they tend to flow with the stream of life rather than constantly struggle against it (Jenkins and colleagues, 1979)

In summary, Kotchen and colleagues (1971), Haggendal and coworkers (1970), Watson and associates (1980) and Elmadjian and colleagues (1958) found that the levels of norepinephrine increase more than the levels of epinephrine during progressive and intense exercise. Watson and associates (1980) felt that this feature may have implications on the alpha-adrenergic stimulation at the mast cell level and cause exercise-induced asthma. Mast cells contain the mediators that are implicated with anaphylaxis and have alpha-adrenergic receptors: thus, they may be stimulated by norepinephrine during exercise.

## 2.1 RATIONALE FOR THE STUDY

Anaphylaxis is a reaction triggered by the release of mediators found in the mast cells and basophils. These cells have several receptor sites, which allow binding of a variety of hormones, neurotransmitters and other chemical agents. When one of the receptor sites, the alpha-adrenergic receptor site, is stimulated, the cell's membrane is activated and its contents are released into the circulation. Norepinephrine is an alpha-adrenergic stimulator and therefore a possible triggering agent of this reaction.

## 2.2 AIM OF THE STUDY

Previous studies, (Kotchen and colleagues,1971; Haggendal and coworkers, 1970; Watson and associates, 1980; Elmadjian and colleagues, 1958; and Simpson et al. 1976) have reported that during exercise, the norepinephrine levels increase with increasing workloads. Middleton (1974), Daniel and coworkers (1970), Coffey and Middleton (1973) Watson and associates (1980) have postulated that the increased norepinephrine levels may play a role in the stimulation of the alpha-adrenergic receptors of the mast cells and basophils. In this thesis we attempted to measure plasma norepinephrine and epinephrine levels during dynamic high- intensity exercise in a group of subjects with exercise-induced anaphylaxis and a group of subjects consisting of Type A and B behaviour patterns.

# Chapter III
# METHODS AND PROCEDURES

## 3.1 THE PROBLEM

The problem in this invasive study was to investigate the effects of high intensity exercise on the levels of plasma epinephrine and norepinephrine. The variables ere divided into experimental and monitor variables.

### 3.1.1 Experimental Variables

1. Plasma norepinephrine
2. Plasma epinephrine

### 3.1.2 Monitor Variables

1. Heart rate
2. Lactate
3. Neutrophil leukocytes
4. Platelets

Each of the experimental and monitor variables was measured at rest and at maximum workloads. Heart rate was monitored continually throughout the testing session.

## 3.2 SUBJECTS

Three female subjects with exercise-induced anaphylaxis were tested and compared with experimental group of 16, healthy female subjects. Of the 16, 8 were of Type A and 8 were of Type B behaviour patterns. The age range of the subjects in the three groups was 18 to 27 years and all of the subjects were selected from a larger population of extremes of Type A and B individuals. All of the subjects had a physical examination by their physician before entering the study. The criteria for selection were based on the subjects' participation in an organized physical activity

program. Each subject exercised 3 times per week, for a minimum of 45 minutes in her organized activity program, for at least six months before entering this study.

## 3.3 TESTING ENVIRONMENT

The subjects came to the cardiopulmonary laboratory at the Ottawa General Hospital . The testing environment (e.g. the temperature, humidity and atmospheric pressure) was recorded at the beginning and end of each test period.

## 3.4 INSTRUMENTATION AND CALIBRATION

A Quinton model, STATUS 1000 treadmill and computerized control unit were used.

## 3.5 TESTING PROCEDURE

Testing for each subject took 2 days. On day 1 all subjects were given the Jenkins Activity Survey (JAS) (Jenkins and associates, 1979) to determine if they were of Type A or Type B behavioural pattern. They were instructed on the protocol of the study and taken to the laboratory to familiarize themselves with the testing equipment. Each subject was instructed to fast for at least 4 hours before the treadmill run.

On day 2 , the subjects reported to the laboratory for a run to self-perceived exhaustion. Initially each subject rested for 20 minutes in a sitting position and then began with a warm-up of 3 mph at 0% grade,for 4 minutes, after which the treadmill speed was increased to 5 mph for three minutes. After this time the treadmill was increased by 1 mph every 3 minutes until the subject felt she could not continue further and therefore terminated the test. Each of the exercise-induced subjects was tested twice, once at

the onset of the testing period (week 1) and once at the end of the testing period (week 8). Each exercise test was run at the same time each day and on the same days of each week.

On day 2 blood amples were taken by a hematologist from the Ottawa General Hospital. The first one, after the 20 minute rest (immediately before the treadmill run,and the second immediately after termination of the run. The blood samples were drawn from the anticubital vein on the ventral side of the arm with butterfly needle and 20 mm of plastic tubing; 20 cc of blood were withdrawn. The samples were divided so that 10 cc were frozen and later analysed for epinephrine and norepinephrine concentrations , using the radioenzymetic isotope technique of Peuler & Johnson (1977). Another 8 cc were analysed for neutrophil leukocyte and platelet counts, and 2 cc were analysed at the kinanthropology laboratory for lactate concentrations using the technique of Gutman & Wahlefeld (1974). Each blood sample was collected into a heparnized test tube containing EDTA (however the tubes contained EGTA for the catecholamine assays). The samples were then centrifuged to seperate the plasma from the cells using a Sorvall N-L 5 centrifuge and stored at -70 C. Time between collection and processing varied from 30 to 90 min. Duplicates were run on the 3 anaphylactic subjects, but only single measurements were done on the Type A and B subjects. Each anaphylactic subject was tested twice, the interassay variation was found to be 20%.

## 3.6 STATISTICAL PROCEDURES

### 3.6.1 Statistical Analysis

This study collected data on six dependant variables:

1. Plasma norepinephrine concentrations
2. Plasma epinephrine concentrations
3. Heart Rate
4. Lactate Concentrations

5. Neutrophil leukocyte count

6. Platelet count

A multivariate analysis of variance was used to analyse thise data. The groups with exercise-induced anaphylaxis was compared to the Type A and Type B groups. Further analysis was done to see if differences existed between the subjects with Type A and B behaviour patterns. The multivariate analysis of variance was done with the computerized program of the Carlson's Full Rank model, designed by Dr. Jim Carlson, Faculty of Education, University of Ottawa.

3.6.2 The Design

The design of this multivariate analysis 2 X 3 factorial design (Table III) and has three independent variables. Variable T (TYPE A, TYPE B) is a grouping factor, while variables D (DAY 2) and L (REST and SELF-PERCEIVED EXHAUSTION WORKLOAD) were the repeated measurements. The dependent variables (norepinephrine, epinephrine lactate, heart rate, neutrophil count and platelet counts) were analysed for statistical significance. Any statistically significant values observed were analyzed with the post-hoc procedure of Wilk'Lamda. (Table III shows the schematic representation of the statistical design).

TABLE III

EXPERIMENTAL DESIGN

| | DAY 2 | |
|---|---|---|
| | REST | SELF-PERCEIVED MAXIUM WORKLOAD |
| ANA-PHYLACTIC | | |
| TYPE A | | |
| TYPE B | | |

Each cell contained data on:

1. Heart rate
2. Plasma norepinephrine concentrations
3. Plasma epinephrine concentrations
4. Lactate concentrations
5. Neutrophil leukocytes
6. Platelets

## 3.7 LIMITATIONS OF THE STUDY

1. Possible drop-outs from the experimental group owing to the length and nature of the study.
2. The anxiety of the environmental and social settings were placed on the subjects outside the testing setting during the testing period.
3. Drop-outs because they had fainted (vasovagal reaction) resulting from venipuncture during the test.
4. Drop-outs because blood could not be obtained at maximum exercise resulting from peripheral vasoconstriction.

## Chapter IV
## RESULTS AND DISCUSSION

The purpose of this study was twofold: one, to measure and compare plasma catecholamines (norepinephrine and epinephrine) immediately before exercise (here on referred to as rest) and immediatly following a self-perceived exhaustion effort (here on referred to as self-perveived exhaustion effort) on a treadmill between a Type A behaviour oriented group with exercise-induced anaphylaxis and a normal group consisting of Types A and B behavior oriented individuals. Two, to measure other parameters, such as heart rate, lactate concentration, neutrophil leukocyte and platelet levels at rest and immediately following a self-perceived exhaustion effort.

Carlson's Full Rank multivariate analysis of variance, which included three univariate analyses of variance was used to analyse the data under the following hypotheses:

1) Group mean differences (the differences between the sums of the three groups of values obtained by averaging the rest and self-perceived exhaustion scores) for each variable.

2) Repeated mean differences (the differences between rest and self perceived exhaustion scores for each variable with the groups being regarded as one).

3) Interaction effects (the differences between the group means at rest and at self-perceived exhaustion) for each variable.

The results of the multivariate analysis of variance showed an overall insignificant ($p<0.05$) difference between the groups for all six variables at rest and at self-perceived exhaustion . Therefore, no post hoc procedures were employed. However, the univariate analysis of variance did show significant repeated differences for the three groups

in all of the variables. Significant interactions for two groups were observed, described and graphically represented. (All of the repeated differences discussed in each section will also be given in percentages of the pre-exercise value).

## 4.1 PHYSICAL CHARACTERISTICS

Table IV provides a summary of physical characteristics for the subjects with exercise-induced anaphylaxis (EX-I-ANA) and those with Type A and B behaviour patterns. No significant differences were observed between these three groups with respect to age, height and weight.

Also provided are the values and means of the self-perceived exhaustion loads reached by each group and their total exercise time. No significant differences were observed between the groups.

TABLE IV

PHYSICAL CHARACTERSTICS OF THE GROUP WITH EXERCISE-INDUCED ANAPHYLAXIS AND THE GROUP WITH TYPE A AND B BEHAVIOUR PATTERNS

| GROUP | S | AGE | HEIGHT (in.) | WEIGHT (lb.) | MAX.LOAD (mph) | TIME (min.) |
|---|---|---|---|---|---|---|
| EX-I-ANA | 1 | 25 | 63 | 107 | 8.5 * | 15'35" * |
| | 2 | 24 | 65 | 115 | 8.5 * | 16' * |
| | 3 | 24 | 68 | 128 | 8.5 * | 16'25" * |
| | mean | 24.33 | 65.33 | 116.67 | 8.50 | 16' |
| | SD | .57 | 2.25 | 10.6 | 0 | 46" |
| TYPE A | 1 | 25 | 63 | 106 | 7 | 14'50" |
| | 2 | 27 | 64.5 | 115 | 7 | 12'50" |
| | 3 | 27 | 69.2 | 138 | 9 | 18'40" |
| | 4 | 18 | 65 | 124 | 7 | 12' |
| | 5 | 21 | 66.3 | 126 | 8 | 16' |
| | 6 | 24 | 66 | 126 | 10 | 20' |
| | 7 | 24 | 64 | 128 | 8 | 15'10" |
| | 8 | 24 | 69 | 129 | 8 | 16' |
| | mean | 23.75 | 65.88 | 124.00 | 8.00 | 15'68" |
| | SD | 3.01 | 2.25 | 9.644 | 1.06 | 3'10" |
| Type B | 1 | 22 | 64 | 130 | 8 | 14'20" |
| | 2 | 21 | 62 | 108 | 7 | 11'50" |
| | 3 | 23 | 63 | 112 | 8 | 14'50" |
| | 4 | 26 | 63 | 120 | 6 | 10' |
| | 5 | 27 | 65 | 127 | 7 | 13' |
| | 6 | 25 | 70 | 150 | 9 | 18'30" |
| | 7 | 22 | 61 | 105 | 8 | 16' |
| | 8 | 25 | 64 | 113 | 8 | 16' |
| | mean | 23.88 | 64 | 120.63 | 7.63 | 14'31" |
| | SD | 2.16 | 2.72 | 14.77 | .91 | 3'07" |

SD:standard deviation S: subjects

EX-I-ANA:exercise-induced anaphylactic * mean of two runs

## 4.2 HEART RATE

Heart rate, measured with the univariate analysis of varaince did not prove to be significantly ($p<0.05$) different for each group (Appendix 3.1). However, a significant ($p<0.0001$) repeated difference (Appendix 3.2) was seen in heart rate for the groups from rest to self-perceived exhaustion effort: the increase was from 85 to 190 beats/min (215%) in the EX-I-ANA group, from 89 to 191 beats/min (225%) for the Type A group and from 75 to 194 beats/min (259%) for the Type B group (Figure 1).

This different increase in heart rate by group Type B has caused a significant ($p<0.05$) interaction effect (Figure 2). The greater increase in heart rate in the Type B group is due to this group's lower pre-exercise heart rate, depicting the more relaxed personality described by Jenkins colleagues (1979). Simpson and associates, (1974) also found that Type B individuals had a lower heart rate before exercise than Type A individuals.

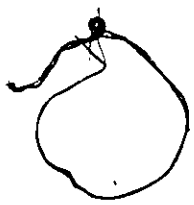


Figure 1

Repeated Mean Differences of Heart Rate at Rest and Self-Perceived Exhaustion

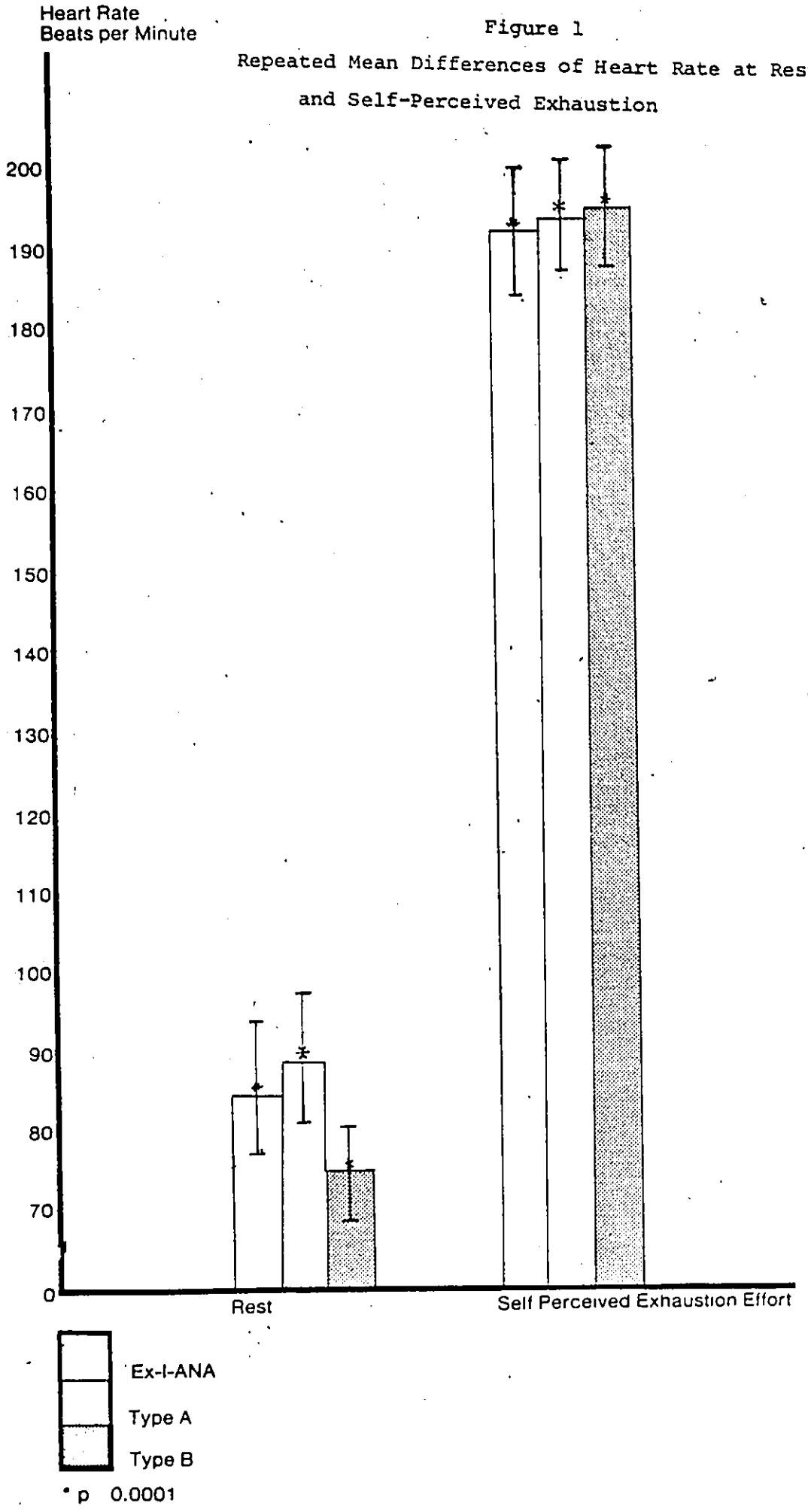
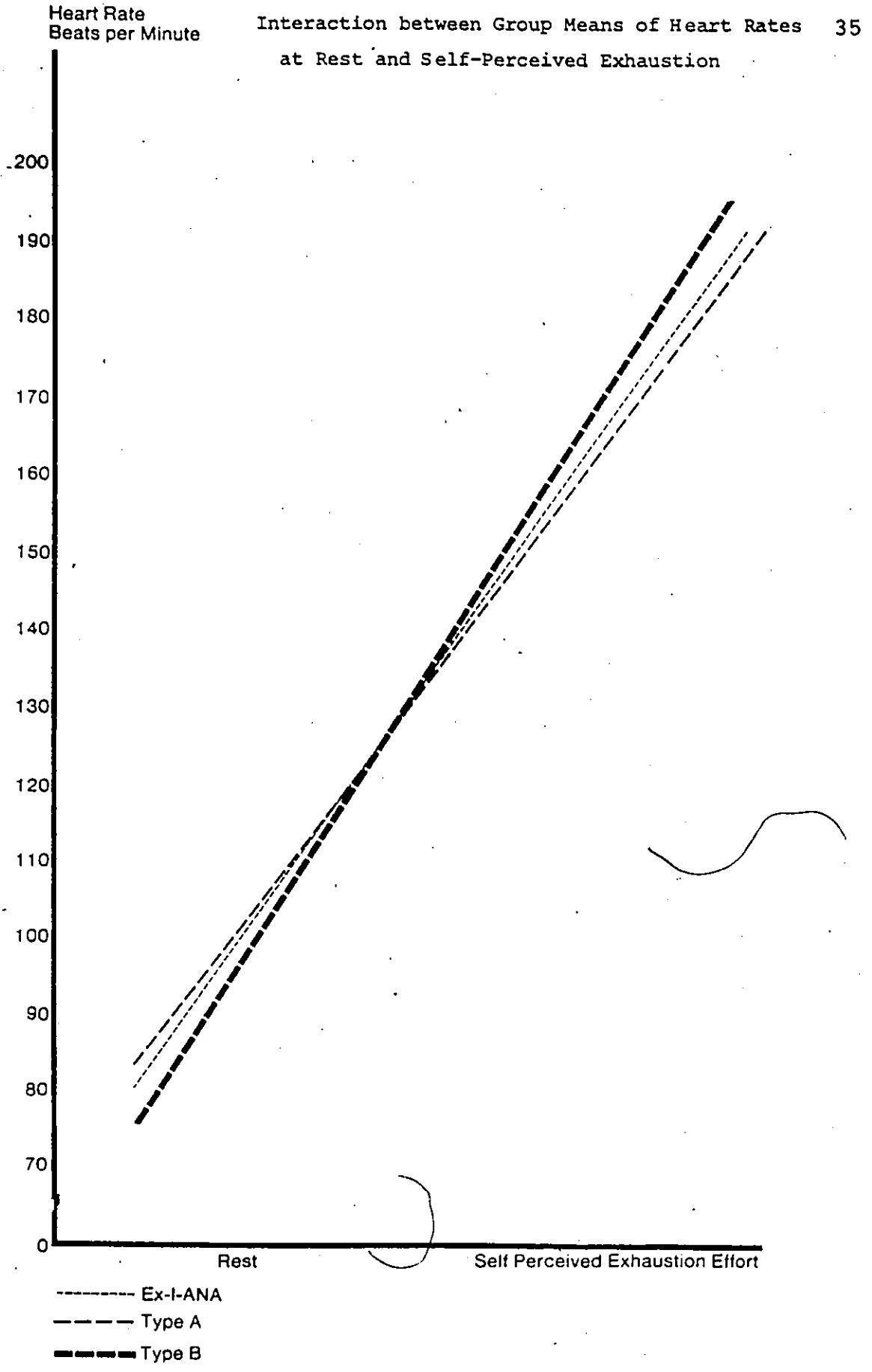


Figure 2

Interaction between Group Means of Heart Rates at Rest and Self-Perceived Exhaustion





## 4.3 LACTATE CONCENTRATION

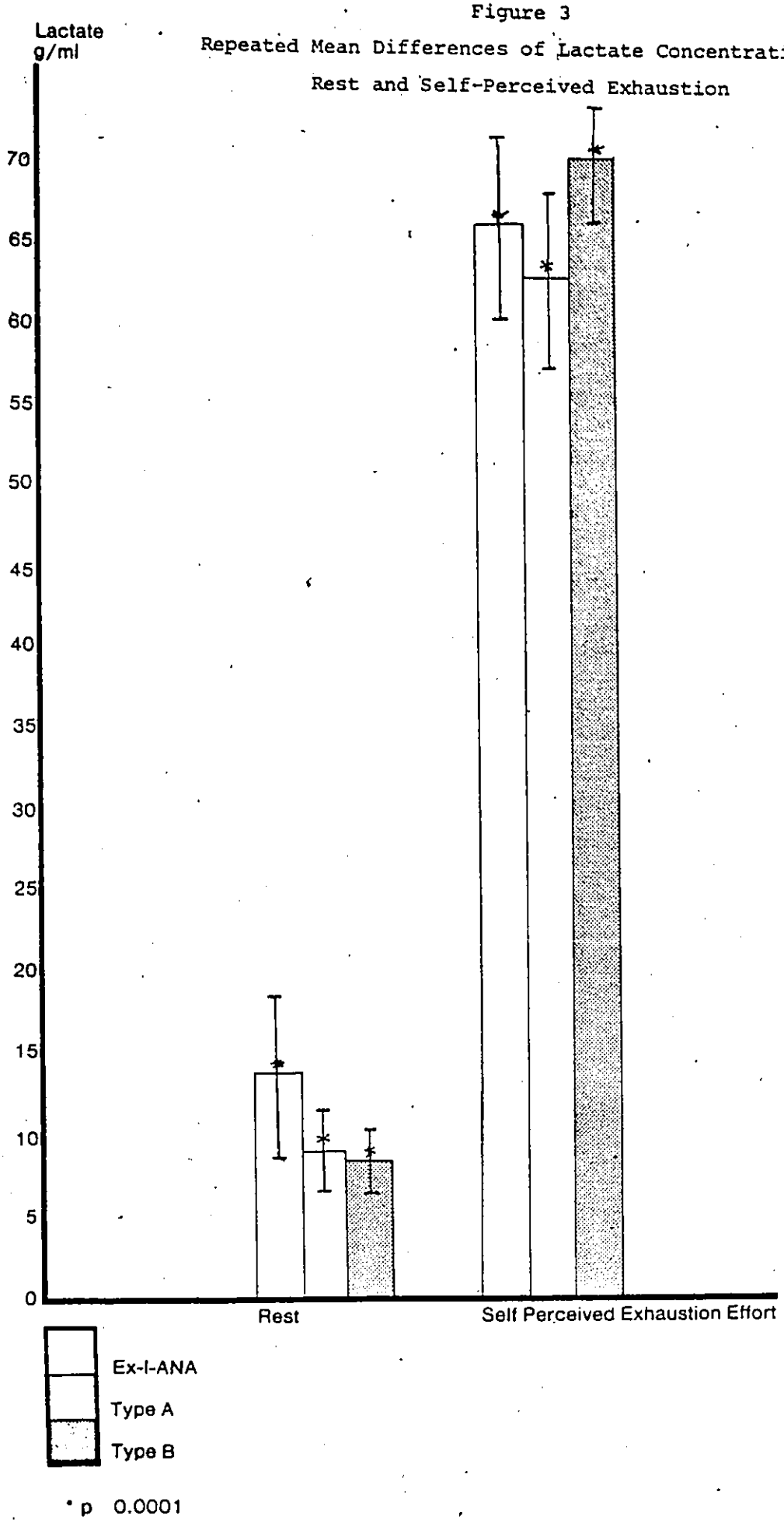
No significant ($p<0.05$) group differences or interaction effects (Appendix 3.1 and 3.3, respectively) were observed for lactate concentrations in the EX-I-ANA group, Type A or B groups respectively. However, significant ($p<0.0001$) repeated differences were observed. The increase in lactate levels from 12.31 to 66.00 g/ml (536%) , in the EX-I-ANA group, from 8.5 to 63.3 g/ml (745%) in the Type A group and from 8.5 to 68.75 g/ml (809%) in the Type B group (Figure 3).

The lactate concentrations observed in our study are in agreement with previousely recorded lactate values for normal subjects undergoing a graded exercise treadmill test (Karlsson, 1971; Karlsson and colleagues, 1970; Astrand and associates, 1963).

Figure 3

Repeated Mean Differences of Lactate Concentration at Rest and Self-Perceived Exhaustion





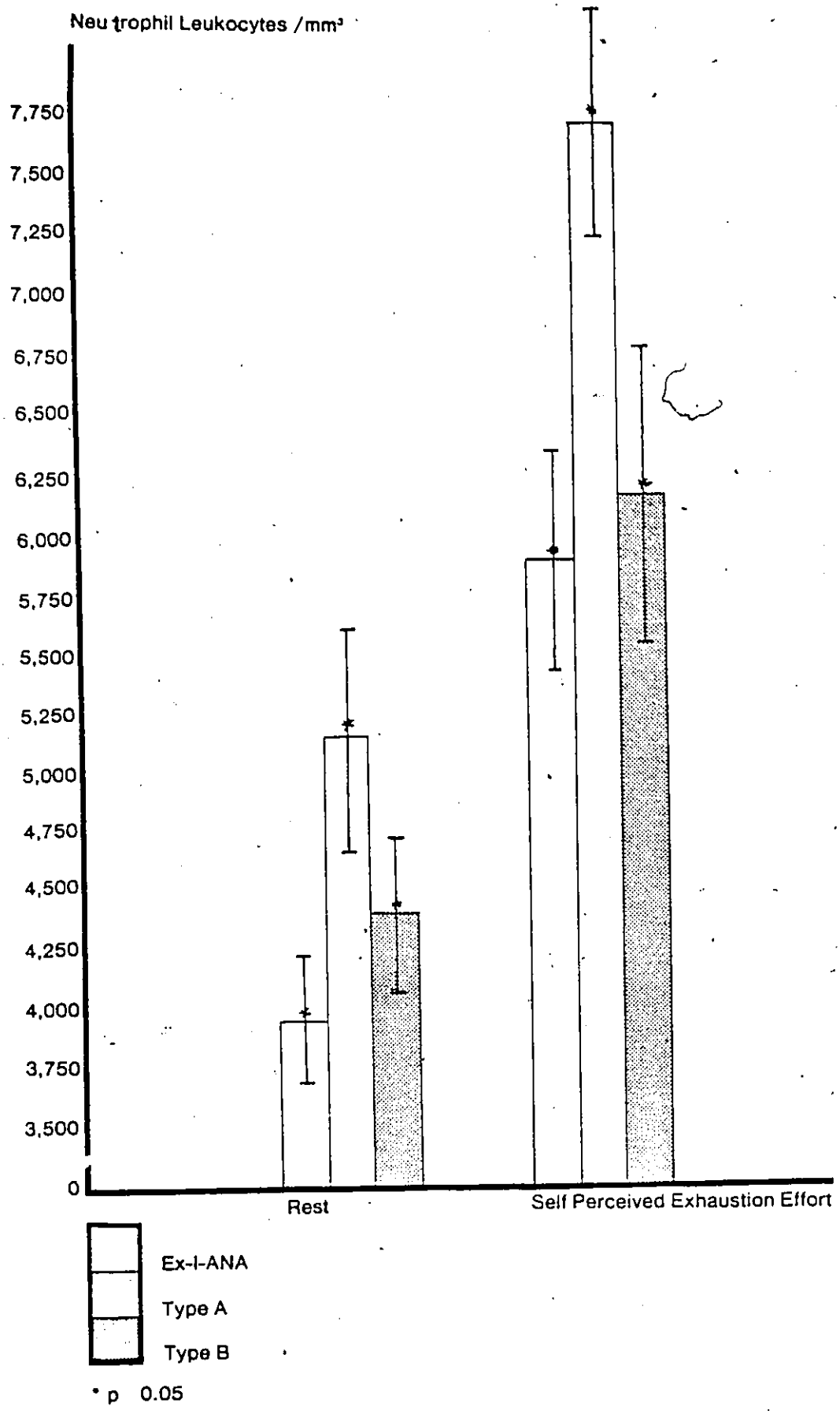
## 4.4 NEUTROPHIL LEUKOCYTES

The neutrophil leukocyte count was not significant ($p<0.05$) for group differences or interaction effects (Appendix 3.1 and 3.3 respectively).

The univariate analysis of variance (Appendix 3.2) showed a significant ($p<0.0001$) repeated difference for the neutrophil leukocyte count . The neutrophil count increased from 3801 to 5811/mm3 (153%) , from 5098 to 7663 mm/3, from 4289 to 6056/mm3 (142%) and from 5098 to 7663/mm3 (150%) in the EX-I-ANA, Type A and B groups respectively, (Figure 4).

Figure 4

Repeated Mean Differences of Neutrophil Leukocyte Count at Rest and Self-Perceived Exhaustion



The above findings are slightly higher than in the study by Ahlorg and Ahlborg (1967) who found a 112% increase from rest in the neutrophil leukocyte count in eight men who exercised on a bicycle ergometer for 30 minutes and whose final mean pulse rate was also 190 beats per minute.

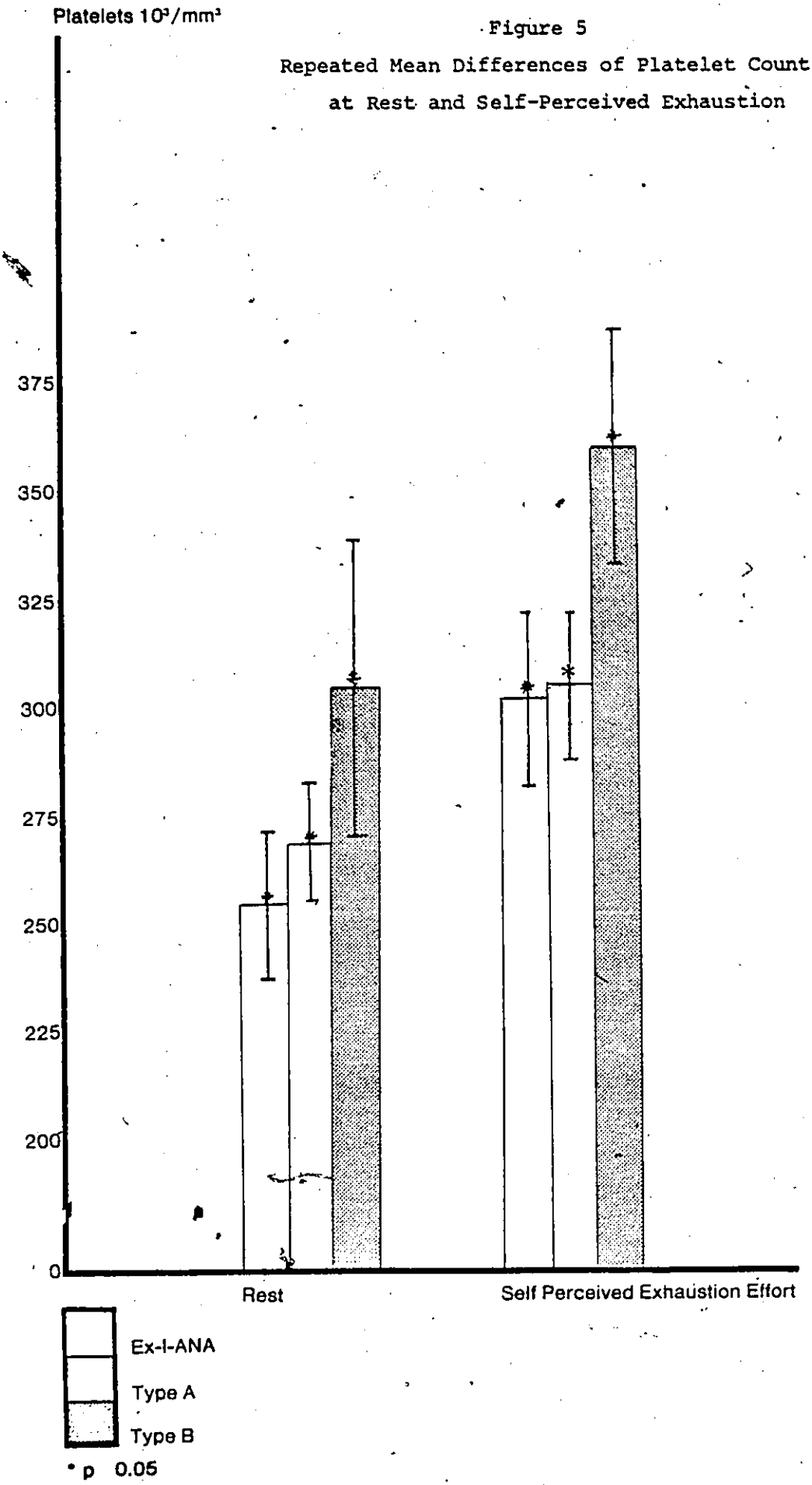
The observed leukocytosis during exercise appears to be the result of beta- receptor stimulation due to the increased release of epinephrine from the adreanal medulla. The increased concentration of epinephrine in blood has a direct effect on the bone marrow causing the release of leukocytes from that store, (Ahlborg and Ahlborg, 1967; Cress and coworkers, 1969).

## 4.5 PLATELETS

The univariate analysis of variance (Appendix 3.1 and 3.3, respectively) failed to show a significance ($p<0.05$) in group differences or interaction effects for platelet count. However, a significant ($p<0.0001$) repeated difference (Appendix 3.2) was revealed. The increase in platelets from rest to self-perceived exhaustion effort for EX-IANA were from 252500 to 306333/mm3 (121%); for Type A group from 265625 to 310203/mm3 (117%) and for Type B group from 310500 to 364500/mm3 (117%), (Figure 5).

Figure 5

Repeated Mean Differences of Platelet Count at Rest and Self-Perceived Exhaustion



Several authors (Biggs and colleagues, 1947; Sarajas and associates, 1961; Pegrun and coworkers, 1967; Dawson and Ogson, 1976) have also reported thrombocytosis after exercise. However, the increase in platelet count ranged from 53 to 353%. Sarajas and associates (1961) reported that moderate, short-term exercise has been shown to raise the platelet count by 350% while prolonged strenuous exercise as well as brief strenous exercise caused a minor (approximately 9%) increase and in some cases even a decrease in platelets; inducing thrombocytopenia, (Dawson and Ogson, 1969).

Biggs and colleagues, (1947) observed a 118% platelet increase after 10 minutes of exercise and a 60 % increase in platelets after 90 minutes of exercise. In our study, the average increase for the three groups was 88% after approximately 15 minutes of exercise. The exercise-induced thrombocytosis is in agreement with Dawson and Ogson (1969) where platelet increase ranged from 55 to 90% and the exercise was classified as brief; moderate to high intensity.

The mechanism of neutrophilic leukocytosis and thrombocytosis in exercise has been clarified by Sarajas and associates, (1961) and Pegrum and coworkers, (1967). They stated that the source of neutrophils and platelets, which appear to be released into the circulation may be from the pulmonary vascular bed, particularly its venous side, which is known to remove and discharge leukocytes and platelets on changing of the circulatory conditions; similar release may also occur in the peripheral vascular compartment (Ambrus and colleagues, 1954).

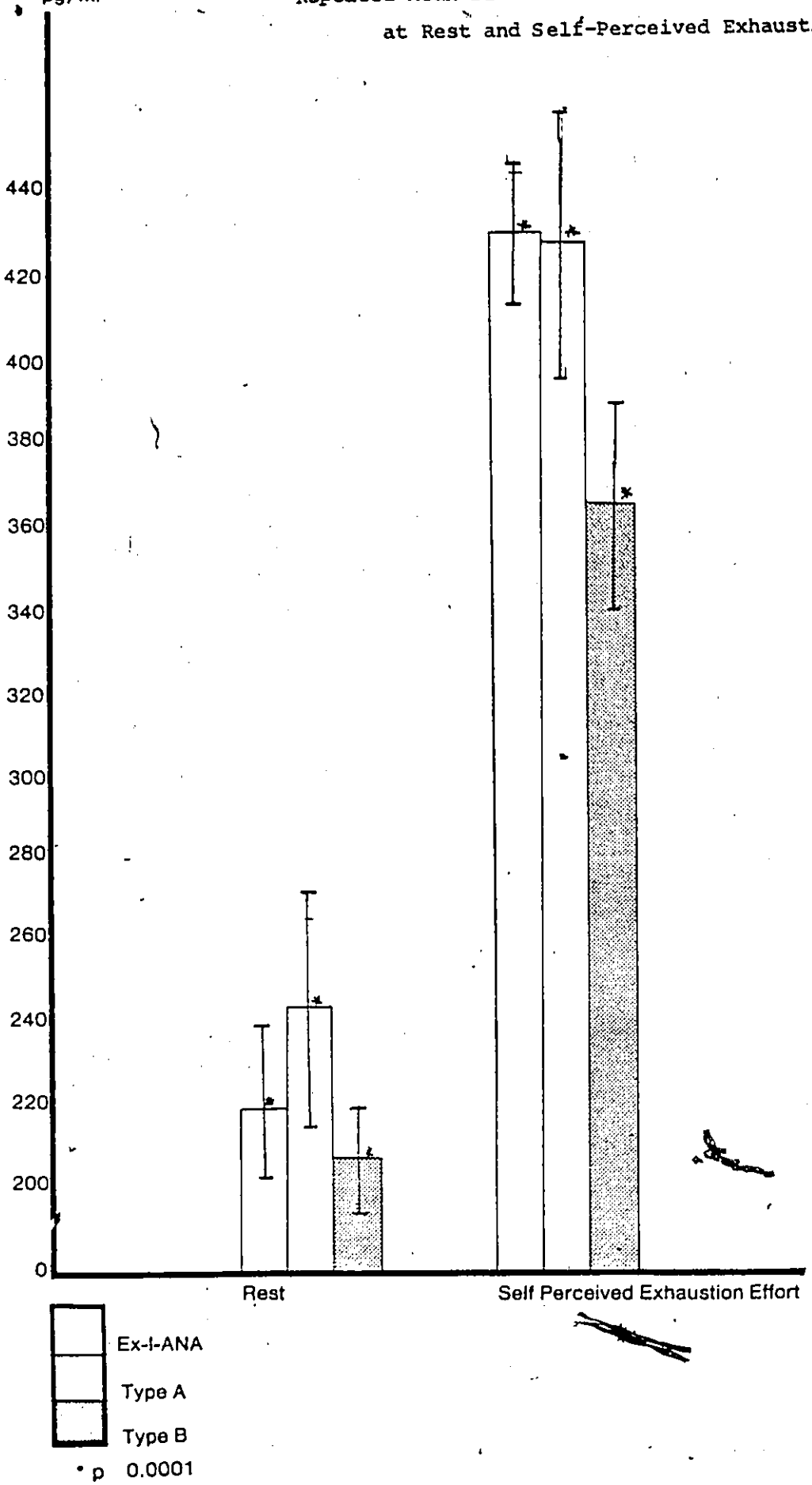
The haematocrit values usually rose but only slightly; the greatest increase encountered was 5.5 vol. percent. The small degree of haemoconcentration indicates that the increased counts of neutrophil leukocytes and platelets cannot be accounted for by concurrent haemoconcentration.

## 4.6 NOREPINEPHRINE AND EPINEPHRINE

No significant ($p<0.05$) group differences or interaction effects (Appendix 3.1 and 3.3, respectively) were revealed by the univariate analysis of variance for plasma norepinephrine levels. However, a significant ($p<0.0001$) difference (Appendix 3.2) was observed for repeated differences. The plasma norepinephrine concentration increased from 218 to 430 pg/ml (49%) in the EX-I-ANA group, from 241 to 472 pg/ml (44%) in the Type A group and from 206 to 363 pg/ml (43%) in the Type B group, (Figure 6).

Figure 6

Repeated Mean Differences of Plasma Norepinephrine at Rest and Self-Perceived Exhaustion



The above-mentioned results show that the EX-I-ANA group who achieved the highest self-perceived load also obtained the highest plasma norepinephrine level at that time; while the Type A group who achieved the second highest self-perceived load also had the second highest plasma norepinephrine level at the termination of the test; and the Type B group achieved the lowest self-perceived load and obtained the lowest plasma norepinephrine at the termination of the test.

These findings are in agreement with the theories on plasma norepinephrine and work reported by Kotchen and colleagues (1971) and Haggendal and coworkers (1970). These latter researchers stated that a direct relationship exists between plasma norepinephrine and intensity of exercise. The higher the intensity the greater the nerve impulse flow from the adrenergic neurons, and the plasma norepinephrine.

Plasma epinephrine levels did not prove to be significantly ($p<0.05$) different between the three groups (Appendix 3.1). However, a significant ($p<0.0001$) repeated difference (Appendix 3.2) was noted . The EX-I-ANA group showed an increase from 142 to 185 pg/ml (197%), The Type A group showed an increase from 119 to 200 pg/ml (196%) and the Type B group showed an increase from 110 to 194 pg/ml (176%), (Figure 7).

A significant ($p<0.05$) interaction (Appendix 3.3) was observed for plasma epinephrine. This interaction was caused by the significantly smaller increase in epinephrine by the EX-I-ANA group (Figure 8).

Figure 7

Repeated Mean Differences of Plasma Epinephrine at Rest and Self-Perceived Exhaustion



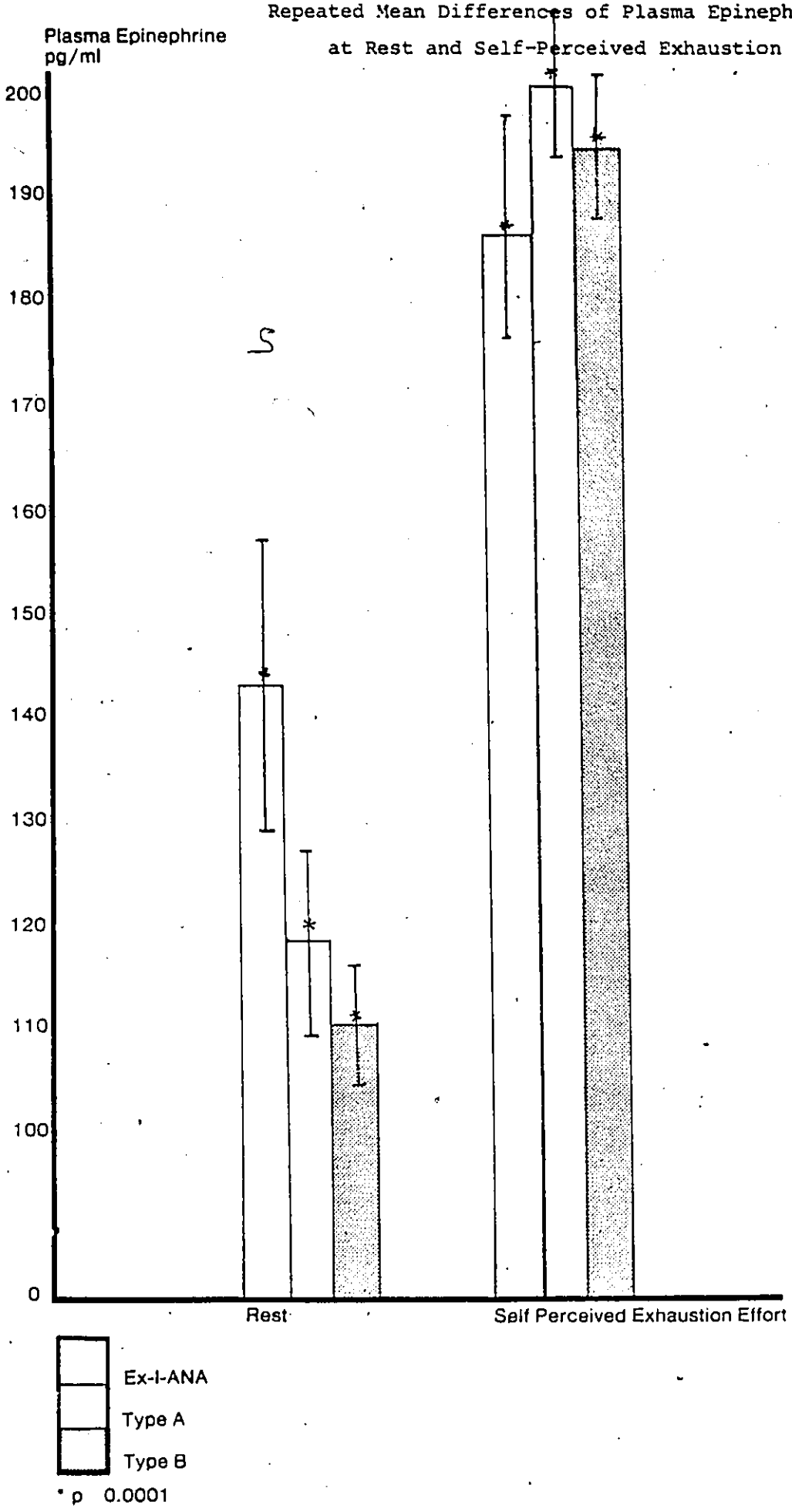
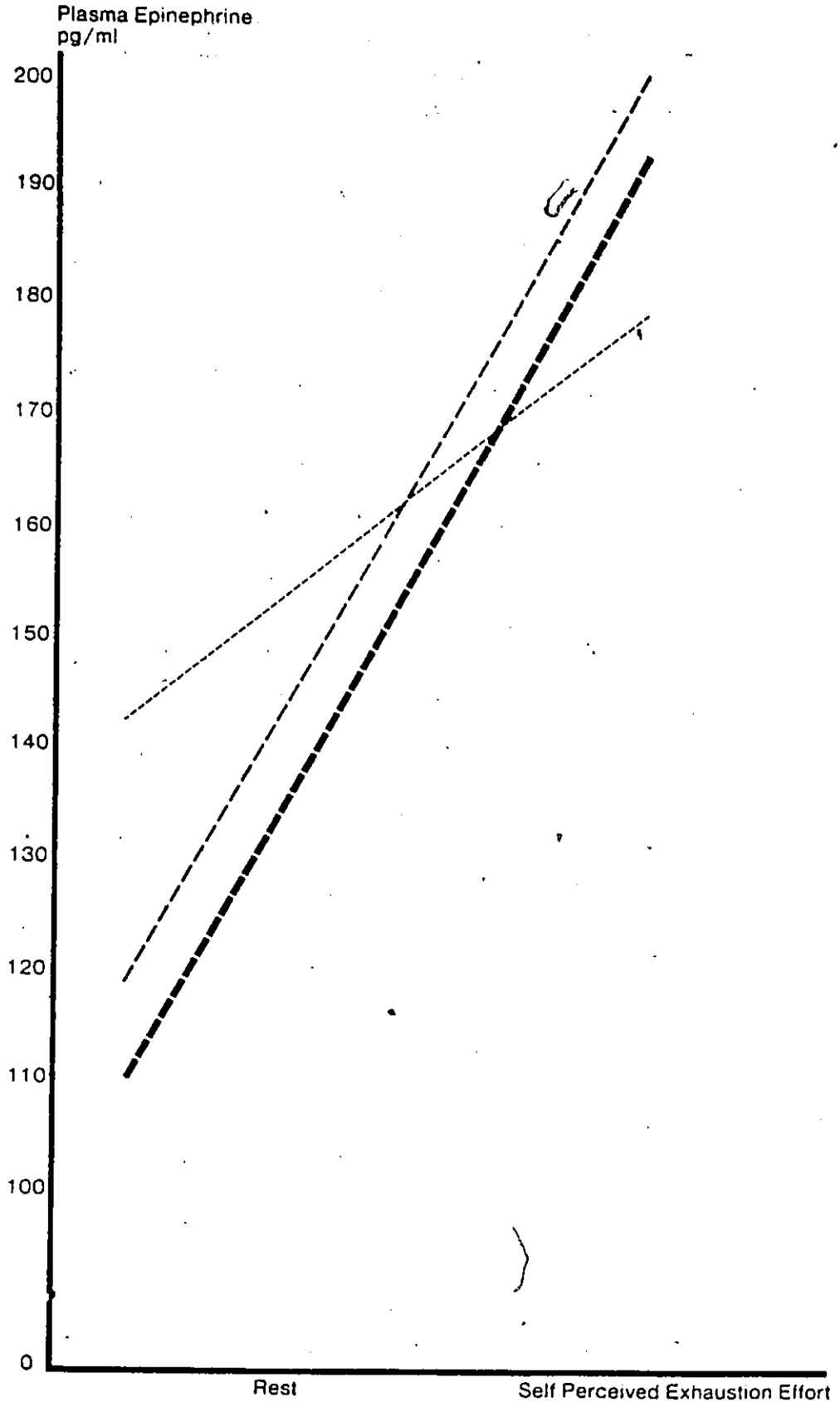


Figure 8

Interaction Between Group Means of Plasma Epinephrine at Rest and Self-Perceived Exhaustion





Dinsdale and Moss (1980) obtained a 210% increase in the norepinephrine levels and a 200% increase in the epinephrine levels in young men who climbed 20 flights of stairs during a 4-minute exercise. Our catecholamine levels were lower; this may be due to the different type of exercise used by Dinsdale and Moss (1980) and also that they used men for their subjects. The catecholamine increases obtained by Pierce and associates (1976) were 190% in plasma norepinephrine and 150% in epinephrine and this is in agreement with our results which show a 190% increase in plasma norepinephrine for the three groups and a 168% and 176% increase in plasma epinephrine for the Type A and B groups. The increase of 130% by the EX-I-ANA group revealed a significant interaction effect and may be the contributing factor to exercise-induced anaphylaxis. However, none of the three subjects developed exercise-induced anaphylaxis during our testing sessions. It was expressed by each subjects that attacks usually occurred only when the subject was under intense "psychological" tension."

The author of this thesis also was able to develop exercise-induced anaphyalxis only when under severe psychological tension. For example before or after before an exam, a deadline for an essay or report, or after a frustrating, emotionally disturbing conversation. Each attack occurred when the author exercised immediately before or after one of the above-mentioned events. Other times, when the author felt relaxed, exercise was enjoyable and no attacks occurred. The author has tried to induce an attack in a laboratory setting and exercise-induced anaphylaxis developed only once out of the six attampts. Once, the author developed exercise-induced anaphyalxis two days prior to the testing session and once the following day.

Research has shown that stress can decrease the beta-adrenergic receptor sensitivity (binding capacity) and increase the alpha-adrenergic receptor sensitivity, to natural and synthetic stimulants, (Kvetansky and U'Richard, 1980).

Due to the decreased stimulation of the beta-adrenergic receptors on the mast cells; the activity of the phophodiastrase enzyme may increase, causing the intracellular concentration of cyclic AMP to decrease and form 5'AMP. Once the concentration of the cyclic AMP are low steps 2 and 3 of the mast cell degranulation can take place and histamine release is in effect.

## Chapter V
## CONCLUSIONS AND RECOMMENDATIONS

The following conclusions have been made from the results of the present study:

1) Plasma norepinephrine levels, lactate concentrations, neutrophil leukocyte and platelet counts do not differ significantly in subjects with exercse-induced anaphylaxis and Type A and B subjects at rest or at self-perceived exhaustion effort.

2) The subjects with exercise-induced anaphylaxis had a significantly different change in plasma epinephrine than the Type A and B groups at self-perceived exhaustion effort.

3) None of the subjects with exercise-induced anaphylaxis manifested anaphylaxis during the exercise tests.

4) The Type B group had a lower mean pre-exercise heart rate which is representative of the more relaxed behaviour pattern.

Therefore it may be stated that plasma norepinephrine is not the triggering agent of exercise induced anaphylaxis.

Based on these conclusions the following recommendations seem warranted:

1) It would be valuable to measure plasma catecholamines, particularly epinephrine levels, in the EX-I-ANA subjects at the onset, during and following an attack of exercise-induced anaphylaxis.

2) An increase in statistical validity by augmenting the number of EX-I-ANA subjects seems warranted.

3) It would also be very useful to perform in vitro studies on leukocytes of EX-I-ANA subjects to determine if the adrenergic receptor number and binding capacity (sensitivity) have been altered.

4) It would be feasible in a future study to exercise subjects with exercise-induced anaphylaxis and concurrently induce "psychological tension" in order to provoke exercise-induced anaphylaxis. Such was the initial plan for this thesis, but due to the rection by the ethics committee, such methodology was not possible.

## REFERENCES


Ahlborg, B., Ahlborg, G. Exercise Leukocytosis with and without BetaAdrenergic Blockade. ACTA MEDICA SCANDINAVICA, 187:241-246, 1970.

Ambrus, C.,M., Ambrus, J.L., Johnson, G. C., Packman, E. W., Chesnuck, W. S., Back, N., Harrison, W. E. Lung and White Blood Cell Level. AMERICAN JOURNAL OF PHYSIOLOGY, 178:33-34, 1954.

Astrand, P-O., Rodhals K. Circulation. In TEXTBOOK OF WORK PHYSIOLOGY, New York: McGraw-Hill, 178, 1977.

Astrand, P.-O., Hallback, I., Hedman, R. I., Saltin, B. Blood Lactates after Prolonged, Severe Exercise. JOURNAL OF APPLIED PHYSIOLOGY, 18:619-629, 1963.

Austen, K.F. Systemic Anaphyalxis in the Human Lung. NEW ENGLAND JOURNAL OF MEDICINE, 291:661-664, 1976.

Austen, K.F. Histamine and other Mediators of Allergic Reactions. IN IMUUNOLOGICAL DISEASES, ed. Samter, M., 2nd edition. Boston:Little, Brown & Co., 211-225, 1971.

Ball, J.M., Kaminsky, N.I., Hardman, J.G., Boards, A.E., Sutherland, E.W., Liddle, G.W. Effects of Catecholamines and Adrenergic Blocking Agents on Plasma and Urinary cyclic Nucleotids in Man. JOURNAL OF CLINICAL INVESTIGATIONS, 51:2124-2150,1972.

Beaven, M.A. Histamine. NEW ENGLAND JOURNAL OF MEDICINE, 294:320-325,1979.

Biggs, R., MacFarlane, R.G., Pilling, J. Observations on Fibronolysis and Experimental Activity Produced by Exercise or Adrenalin. LANCET, 252:402-409, 1947.

Broder, I. Anaphylaxis. In INFALMMATION, IMMUNITY AND HYPERSENSITIVITY. 2nd edition. Ed. Movat, H.Z. New York: Harper and Row, 320-36-, 1979.

Butcher, R.S., Robinson, G.A., Sutherland, E.W. Cyclic AMP and Hormone Action. In BIOCHEMICAL ACTIONS OF HORMONES, Vol. 2. Ed. Litweck, G. New York: Academic Press,81-107,1972.

Christenson, N.J., Galbo, J.F,, Hanson, J.F,, Hesse, B., Richter , E.A. Catecholamines and Exercise. DIABETES, 28:58-62,1979.

Christenson, N.J., Brandesborg, O. The relationship between Plamsa Catecholamine Concentration and Pulse Rate during Exercise and Standing. EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, 3:299-306.

Cloves, G.H.A., O'Donnelll, T.F. Heat Stroke. NEW ENGLAND JOURNAL OF MEDICINE, 29;564-566,1974.

Coffey, R.B., Middleton, E. Release of Histamine from Rat Mast Cells by Lysosomal Cationic Protein. INTERNAL ARCHIVES OF ALLERGY, 45:543-560, 1973.

Costill, D.l. Sweating: Ist Composition and Effects on Body Fluids. ANNALS OF NEW YORK ACADEMY OF SCIENCE, 310:160-174,1977.

Cousineau, D., Ferguson, R,J., deChamplain, J. Catecholamine in Coronary Sinus during Exercise in Man Before and After Training. JOURNAL OF APPLIED PHYSIOLOGY, 43(5):801-806, 1977.

Cress, C.H., Clare, F.B., Gelhorn, E. The Effects of Anoxia and Anemia on the Leukocyte Count. THROMBOSIS DIAPHESIS HEAMATOLOGICA, 42:247-253,1969.

Creyer, P. E., Isotope-derivative Measurments of Plasma Norepinephrine and Epinephrine in Man. DIABETES, 25:1071-1082,1976.

Davis, C., Few, J., Foster, K.G., Sargeant, A.J. Plasma Catecholamines concentration during Exercise Involving Different Muscle Groups. JOURNAL OF PHYSIOLOGY, 236:21P-22P, 1974.

Dawson, A.A., Ogson, D. Exercise-Induced Thrombocytosis. ACTA HAEMATOLOGICA, 42:247-253,1969.

Dimsadale, G.E., Moss, J. Plasma Catecholamines in Stress and Exercise. JOURNAL OF AMERCIAN MEDICAL ASSOCIATION, 242:340-342, 1980.

Elmadjian, F., Hope, J.M., Lamson, E.T. Excretion of Epinephrine and Norepinephrine under Stress. RECENT PROGRESS IN HORMONE RESEARCH, 14:513-525,1958.

Engel, G.L. FAINTING: PHYSIOLOGICAL AND PSYCHOLOGICAL CONSIDERATIONS, Illnois:Bannerstone House, 2-25, 1950.

Goodman, L.S., Gilian, A. THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. New York: McMillan, 245-259, 1965.

Gutmann, J., Wahlefeld, A.W. L-(+)-Lactate. Determinations with Lactate Dehydrogenase and NAD. In: METHODS OF ENZYMATIC ANALYSIS. 2nd edition. Ed. Bergmeyer, H.W. New York: Academic Press, 1464, 1974.

Haggendal, J., Startly, L.H., Saltin, B. Arterial Norepinephrine Concentraions during Exercise in Relations to Relative Work Levels. SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATIONS, 26:337-342, 1970.

Hanson, P.G. Heat Injuries in Runners. THE PHYSICIAN AND SPORTSMEDICINE, 7:91-96, 1979.

Hedquist, P. Studies on the Effect of Prostaglandins E1 and E2 on Sympathetic neuromusclular transmmison in some animals. ACTA PHYSIOLOGICA SCANDINAVICA. Suppl. 435:139-141, 1970. Hickler, R.B., Howe, J.P. Syncope: Its Etiology, Pathophysiology and Management. In: PRIMARY CARDIOLOGY, 46-51, 1979.

Howley, E.T. The Effects of Different Intensities of Exercise on the Excretion of Epinephrine and Norepinephrine. MEDICAL SCIENCE AND SPORT. 8:219-222, 1976.

Hynie, V. (personal Communications), 1980.

Jack, D. E. Adrenergic Agents. In: ALLERGY, Vol 2, eds. Middleton, E., Reed. C.F., Ellis, E.F. St. Louis: The C.V. Mosby Co., . 234-245, 1978.

Jenkins, C.D., Zyzanski, S.J., Rosenman, R.H. JENKINS ACTIVITY SUREVY MANUAL, New York: Harcourt, Brance and Jovanovich Inc. 1-13, 1979.

Karlsson, J. Lactate in Working Muscles after Prolonged Exercise. ACTA PHYSIOLOGICA SCANDINAVICA. 82:123-130,1971.

Karlsson, J. Diamant, B., Saltin B. Muscle Metabolites during Submaximal and Maximal Exercise in Man. SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATIONS, 29:598-602, 1970.

Kopin, J.J., Lake, R.C. Zeigler, M. PLasma Levels of Norepinephrine. ANNALS OF INTERNAL MEDICINE, 88: 671-680, 1978.

Levine, R. A. The Role of cAMP and Prostaglandins in Hepatic and Gastrointestinal Functions. In:PROSTAGALNDINS AND CYCLIC AMP: BIOLOGICAL AND CLINICAL APPLICATIONS. Eds: Kahn, R.H., Lands, W.E.M. New York: Academic Press, Inc. 75-96, 1973.

Manehm, P., Lecerof, H., Hokfelt, B. Plasma catecholamine levles in the Left Renal Vein and Peripheral Vessels in Healthy Males at Rest and During Exercise. ACTA PHYSIOLOGICAL SCANDINAVICA, 104: 364-369,1978.

Mathews, K.O., Pan, P. Post-Exercise Hyperhistamenia, Dermographia and Wheezing. ANNALS OF INTERNAL MEDICINE, 72:241-249, 1970.

Maulits, R.N. Exercise-Induced Anaphylactic Reaction to Shellfish. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, 63:433-434, 1979.

Mason, J. W., Hartley, L.H, Kothcen, T.A., Mougey, E.Sh., Ricketss, P.T., Jones, L.G. Plasma Cortisol and Norepinephrine Responses in Anticipation of Muscular Exercise. PSYCHOSOMATIC MEDICINE, 35:406-414,1973.

McIntire, F.S. Histamine Release by Antigen-Antibody Reactions. In INTERNAL ENCYCLOPEDIA OF PHARMACOLOGY AND THERAPEUTICS, Section 74, Vol I, Eds. Bovet, D., Burgen, A.S.V., Cheymol, G., Koelle, G., Michelson, M.J., Peter, J. New York:Pergamon Press, 45-79, 1973.

Movat, H.Z. Chemical Mediators of the Vascular Phenomena. MEDICAL CLINICS OF NORTH AMERCIA, 56:541-556,1972.

Orange, R.P., The Immunological Release of Chemical Mediators. In APPROACHES TO PHARMACOLOGICAL ANTAGONISM, eds: Beers, R.F., Basset, E.G. New York: Raven Press, 324-350,1976.

Orange, R., Donsky, G.J. Anaphylaxis. In ALLERGY, Vol 2, eds. Middleton,E., Reed, C.E., Ellis, E.F. St. Louis: The C.V. MOsby Co., 563-573, 1978.

Pegrun, G.D., Harrison, K.M., Shaw, S., Haselton, A., Wolfe, S. Effect of Prlonged Exercise on Platelet Adhesivness. NATURE, 213:301-302, 1967.

Peuler J. D., Johnson, G.A. Simultanoues Single Isotope Radioenzymatic Assay of Plasma Norepinephrine, Epinephrine and Dopamine. LIFE SCIENCES, 21:625-636, 1977.

Pierce, D., Kuppart, I., Harry, D. Urinary Epinephrine and Norepinephrine Levels in Women Athletes during Training and Competition. EUROPEAN JOURNAL OF APPLIED PHYSIOLOGY. 36:1-6, 1976.

Plaut, M., Lichtenstein, L.M. Cellular and Chemical Basis of Allergic Inflammatory Response. In ALLERGY, Vol I, eds. Middleton E., Reed, C.E., Ellis, E.F. St. Louis: The C.V. Mosby Company, 115-138, 1978.

Ranadive, N. S., Ruben, D. H., Histamine Release from Mast Cells, and Basophils. In: INFLAMMATION, IMMUNITY, HYPERSENSITIVITY, ed. Movat, H.Z. New York, Harper and Row, 376-409, 1979.

Ranadive, N.S., Ruben, D. H. Mechanism of Histamine Release from Rat Mast Cells by Compound 48/80, Comparison with the Release Induced by Cationic Protein. INTERNAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY, 44:745-758, 1973.

Rang H. P., Ritter, R.W. On the Mechanism of Desensitization at Cholinergic Receptors. MOLECULAR PHARMACOLOGY, 6: 357-360, 1970.

Richter, M. Immunopathology. in PHYSICIAN's GUIDE TO THE THEORY AND PRACTICE OF CLINICAL IMMUNOLOGY, Ottawa: University Press, 54-68, 1980.

Schayer, R. Evidence that Induced Histamine is an Intrinsic Regulator of Microvasculature. AMERICAN JOURNAL PHYSIOLOGY, 202:66-72, 1970.

Sheffer, A., Austen, K.A. Original Article: Exercise-Induced Anaphylaxis. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, 66:106-110, 1980.

Siegal, A.J. Exercise-Induced Anaphylaxis. THE PHYSICIAN AND SPORTSMEDICINE, 8:95-98, 1980.

Simpson, M.T., Olewine, D.A., Jenkins, C.D., Ramsing, F. H., Zyznaksi, S. J., Thomas, G. Hames, G. C. Exercise-Induced Catecholamine and Platelet Aggregation in the Coronary-Prone behavior Pattern. PSYCHOSOMATIC MEDICINE. 36:476-487, 1974.

Soter, A.A., Waverman, S.I., Austen, K.F. Cold Uricaria: Release into the Circulation of Histamine and Eosinophilic Factor of Anaphylaxis during Cold Challange. NEW ENGLAND JOURNAL OF MEDICINE, 294;687-690, 1976.

Stanworth, D.R. The Role of the Antibody in Immediate Hypersensitivity Reactions. In MECHANISMS IN ALLERGY;REAGIN-MEDIATED HYPERSENSITIVITY, Vol VI ed. Goodfreind, L., Sehorn, A.H., Orange, R.P., New York: Marcel Dekker, Inc. 369-383, 1972.

U'Richard, D. C., Kvetansky, R. Central and Peripheral Adrenergic Receptors in Acute and Repeated Immobilization Stress. CATECHOLAMINES AND STRESS;RECENT ADVANCES, ed. Kvetansky, R., Kopin, D. North Holland:Elsevier Inc. 299-308, 1980.

Uvnas, B. Correleation Between Morphological and Biochemical Events in Antigen-Antibody Histamine Release from Mast Cells. In: MECHANISMS IN ALLERGY-REAGIN MEDIATED HYPERSENSITIVITY Vol VI, eds. Goodfried, L., Sehorn, A.H., Orange, R. P, New York:Marcel Dekker, Inc. 363-393, 1972.

Watson, R.D.S., Hamilton, C.A., Jones, D.K., Ried, J.L. Stellard, T.J., Littler, W.A. Sequential Changes in Plasma Noradenraline during Bicycle Exercise. Clinical Science, 58: 37-43, 1980.

# APPENDICES

# APPENDIX 1

APPENDIX 1 Multistage stress test protocol

| Stages | Speed (mph) | Time (min.) |
|---|---|---|
| 1 | 3 | 0-4 |
| 2 | 5 | 4-7 |
| 3 | 6 | 7-10 |
| 4 | 7 | 10-13 |
| 5 | 8 | 13-16 |
| 6 | 9 | 16-19 |

# APPENDIX 2

APPENDIX 2 Raw scores at rest and at self-perceived exhaustion effort for the six variables.

APPENDIX 2.1 Raw data for HEART RATE in beats per minute at rest and self-perceived exhaustion effort.

| GROUPS | S | REST | SELF-PERCEIVED EXHAUSTION EFFORT |
|---|---|---|---|
| EX-I-ANA | 1 | 76 | 184 |
| | 2 | 94 | 189 |
| | 3 | 86 | 198 |
| TYPE A | 1 | 95 | 192 |
| | 2 | 85 | 205 |
| | 3 | 96 | 185 |
| | 4 | 70 | 173 |
| | 5 | 91 | 189 |
| | 6 | 90 | 200 |
| | 7 | 94 | 187 |
| | 8 | 91 | 195 |
| TYPE B | 1 | 77 | 195 |
| | 2 | 55 | 182 |
| | 3 | 99 | 204 |
| | 4 | 68 | 198 |
| | 5 | 61 | 193 |
| | 6 | 67 | 194 |
| | 7 | 78 | 200 |
| | 8 | 95 | 190 |

APPENDIX 2.2 Raw data for PLASMA NOREPINEPHRINE in pg/ml at rest and self-perceived exhaustion effort.

| GROUPS | S | REST | SELF-PERCEIVED EXHAUSTION EFFORT |
|---|---|---|---|
| EX-I-ANA | 1 | 194 | 417 |
| | 2 | 187 | 428 |
| | 3 | 273 | 445 |
| TYPE A | 1 | 240 | 520 |
| | 2 | 190 | 455 |
| | 3 | 219 | 386 |
| | 4 | 285 | 395 |
| | 5 | 260 | 416 |
| | 6 | 245 | 428 |
| | 7 | 280 | 430 |
| | 8 | 210 | 392 |
| TYPE B | 1 | 205 | 426 |
| | 2 | 300 | 451 |
| | 3 | 246 | 355 |
| | 4 | 194 | 312 |
| | 5 | 245 | 345 |
| | 6 | 040 | 340 |
| | 7 | 238 | 360 |
| | 8 | 180 | 310 |

APPENDIX 2.3 Raw date for PLASMA EPINEPHRINE in pg/ml at rest and self-perceived exhaustion effort.

| GROUPS | S | REST | SELF-PERCEIVED EXHAUSTION EFFORT |
|---|---|---|---|
| EX-I-ANA | 1 | 127 | 188 |
| | 2 | 139 | 170 |
| | 3 | 160 | 198 |
| TYPE A | 1 | 100 | 170 |
| | 2 | 146 | 212 |
| | 3 | 110 | 186 |
| | 4 | 140 | 220 |
| | 5 | 135 | 218 |
| | 6 | 126 | 224 |
| | 7 | 105 | 190 |
| | 8 | 090 | 184 |
| TYPE B | 1 | 099 | 183 |
| | 2 | 130 | 209 |
| | 3 | 094 | 195 |
| | 4 | 120 | 185 |
| | 5 | 128 | 186 |
| | 6 | 098 | 170 |
| | 7 | 096 | 245 |
| | 8 | 118 | 182 |

APPENDIX 2.4 Raw data for LACTATE CONCENTRATION in g/ml at rest and at self-perceived exhaustion effort.

| GROUPS | S | REST | SELF-PERCEIVED EXHAUSTION EFFORT |
|---|---|---|---|
| EX-I-ANA | 1 | 18.44 | 80.79 |
| | 2 | 7.62 | 66.45 |
| | 3 | 10.87 | 51.05 |
| TYPE A | 1 | 14.34 | 53.30 |
| | 2 | 8.55 | 90.25 |
| | 3 | 10.54 | 58.00 |
| | 4 | 6.12 | 56.40 |
| | 5 | 5.30 | 46.57 |
| | 6 | 9.84 | 99.28 |
| | 7 | 9.76 | 43.77 |
| | 8 | 4.85 | 59.35 |
| TYPE B | 1 | 6.67 | 63.89 |
| | 2 | 7.11 | 58.80 |
| | 3 | 10.07 | 32.46 |
| | 4 | 7.99 | 68.16 |
| | 5 | 10.90 | 79.97 |
| | 6 | 8.46 | 91.82 |
| | 7 | 5.80 | 71.81 |
| | 8 | 10.97 | 83.12 |

APPENDIX 2.5 Raw date for NEUTROPHIL LEUKOCYTES /mm3 at rest and at self-perceived exhaustion effort.

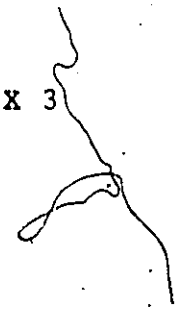
| GROUPS | S | REST | SELF-PERCEIVED EXHAUSTION EFFORT |
|---|---|---|---|
| EX-I-ANA | 1 | 3075 | 4820 |
| | 2 | 3345 | 4885 |
| | 3 | 4984 | 7730 |
| TYPE A | 1 | 4900 | 9150 |
| | 2 | 4830 | 8570 |
| | 3 | 6800 | 8700 |
| | 4 | 4050 | 7050 |
| | 5 | 7680 | 8980 |
| | 6 | 4300 | 5700 |
| | 7 | 2624 | 4160 |
| | 8 | 5600 | 9000 |
| TYPE B | 1 | 4910 | 9150 |
| | 2 | 6480 | 8190 |
| | 3 | 2770 | 5810 |
| | 4 | 3220 | 5320 |
| | 5 | 3310 | 5415 |
| | 6 | 4340 | 5725 |
| | 7 | 5010 | 5995 |
| | 8 | 4200 | 4850 |

APPENDIX 2.6 Raw data for PLATELETS /mm3 at rest and at self-perceived exhaustion effort.

| GROUPS | S | REST | SELF-PERCEIVED EXHAUSTION EFFORT |
|---|---|---|---|
| EX-I-ANA | 1 | 29750 | 348000 |
| | 2 | 24600 | 301500 |
| | 3 | 21700 | 269500 |
| TYPE A | 1 | 25600 | 275000 |
| | 2 | 25000 | 298000 |
| | 3 | 23700 | 291000 |
| | 4 | 28400 | 260550 |
| | 5 | 24600 | 266000 |
| | 6 | 27300 | 348580 |
| | 7 | 36300 | 492500 |
| | 8 | 21600 | 260000 |
| TYPE B | 1 | 25900 | 339000 |
| | 2 | 50000 | 551000 |
| | 3 | 31100 | 359000 |
| | 4 | 35100 | 407000 |
| | 5 | 27300 | 333000 |
| | 6 | 27300 | 348000 |
| | 7 | 29200 | 309000 |
| | 8 | 22500 | 270000 |

# APPENDIX 3

## LEGEND FOR APPENDIX 3



| | |
|---|---|
| SSHYP | Sum of Squares for Hypothesis |
| SSERR | Sum of Squares for Error |
| DFHYP | Degrees of Freedom for Hypothesis |
| DFERR | Degrees of Freedom for Error |
| MSHYP | Mean Square for Hypothesis |
| MSERR | Mean Square for Error |
| F | F Ratio |
| P-VALUE | Probability |
| VAR | Variate |
| A1 | HEART RATE |
| A2 | LACTATE CONCENTRATION |
| A3 | PLATELET COUNT |
| A4 | NEUTROPHIL LEUKOCYTE |
| A5 | PLASMA NOREPINEPHRINE |
| A6 | PLASMA EPINEPHRINE |

APPENDIX 3.1 Univariate analysis of variance for hypothesis 1 GROUP DIFFERENCES

UNIVARIATE SUMMARY

| VAR | SSHYP | SSERR | DFHYP | DFERR | MSHYP | MSERR | F | P-VALUE |
|---|---|---|---|---|---|---|---|---|
| A1 | 105.75 | 1211.54 | 2 | 16 | 52.87 | 75.72 | 0.698 | 0.5120 |
| A2 | 36.24 | 1532.01 | 2 | 16 | 18.12 | 95.75 | 0.189 | 0.9294 |
| A3 | ****** | ******* | 2 | 16 | ***** | ***** | 1.279 | 0.3053 |
| A4 | ****** | ******* | 2 | 16 | ***** | ***** | 1.837 | 0.1913 |
| A5 | 10645.23 | 27967.19 | 2 | 16 | 5322.62 | 1747.94 | 3.045 | 0.0757 |
| A6 | 363.64 | 4247.04 | 2 | 16 | 181.44 | 265.44 | 0.685 | 0.5183 |

******* replaces the number which is too large for the summary table

APPENDIX 3.2 Univariate analysis of variance for hypothesis 2

REPEATED DIFFERENCES

UNIVARIATE SUMMARY

| VAR | SSHYP | SSERR | DFHYP | DFERR | MSHYP | MSERR | F | P-VALUE |
|---|---|---|---|---|---|---|---|---|
| A1 | ***** | 2039.50 | 1 | 16 | ****** | 127.47 | 1431.46 | p<.0001 |
| A2 | 48815.03 | 5450.45 | 1 | 16 | 48815.04 | 340.65 | 143.29 | p<.0001 |
| A3 | ******* | ******* | 1 | 16 | ******** | ***** | 36.06 | p<.0001 |
| A4 | ****** | ******* | 1 | 16 | ******** | ***** | 48.06 | p<.0001 |
| A5 | ****** | 595999.75 | 1 | 16 | ******** | 3724.98 | 141.76 | p<.0001 |
| A6 | 74762.33 | 7460.67 | 1 | 16 | 76762.33 | 466.29 | 160.33 | p<.0001 |

****** replaces the number which is too large for the summary table

APPENDIX 3.3 Univariate analysis of variance for hypothesis 3
INTERACTION EFFECT

UNIVARIATE ANALYSIS

| VAR | SSHYP | SSERR | DFHYP | DFERR | MSHYP | MSERR | F | P-VALUE |
|---|---|---|---|---|---|---|---|---|
| A1 | 1340.18 | 2039.50 | 2 | 16 | 670.09 | 123.47 | 5.260 | 0.0176 |
| A2 | 157.89 | 5450.45 | 2 | 16 | 78.96 | 340.65 | 0.232 | 0.7958 |
| A3 | ****** | ******* | 2 | 16 | ****** | ****** | 0.178 | 0.8390 |
| A5 | 7804.04 | 59599.75 | 2 | 16 | 3902.02 | 3724.98 | 1.05 | 0.3737 |
| A6 | 3950.07 | 7460.67 | 2 | 16 | 1975.04 | 466.29 | 4.24 | 0.0334 |

****** replaces the number which is too large for the summary table

APPENDIX 3.4 The mean scores for the three groups at rest and at self-perceived exhaustion for the six variables.

| | GROUP | R1 | R2 | R3 | R4 | R5 | R6 |
|---|---|---|---|---|---|---|---|
| REST | EX-I-ANA | 85 | 12.3 | 253500 | 3801 | 218 | 142 |
| | TYPE A | 89 | 8.6 | 265625 | 5098 | 241 | 119 |
| | TYPE B | 75 | 8.4 | 310500 | 4280 | 206 | 110 |
| S-PD-EX | EX-I-ANA | 190 | 66.1 | 306333 | 5811 | 430 | 185 |
| | Type A | 190 | 63.4 | 310203 | 7663 | 427 | 200 |
| | TYPE B | 194 | 68.8 | 364500 | 6056 | 362 | 194 |

EX-I-ANA; Subjects with exercise-induced anaphylaxis
S-PD-EX: Self-perceived Exhaustion
R1: Heart Rate at rest
R2: Lactate concentration at rest
R3: Platelet count at rest
R4: Neutrophil leukocyte count at rest
R5: Plasma norepinephrine at rest
R6: Plasma epinephrine at rest

M1: Heart Rate at S-PD-EX
M2: Lactate concentration at S-PD-EX
M3: Platelet count at S-PD-EX
M4: Neutrophil leukocyte count ar S-PD-EX
M5: Plasma norepinephrine at S-PD-EX
M6: Plasma epinephrine at S-PD-EX

# APPENDIX 4

LEGEND FOR APPENDIX 4

A : Type A
S : Speed and Impatience
J : Job Involvment
H : Hard-Driving and Competativeness
RS : Raw Score
% tile: Percentile

APPENDIX 4 Raw scores and Percentiles for the three groups of the Jenkins Activity Survey

| GROUP | A RS | A %tile | S RS | S %tile | J RS | J %tile | H RS | H %tile |
|---|---|---|---|---|---|---|---|---|
| EX-I-ANA | 345 | 93 | 186 | 55 | 251 | 70 | 99 | 65 |
| | 328 | 90 | 96 | 10 | 227 | 55 | 144 | 75 |
| | 360 | 95 | 290 | 95 | 278 | 85 | 143 | 75 |
| TYPE A | 285 | 75 | 208 | 40 | 314 | 99 | 151 | 15 |
| | 255 | 69 | 118 | 20 | 216 | 67 | 164 | 85 |
| | 297 | 80 | 225 | 75 | 287 | 90 | 116 | 45 |
| | 354 | 95 | 195 | 60 | 284 | 85 | 114 | 40 |
| | 245 | 69 | 108 | 15 | 266 | 75 | 198 | 76 |
| | 279 | 70 | 196 | 60 | 278 | 80 | 178 | 71 |
| | 271 | 69 | 154 | 50 | 295 | 90 | 94 | 15 |
| | 360 | 99 | 183 | 9 | 287 | 87 | 163 | 84 |
| TYPE B | 212 | 45 | 97 | 10 | 134 | 10 | 112 | 35 |
| | 208 | 40 | 63 | 3 | 284 | 75 | 160 | 45 |
| | 212 | 45 | 171 | 50 | 175 | 25 | 107 | 35 |
| | 164 | 25 | 182 | 50 | 187 | 30 | 65 | 1 |
| | 189 | 35 | 158 | 65 | 254 | 70 | 96 | 20 |
| | 147 | 20 | 108 | 15 | 306 | 95 | 103 | 25 |
| | 201 | 40 | 131 | 25 | 232 | 60 | 116 | 45 |
| | 120 | 15 | 111 | 15 | 195 | 35 | 143 | 75 |

# APPENDIX 5

## APPENDIX 5 CASE HISTORIES OF THE THREE EXERCISE-INDUCED ANAPHYLACTIC SUBJECTS

Each of the three anaphylactic subjects had a different history of exercise-induced attack occurrences.

The first subject experienced three attacks. The first one manifested the symptoms of localized pruritus and urticarial wheals to face, abdomen, inner thighs and back of the knees. This attack was percipitated by a 3 mile jog outdoors.

The second attack occurred 3 months after the first, had symptoms of the first, however the urticaria was more widespread and facial angioedema was also experienced. This attack occurred after a jogging period of twenty minutes indoors.

The third attack occurred five months after the second, while the subject was playing basketball indoors. The urticaria and pruritus were experienced all over the subject's body, and the wheal formation included small and giant hives. The subject also experienced nausea, intermittent fainting and abdominal cramps. The subject was treated at the hospital for mild anaphylactic shock and released in two hours after her admission.

No other attacks have been experienced since by this subject even while she was tested on a treadmill for this experiment on two different occasions. This subject suffered from several allergies to pollen, hayfever and dust. These allergies are familial. This subject is still jogging regularly and has not experienced an attack since the third one described above.

Subject two is a monozygous twin who experienced two attack in sucesion, one in the evening and the second the

following morning. She had been rehearsing for a jazz performance and after approximately one-half hour she began to feel itchy in the lip area and around her eyes. She became very red (she described it as "red like a lobster") and then she developed white wheals. These urticarial wheals and pruritus was also seen in the abdominal area, arms, thighs and back. The subject began to feel very dizzy and became semi-conscious. By the time she reached the hospital she felt nauseated but did not experience vomiting. She was treated with epinephrine and released after approximately three hours after admission.

The following morning she resumed her jazz rehearsal and within ten minutes she experienced identical symptoms and was readmitted to the hospital. After one day of observation she was released. This subject has not experienced any more of these attacks, but she also does not take jazz anymore. She does not jog regularly, and has never experienced an attack jogging or performing any other activity. She is allergic to a great variety of foods, pollens and suffers from seasonal hay fever.

This subject's twin sister has never suffered from any allergies nor have any other members of her family. This subject commented on that although her sister and her were brought up in the same way she is very different from her sister. This subject feels much more active, "hyperactive" than her sister. She hold two jobs, exercises regularly, is involved in a number of social activities and feels more energetic than her twin. She also scored in the 90th percentile on the Type A assesment while her sister scored in the 35th percentile.

This subject mentioned that she keeps all her feeling inside while her sister explodes anytime anything bothers her.

Subject 3 (the author of this thesis) has an extensive history of exercise-induced anaphylaxis. The first one

occurred at the age of 13, while she was playing soccer. The attack consisted of severe facial angioedema, urticaria and pruritus originating in the palms, soles and abdominal area, spreading to the back of the thighs and arms.

The second attack exhibited the same symptoms as the first, and occurred at the age of 17 while the subject was rehearsing for a ballet performance at her high school. Each time the subject was hospitilized, treated with antihistamines and epinephrine. From the age of 18 to 21, the subject suffered five attacks each one manifesting the same symptoms as previously mentioned, however more severe during each attack. During this time the subject was involved in regular fitness and dance classes, but jogged only occasionally. Two of the attacks occurred while the subject was in a fitness class, one in a dance class, and two while jogging. Both of the jogging-induced attacks were more severe in symptomatology and in duration.

Between the ages of 22 to 24, the frequency of the attacks increased; the patient experienced 18 attacks. A greater number of activites brought on the attacks. These activities included horseback riding, roller skating, cross-country skiing, ice skating, "disco-dancing" and ballet lessons. These above mentioned activites brought on symptoms of no greater severity than the previously mentioned, however jogging triggered a severe systemic reaction along with the urticaria. The subject experienced severe vasodilatation, (BP 70/0, 50/50) fingernail bed cyanosis and loss of body temperature, (35-34 C) was also exemplified. The subject experienced bradycardia, unconsciousness up to 30 sec. abdominal cramps, vomiting and diarrhea, along with laryngeal constriction. The subject was hospitalized for 10 of these attacks. After one of these attacks the subject was admitted to the hospital for two days for observation, however no findings were reported.

The subject had skin allergy tests performed at the age of 18. She was told that she was allergic to a number

of foods, (peanuts, pork, citrus fruit and chocolate). She never experienced any allergic symptoms direcly after ingestion of these foods or at any other times. A second set of allergy tests were done at the age of 23, when the subject was told that she was not allergic to anything. At the age of 24, the subject developed urticaria to aspirin on two separate occasions.

None of the three subjects experienced exercise induced anaphylaxis during the testing session for this experiment.