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CHAPTER ONE

GENERAL INTRODUCTION

The effects of exercise on the immune system has been the subject of increasing research interest over the last decade (Keast et al, 1988; Nieman and Nehlsen-Cannarella, 1991; McKinnon 1994). Most athletes believe that regular exercise will produce health benefits, including improved resistance to infection (MacKinnon and Tomasi, 1986). However, Peters and Bateman (1983) have suggested that there is a relationship between acute exercise stress and the susceptibility to upper respiratory tract infections within two weeks of completing a 56 kilometer ultramarathon running race. In this study 33% of the 140 athletes reported post-race upper respiratory tract infection symptoms, compared to 15.3% of the age-matched non-running controls. Upper respiratory tract infection symptoms were more prevalent in the more highly trained athletes, who completed the race in less than four hours. The susceptibility to infection was attributed to (i) possible drying of the mucosal surfaces resulting from hyperventilation of cold, dry air and/or (ii) immuno-suppression resulting from elevated serum cortisol levels during prolonged strenuous exercise.

An extension of Peters and Bateman's (1983) study was repeated at a running event of the same distance, held at altitude (Peters 1990). It was proposed that if mucosal damage due to hyperventilation and mouthbreathing was a major factor in increased upper respiratory tract infection symptoms after such an event, that this effect would be exacerbated at a lower barometric pressure and relative humidity. However, this hypothesis was not confirmed and the increased susceptibility to infection in runners completing an ultradistance event was attributed to systemic factors (Peters 1990).

A subsequent study (Peters et al 1993) further confirmed the findings of Peters and Bateman (1983), that athletes were more likely to develop upper respiratory tract symptoms than non-running controls, and that those who were overtrained and ran the fastest times were more likely to become ill than those who were undertrained and completed the race in a longer time period. In this report, 68% of runners reported the development of symptoms of upper respiratory tract infections within two weeks after the 90 kilometer Comrades ultra-marathon race. The incidence of upper respiratory tract infection was greatest amongst the runners who trained the hardest prior to the race. That is, 85% of the highly-trained vs 45% of the medium- or low-trained runners developed symptoms of upper respiratory tract infection.

The relationship between exercise and susceptibility to upper respiratory tract infections has also been investigated in other countries. Linde (1987), found rates of URTI in 44 Danish elite orienteers to be 2.5 episodes per year while that of the non-athletic control subjects was 1.7. One third of the controls reported no upper respiratory tract infection episodes during the year long study, but this was the case for only 10% of the orienteers. Nieman et al (1989) found that among recreational runners, 25% of those running 25 or more kilometers per week reported at least one upper respiratory tract infection episode over a two-month period as opposed to 34.3% of those training less than 25 kilometers per week. During the week following the road races (5-km, 10-km or 21.1-km events), runners did not report an increase in upper respiratory tract infection episodes as compared with the week prior to the race. From these findings, Nieman et al (1989) propose that running an average of 42 kilometers per week as opposed to 12 kilometers per week is associated with a slight reduction in upper respiratory tract infection incidence, and racing 5 to 21.1 kilometers does not increase the risk of infection in the post-race period.

Nieman et al (1990a) subsequently reported that 12.9% of athletes competing in the Los Angeles Marathon reported an infectious episode during the week following the race in comparison to only 2.2% of similarly experienced runners who had entered but did not particpate in this event for reasons other than illness. Forty percent of the runners also reported at least one upper respiratory tract infection during the two-month winter period prior to the marathon. Nieman et al (1990a) calculated that the marathon participants were six times

more likely to develop an upper respiratory tract infection than the non-participants. Furthermore, those training more than 96 kilometers per week were at double the risk for infection than those who trained less than 32 kilometers per week.

Nieman et al (1990b) found that mildly obese females undergoing a walking training programme experienced fewer days with an upper respiratory tract infection than did the non-exercising control group. Nieman et al (1993) have also reported the incidence of upper respiratory tract infection among elderly women to be 8% in the highly exercise-trained group, 21% in a group engaged in a walking programme and 50% in the sedentary controls.

The idea that acute stress of running predisposes the athlete to infectious illness is a view supported by Heath et al (1991). These workers collected longitudinal data on upper respiratory tract infection symptoms in a population of 530 trained runners over a one-year period. Those running less than 16 kilometers per week were the least likely to develop a URTI, while those running more than 27 km per week were significantly more likely to develop a URTI. The authors conclude that total running distance for a year is a significant risk factor for upper respiratory tract infection among runners, with risk increasing proportionately with total running distance.

These epidemiological studies suggest that strenuous acute or chronic exercise is associated with an increased risk of upper respiratory tract infection. This risk appears to be highest during the one- or two-week period following marathon-type race events. These studies have also suggested that, amongst runners varying widely in training habits, the risk for upper respiratory tract infection is slightly elevated for those training the highest mileages but only when several confounding factors are controlled for.

However, all of these studies are limited by self-reporting of symptoms and the link between exercise, immunological changes and symptoms of upper respiratory tract infection remains unsubstantiated (Keast et al 1988; MacKinnon and Tomasi, 1986; Nieman and Nelson-Cannarella, 1991). It is also not clear whether the apparent increase in upper respiratory tract infection symptoms after competitive sports events can be general or local impairment of defenses.

The effect of anti-oxidant supplementation such as ascorbic acid and beta-carotene on URTI rates is also the subject of current research. Peters et al (1993) have shown that ascorbic acid supplementation may enhance resistance to upper respiratory tract infections that occur commonly in competitive ultra-marathon runners. Other researchers (Bucca et al, 1989; Fishbaine and Butterfield, 1984; Marobia et al, 1989; Peters et al, 1992) have considered beta-carotene supplementation both as an aid to running performance and to increase resistance to infection.

The protective effect of free radical supplementation is thought to be due to two main factors:-

1. Exercise apparently induces a change in the distribution, metabolism, and excretion of ascorbic acid via urine and sweat. Hence an increased ascorbic acid requirement in athletes undergoing daily training.

2. Exercise increases the production of free oxygen radicals (Dreosti, 1988) which may inhibit leukocyte chemotaxis. Anti-oxidant requirements are therefore increased in order to counteract these free radicals.

1.1. Aim of the study

The aim of this study was to determine whether anti-oxidant supplementation had any effect on the incidence and severity of upper respiratory tract infection experienced by distance runners in the two week period after competing in an ultra-marathon running event.

1.2. Hypothesis of the study

To determine whether supplementation of ascorbic acid and beta-carotene has any effect on the rate of post-race URTI in ultramarathon runners.

CHAPTER TWO

LITERATURE REVIEW

2.1. Overview of the Immune System

The human immune system is a diverse and complex network of interacting cellular and humoral components that give rapid and highly specific protection against a myriad of potentially pathogenic micro-organisms such as bacteria, fungi and viruses, as well as parasites (MacKinnon, 1992). The immune system also eliminates dead and transformed body cells.

The immune system is comprised of two functional divisions: the innate (natural or nonspecific), which acts as a first line of defence against infectious agents, and the adaptive, which, when activated, produces a specific reaction and immunological memory to each infectious agent. The major components of the adaptive or specific division of the immune system are the T- and B-lymphocyte cells (Male and Roitt, 1989).

The innate immune system is comprised of natural killer (NK) cells and phagocytes, including neutrophils, eosinophils, basophils, monocytes and macrophages, and soluble factors. The latter includes the acute phase proteins, complement fragments and other microbicidal agents such as lysozyme and interferons. These mechanisms work, in part, by creating a hostile environment to invading microbes. This occurs through the elevation of normal body temperature (fever) and the secretion of proteins that sequester essential nutrients. Vulnerable pathogens are then destroyed via a combination of microbicidal enzymes, complement fragments, and effector cells.

A major component of nonspecific immunity involves the triggering by infection, trauma and, to a lesser extent, exercise, of a sequence of events known collectively as the acute-phase response. Leukocytosis, fever, compliment activation and the increased synthesis and release into the circulation of a variety of hepatic acute-phase proteins are the predominant features of this reponse (MacKinnon, 1992). It has been suggested that the physiological consequences of strenuous exercise are analogous to those of the acute-phase response (Weight et al, 1991). MacKinnon and co-workers (1986, 1989) have shown that moderate exercise and strenuous training runs have opposite effects on the immune system. These nonspecific immune mechanisms are not affected chronically by a prior infection.

The dual limbs of the immune system are the thymus-derived (T) lymphocyte and the bone marrow-derived or bursa-equivalent (B) lymphocyte, both of which derive from a common stem cell. T-lymphocytes arise from yolk sac, foetal liver and bone marrow precursor cells that migrate to the thymus during foetal and early postnatal life. T-lymphocytes differ from other immune effector cell types in that the pool of effector T-cells is established in the thymus early in life and is maintained throughout life by antigen-driven expansion of long-lived T-cells that reside primarily in peripheral lymph organs and recirculate in blood and lymph. T-cells are the primary effectors of cell-mediated immunity with subsets of T-cells maturing into cytotoxic cells capable of lysis of virus infected or foreign cells. T-cells regulate ethrythroid cell maturation in bone marrow. Mature B-cells

comprise 10-15% of human peripheral blood lymphocytes, 50% of splenic lymphocytes and approximately 10% of bone marrow lymphocytes. The primary function of B-cells is to produce antibodies (Harrison, 1991).

The adaptive or specific division of the immune system (lymphocytes: B- & T- cells) is responsible for distinguishing self from non-self. Like any ligand-receptor interaction, lymphocytes recognise unique structural patterns on non-self (antigenic) molecules, for example, infectious agents or infected host cells. The ability of the myriad of B- & T- cell clones (where each clone can react with one antigenic determinant only) to differentiate between the plethora of infectious agents, and persistance of memory T-cells and anti-bodies in the body after the primary infection, has enabled vaccines to be developed against some pathogens. Immunological memory enables the response to a subsequent challenge from the same infectious agent to be more rapid and greater in magnitude (MacKinnon, 1992).

Although many infectious agents can be eliminated by the innate mechanisms, without the involvement of adaptive processes, the two systems are intrinsically linked (Eichmann, 1991). For example, some microbes cannot be ingested by phagocytes unless they are first coated (opsonized) with antibody. Cytokines which behave as humoral mediators are immunoregulatory proteins secreted from most immune cells that can amplify or diminish most types of immune activities.

2.1.1. The concept of psychoneuroimmunology

The immune system does not operate in isolation, but interacts reciprocally with the cardiovascular, endocrine and nervous systems. Psychoneuroimmunology or behavioural immunology is a cross-disciplinary field that includes exercise science, psychology, immunology, physiology, neuroendocrinology, and medicine.

It is now generally accepted that there is two-way communication between the neuroendocrine and immune systems. Stress hormones, for example, adrenalin and cortisol, have long been known to modulate immune function. Exercise can be considered a form of physical stress, since plasma concentrations of many of the stress hormones rise during exercise. Those models used to explain the immune response to exercise have neuroendocrine factors playing a pivotal role (Keast et al, 1988; MacKinnon, 1992; McCarthy and Dale, 1988).

Environmental conditions of a psychosocial or physical nature may influence the body's defence. The magnitude of the change in immune reactivity is partly determined by the individual's evaluation of the psychological or physical stimulus. This is illustrated by pharmacological modification of perception resulting in more pronounced stress-induced immunomodulation (Ballieux, 1992).

It has been demonstrated in man that recently experienced life stress, particularly daily hassles, can codetermine the effect of an experimental stressor applied for a short period of time on the immune system. An intriguing finding relates to the synthesis and secretion of hormones and neuropeptides by immune cells. These chemical messengers act as autocrine or paracrine immunoregulatory molecules on the one hand, and as messengers for communication with the brain and peripheral nervous system on the other (Ballieux, 1992).

There is no doubt that a bidirectional communication between the brain and the immune system exists. The implication is that investigations focused on one of the two systems should take into account the possible significance of the functional connection between these two physiological systems (Ballieux, 1992).

2.2. Free radicals : structure and function

The subject of free-radical tissue damage and the protective role of anti-oxidant nutrients had its origins almost 50 years ago. The entire subject of free-radical biology has expanded considerably in the last 10-15 years, and although there are many scientific issues to be resolved it is clear that free radicals are involved in many

disease processes. Consequently, anti-oxidant nutrients play an important role in protecting the body against free-radical tissue damage (Machlin, 1992).

Free radicals are defined as atoms, ions or molecules which contain one or more unpaired electrons. The unpaired electron makes the radical highly reactive as it seeks to acquire or give up a single electron to achieve stability. By attacking other non-radical molecules, free radicals can induce chain reactions and hence form a new radical. Most of the biological free radicals contain oxygen such as superoxide anion radical, hydroperoxyl radical and hydroxyl radical. Active forms of oxygen such as singlet oxygen, and hydrogen peroxide, although not radicals themselves, but reactive oxygen-derived molecules, lead to free radical formation and can also cause tissue damage (Machlin, 1992).

These highly unstable free radicals are produced both exogenously and endogenously. The main source of endogenous free radicals are derived from normal oxygen metabolism (Smith et al, 1988). About 98% of the oxygen that enters the body through breathing is converted to water in the process of normal respiration, however, about 2% of the oxygen is converted to toxic free radicals.

The formation of highly reactive, oxygen-containing molecular species is also a normal consequence of a variety of essential biochemical reactions, for example, cell oxygen metabolism, phagocytosis and lipid peroxidation.

Intracellular free radicals are generated from the auto-oxidation and consequent inactivation of small molecules such as reduced flavins and thiols, catecholamines, and from the activity of certain oxidases, cyclo-oxygenases, lipoxygenases, dehydroenases and peroxidases. Oxydases and electron transport systems are prime continuous sources of intracellular, reactive, oxygenated free radicals. Electron transfer from transition metals, such as iron, to oxygen-containing molecules can initiate free-radical reactions. The sites of free-radical generation encompasses all cellular constituents including mitochondria, lysosomes, peroxisomes, as well as nuclear, endoplasmic reticular and plasma membranes and sites within the cytosol (Machlin and Bendich, 1987; Machlin, 1992). While some of the endogenous free radical sources are both generated and active intracellularly, others are released into the surrounding tissue.

There are many exogenous sources of free radicals, the principle one being tobacco smoke. Moreover, smoke-induced inflammation of the lungs further enhances free-radical production by neutrophils and macrophages, leading to alveolar cell damage and even emphysema (Smith et al 1988). Air pollutants such as ozone, nitrogen dioxide and dust, as well as certain drugs, alcohol, pesticides and anaesthetics are also potent sources of free-radicals. Radiation from X-rays and radio-active sources or ultra-violet radiation results in free radical formation in the exposed tissues. Certain foodstuffs, carcinogens, heat shock and sunlight (which generates singlet oxygen) further contribute to the exogenously derived free radcial load (Machlin and Bendich, 1987; Machlin 1992).

As to the damaging effect, virtually all major organic constituents of a cell are at risk from oxidative damage caused by free radicals. Free radicals have four major target sites within a cell: the membrane lipids, nucleic acids, proteins and carbohydrates. Free radicals can damage DNA, causing cell injury and mutagenesis, and protein, leading to denaturation and decreased enzyme activity. The amino acids histidine, trytophan, methionine and cysteine are particularly prone to attack. Damage to carbohydrate can result in alteration of receptors and depolymerisation of substances such as hyaluronic acid. Free radical-induced lipid oxidation can cause direct damage to the membrane by causing alterations in the polyunsaturated fatty acids and indirect damage by forming secondary products such as reactive aldehydes (Dreosti, 1988; Machlin, 1992). Free radicals do, however, serve at least one important function. Phagocytic cells, having engulfed invading bacteria, kill them by free-radical bombardment. However, this means that any abnormal activation of phagocytic cells has potentially devastating consequences for the host (Machlin and Bendich, 1987; Machlin,

1992). Indeed, many diseases can be considered the consequences of an over-reaction or an overproduction of free radicals by immune reactive cells (Dreosti, 1988).

It is now generally accepted that free radical involvement is implicated in a wide range of clinical conditions both acute and chronic (Machlin, 1992). The major free radical-related diseases include cancer, cataracts and cardiovascular disease, as well as several degenerative conditions such as rheumatoid arthritis. Causal links between free radicals and these pathologies can be demonstrated.

2.3. The anti-oxidant vitamins

Oxygen, while being vital to life, can also be destructive (Dreosti, 1988). Hence there are a series of cooperative defence systems against free radicals. Enzymatic sources are catalase, glutathione peroxidase and superoxide dismutase. Other enzymatic mechanisms include the anti-oxidant micronutrients (ascorbic acid, L-tocopherol, beta-carotene, zinc, selenium, copper, iron and manganese), flavonoids, urate and certain drugs (Machlin and Bendich, 1987).

Anti-oxidant enzymes are synthesized intra-cellularly while anti-oxidant vitamins, including ascorbic acid, beta-carotene, L-tocopherol, selenium and zinc are absorbed from exogenous dieteray sources.

The effectiveness of the primary anti-oxidants (trace elements such as zinc, copper, manganese and selenium) and the secondary anti-oxidants (such as retinol, ascorbic acid and L-tocopherol) depends on their balance and distribution in the body, and on the way they interact. There is no case for massive anti-oxidant supplementation except possibly in the prevention and treatment of specific degenerative diseases. The role of multi-vitamin and mineral supplementation in enhancing immune functioning has not been adequately addressed (Van den Beek, 1985 and 1991; Weight, 1988).

Studies by Packer (1986) and Smith et al (1988) have shown that during prolonged exercise, during which oxygen consumption is elevated eight to twelve times the basal levels, production of immunosuppressive oxygen radicals is enhanced (Packer, 1986). Indirect evidence thus exists that athletes participating in prolonged exercise need, in addition to extra caloric intake, to consume proportionately higher amounts of anti-oxidant vitamins to deactivate the free radicals (Anderson, 1984). These include ascorbic acid, L-tocopherol and beta-carotene (Beizel, 1982).

2.3.1. Ascorbic acid (Vitamin C)

Exercise has been shown to induce a change in the distribution, metabolism and excretion of ascorbic acid. For example, the plasma ascorbic acid concentrations of runners competing in a 21 km race were significantly (20%) reduced 24 hours after completing the race, and remained low for at least a further 24 hours (Gleeson et al, 1987).

Fishbaine and Butterfield (1984), have shown a positive relationship between physical activity level and serum ascorbic acid concentration. There is a shift in the tissue distribution of the vitamin resulting in an increased metabolic turnover of the vitamin during exercise. Hence, these authors suggest that the daily ascorbic acid requirements of athletes are greater than those of non-exercising individuals (Fishbaine and Butterfield, 1984). Moreover, as exercise intensity increases, so does the production of free oxygen radicals (Packer, 1986). Agents with anti-oxidant properties such as ascorbic acid may therefore be required in increased quantities in athletes in order to inactivate the free radicals which, among other things, inhibit leucocyte chemotaxis (Benedict et al, 1986).

Peters et al (1993) have studied the effect of ascorbic acid supplementation on the incidence of upper respiratory tract infections in ultramarathon runners during the post-race fortnight. Sixty eight percent of those

who had received 600 mg ascorbic acid for three weeks prior to the 90 km race reported symptoms of upper respiratory tract infection as opposed to 33% of the placebo group. The incidence of symptoms was greatest among those who trained the hardest and ran the fastest as judged by their faster finishing times. Furthermore, 85% of the runners who had trained high mileages became symptomatic, whereas the incidence of symptoms in those doing medium to low mileage was 42% and 48% respectively. The authors suggest that anti-oxidants countered the immuno-suppressive effects of free radicals.

2.3.2. Beta-carotene (Precursor of retinol)

Beta-carotene is a precursor (provitamin) of retinol to which it is readily enzymatically converted in the intestinal mucosa when required. While the specific activities of beta-carotene are poorly understood, those of retinol are well documented. Increased retinol turnover has been reported in prolonged stress situations, resulting in a reduction of plasma retinol and plasma retinol-binding protein levels. Retinol is essential to the integrity and function of mucosal and epithelial surfaces so a deficiency thereof is evidenced in abnormalities in the respiratory epithelium with bacterial colonisatiion and infection (Bloem et al, 1990). Retinol is also important in first-line, non-specific anti-microbial defences, so that retinol deficiency is associated with increased infection risk, accompanied by low levels of serum immunoglobulins, a depressed lymphocyte mitogenic response, and reduced levels of natural killers (Olson, 1991). Retinol supplementation in children suffering from measles has resulted in reduced incidence of mortality (Hussey et al, 1990).

The possible role of beta-carotene itself (and not retinol) in resistance to infection has not been well researched, although beta-carotene does appear to influence some components of the immune system (Van den Beek, 1991; Ji, 1995). For example, beta-carotene has anti-oxidant properties, scavenging free radicals, and is also a singlet oxygen quencher. Beta-carotene stimulates the T-cell lymphocyte response to mitogens, thereby enhancing immuno-competence.

Peters et al (1992) have also investigated the effect of retinol supplementation on the incidence of upper respiratory tract infetion in distance runners during the post ultramarathon race period. There was no difference in the incidence of upper respiratory tract infections between the retinol-supplemented runners and those taking a placebo. Peters et al (1992) suggest that despite the possibility that retinol turnover is increased with exercise training, runners with normal retinol status do not further enhance their immune status with retinol supplementation.

2.3.3. L-Tocopherol (Vitamin E)

L-Tocopherol is the most important lipid-soluble anti-oxidant. Its unique membrane-borne cellular location enhances its efficiency to quench the free radicals orginating from mitochondria. L-Tocopherol deficiency exacerbates muscle- and liver-reactive oxygen species generation, enhances lipid peroxidation and promotes mitochondrial dysfunction in rats exercised to exhaustion (Davies et al, 1982). On the other hand, dietary supplementation of L-Tocopherol has been shown to increase tissue resistance to exercise-induced lipid peroxidation, and to attenuate lipid peroxidation in the plasma and leg muscles of exercising rats (Ji, 1995). Endurance performance reportedly decreases in rats fed L-Tocopherol deficient diets (Davis et al, 1982). These findings suggest that humans involved in strenuous sports and exercise increase their daily L-Tocopherol intake since endurance training has been shown to deplete L-Tocopherol levels/reserves.

2.3.4. Selenium

Selenium is an essential component of glutathione peroxidase, an enzyme important in the decomposition of both hydrogen peroxide and lipid peroxides. It therefore plays a protective role in cellular damage from peroxidation (Underwood, 1977). The selenium recommended daily intake of (50-200 mg/day) is usually met by a varied and balanced diet (Underwood, 1977). Whether physical activity modifies selenium levels is not

known. However, given its role in the removal of the free radicals produced by peroxidation, selenium is an important micronutrient for a training athlete.

2.3.5. Zinc

Zinc is a fundamental component in over 200 enzymatic activities, and is directly involved in numerous physiological functions, such as lipid, protein and nucleic acid metabolism (Underwood, 1977). The relationship between physical activity, plasma and intracellular zinc concentrations and the activity of zinc-containing enzymes, specifically erythrocyte carbonic anhydrase, has been explored (Ohno et al, 1985). Following an eight kilometer running event plasma zinc levels were significantly reduced only two hours post run. This was attributed to a redistribution of the zinc from the vascular to the cellular compartment (Anderson et al, 1984). Physical exercise modifies the metabolism and distribution of zinc, so that an athlete may present with a pseudo-deficiency (Ohno et al, 1985). The physiological significance of such modifications has not yet been clarified, but it has been demonstrated that dietary zinc supplementation reduces fatigue in the striated muscle. It seems to act by favouring the removal of haematic lactate through the stimulation of lactic dehydrogenase activity (Vecchiet et al, 1992). During physical exercise urinary excretion of zinc may also increase with losses which may reach 20% of the total intake (Anderson et al, 1984).

2.4. Exercise and Immune Function

From a clinical perspective the influence of exercise on the immune system remains an enigma (Smith, 1994). There is a perception that while physical fatigue may increase susceptibility to illness, regular exercise at moderate capacity may well prevent common infections (MacKinnon, 1992). Epidemiological evidence of changes in susceptibility to infection provides some support to these observations (MacKinnon, 1982). Independently of exercise, psychological stress has similar immunosuppressive effects (Smith 1994). Hence athletes undertaking strenuous training and under psychological stress may at high risk, especially from primary infections.

Exercise has both acute and chronic effects on immune mechanisms. Intense exercise is generally immuno-suppressive, although some conflicting results have been reported. Exercise at maximal aerobic capacity suppresses most types of functional immunological responses measured in vitro, for up to several hours post exercise. Exercise-induced alterations in immune status may be due to changes in total leukocyte numbers or percentages rather than functional changes at the single cell level. In contrast, the functional reserve of immune cells may have to fall below a critical threshold before susceptibility to infection increases (Smith, 1994). Furthermore, there are wide discrepancies in the literature with regard to exercise-induced changes in blood lymphocyte subset numbers, lymphocyte proliferation, natural killer (NK) cells cytotoxicity as well as cytokine concentrations and immunoglobulin levels (MacKinnon, 1992). These discrepancies may be due to the small magnitude of the changes found. Small swings in either direction may reach statistical significance (Smith, 1994).

The differential effects of exercise on immunity mamy be related to the intensity-dependent release of stress hormones, some of which have potent regulatory effects (MacKinnon, 1992). For example, high levels of growth hormone, which are found at low exercise intensity, while the immuno-suppressive hormones cortisol and ephinephrine is not activiated until workload intensity exceeds 60% VO_2 max (Smith, 1994).

2.4.1. The effect of exercise on the sequence and mechanisms of the leukocyte response

Exercise induces a leukocytosis, the magnitude of which is dirctly proportional to the intensity and duration of exercise, and inversely proportional to the level of fitness of the individual. This might temporarily enhance certain facets of immune defence. In the early stages of exercise, the leukocytosis is due to an increase in both granulocytes (mainly polymorphonuclear neutrophils) and lymphocytes. The early rise in

polymorphoneutrophils is mediated by the mechanical effects of an increased cardiac output and the physiologic effects of epinephrine. These two forces move the polymorphonuclear neutrophils away from the endothelium of blood vessels and into the circulating blood, so they enter the blood from reservoirs in the spleen, liver and lung. These two forces may also mediate the early lymphocytosis (Eichner, 1993).

If the exercise is strenuous and especially if it lasts 30 minutes or longer there tends to be a secondary peak in the white cell count over the next two to four hours (Nieman et al, 1992). This delayed response can be attributed primarily to an increase in polymorphonuclear neutrophils associated with the release of cortisol, and is more pronounced when the exercise involves a muscle-damaging eccentric component, such as downhill running. It appears that strenuous exercise that involves muscle tissue damage can evoke a form of acute phase response (Eichner, 1993). Following brief exercise, where there is no tissue damage, the white cell count usually returns to baseline within 1 to 2 hours. However, after prolonged exercise, this may take 24 hours or longer (Nieman et al, 1992).

2.4.2. Effect of exercise on leukocyte function

In addition to increasing the number of polymorphonuclear neutrophils in the blood, exercise may also activate polymorphoneuclear neutrophils. In contrast to the delayed rise in polymorphonuclear neutrophils discussed above (Eichner, 1993), the relative lymphocytosis induced by exercise is attenuated soon after exercise ceases. For example, Eichner (1993) reports that after cycling to exhaustion, the lymphocyte count five minutes into recovery was lower than that recorded immediately on finishing exercise. On cessation of exercise, the fall in the lymphocyte count and the rise in the polymorphonuclear neutrophil count are probably both due to the unopposed action of cortisol. The adrenergic response during exercise results in the increase of lymphocytes in the circulating blood and is reversed by cortisol which redirects lymphocytes back into the lymphatic system, lymph nodes and the spleen (Eichner, 1993). During this phase, cortisol may also temporarily suppress the immunological function of lymphocytes (Nieman et al, 1992).

Among the lymphocyte subsets, NK cells selectively tend to increase in numbers and activity during strenuous exercise, regardless of level of training or state of fitness of the individual (Nieman et al, 1992). There is the suggestion that the increase in NK cells is a general response to stress and not a specific response to exercise. This exercise-enhanced NK number and function is mediated largely by epinephrine and also possible by the interleukins and interferon. In contrast to the increase during exercise, NK numbers and function decrease soon after stopping exercise, falling to pre-exercise baseline or below within one to two hours of recovery (Eichner, 1993).

2.4.3. Exercise and immunoglobulins

The serum immunoglobulin levels of athletes are within the normal range, especially when adjusted for plasma volume. Exhausting endurance exercise may cause minimal declines in serum levels (Nieman, 1992). One study suggests that moderate training may cause slight increases in serum levels (Eichner, 1993).

Although serum and salivary immunoglobulins may be low in some athletes, especially elite athletes during the competitive season, data to link these low levels of immunoglobulins to increased acute respiratory infection is unconvincing (MacKinnon, 1992).

2.4.4. Exercise and other immune factors

Strenuous or prolonged exercise can activiate the compliment system and may lead to the release of tumor necrosis factor, interferon, and the interleukins (Eichner, 1993). It is at present unclear to what extent these may alter immunity. The increased susceptibility of some endurance athletes to upper respiratory tract

infection may be better explained by exercise-induced lower serum complement levels (Nieman et al, 1989), together with decreased phagocytic function (Lewicki et al, 1987) than by alterations in adaptive immunity.

2.5. Overtraining and its effect on immune function

To date, no large scale systematic studies of immune function have been performed on overtrained athletes. It is tempting to speculate that changes in the immune parameters may be indicators of overtraining (chronic fatigue). If this could be verified, it could be a useful tool in athlete management (Keast et al, 1988). The overtraining syndrome is a complex clinical condition, and it may develop in athletes when training periods are too frequent, too intense, or too prolonged, and when training is combined with inadequate nutrition and psychological stress (Newsholme et al, 1994). Such athletes experience symptoms indicative of immunosuppression, and may suffer from increased incidence of viral and bacterial infections and display poor recovery from injury and impaired wound healing. Possible explanations for the poor immune status of overtrained athletes who undergo frequent, intense, and long duration exercise include the associated hypercortisolemia and the low plasma glutamine levels. Glutamine plays a role in white cell substrate utilisation. It is an important fuel in a number of rapidly dividing cells and lymphocytes (Newsholme et al, 1994). It has been suggested that some of the anecdotal evidence that well trained athletes may be more susceptible to minor infections may stem from the fact that under intense physical exercise, the demands on muscle and other organs for glutamine are such that the lymphoid system may be forced into glutamine debt which temporarily affects its function.

2.6. Exercise and upper respiratory tract infections

Most athletes believe that regular exercise will produce health benefits, among these that exercise improves their resistance to infection and they will experience fewer upper respiratory tract infections (MacKinnon and Tomasi, 1986). However, epidemiological studies suggest that there is a relationship between acute exercise stress and the susceptibility to upper respiratory tract infections. For example, Peters and Bateman (1983) reported that 33% of 150 athletes developed URTIs within two weeks of completing a 56 kilometer ultra-marathon foot race. In comparison, 15.3% of the age-matched non-running controls experienced URTIs. Upper respiratory tract infection symptoms were more prevalent in the more highly trained athletes, who completed the race in less than four hours. The susceptibility to infection was attributed to (i) possible drying of the mucosal surfaces resulting from hyperventilation of cold, dry air and/or (ii) immunosuppression resulting from elevated serum cortisol levels during prolonged strenuous exercise.

An extension of Peters and Bateman's (1983) study was repeated at a running event of the same distance, held at altitude (Peters, 1990). It was proposed that, if mucosal damage due to hyperventilation and mouth breathing was a major factor in increased upper respiratory tract infection symptoms after such an event, this effect would be exacerbated at a lower barometric pressure and relative humidity. However, this hypothesis was not confirmed and the increased susceptibility to infection in runners completing an ultradistance event was attributed to systemic factors (Peters 1990).

A subsequent study (Peters et al, 1993) further confirmed the findings of Peters and Bateman (1983) that athletes were more likely to develop upper respiratory tract symptoms than non-running controls, and those who were overtrained and ran the fastest times were more likely to become ill than those who were undertrained and completed the race in a longer time period. In this report 68% of runners reported the development of symptoms of URTI's within two weeks after the 90 kilometer Comrades Marathon. The incidence of URTI's was greatest amongst the runners who trained the hardest prior to the race. That is, 85% of the highly-trained versus 45% of the low- or medium-trained runners developed URTI symptoms.

The relationship between exercise and susceptibility to upper respiratory tract infections has also been studied in other athletic populations. Linde (1987) documented upper respiratory tract infection rates in a group of 44

Danish elite orienteers to 2.5 episodes and that of the non-athletic control subjects to be 1.7 during a one year period. One third of the controls reported no upper respiratory tract infection episodes during the year long study, but this was the case for only 10% of the orienteers. Nieman et al (1989) found that among recreational runners, 25% of those running 25 or more kilometers per week reported at least one upper respiratory tract infection episode over a two-month period as opposed to 34.3% of those training less than 25 kilometers per week. During the week following the road races (5-km, 10-km and 21.1-km events run the same morning of the Redlands Race in California in March each year), runners did not report an increase in upper respiratory tract infection episodes as compared with the week prior to the race. From these findings, Nieman et al (1989) proposed that running an average of 42 kilometers per week as opposed to 12 kilometers per week is associated with a slight reduction in upper respiratory tract infection incidents, and racing 5 to 21.1 kilometers does not increase the risk of infection in the post-race period.

Nieman et al (1990a) subsequently reported that 12.9% of athletes competing in the Los Angeles Marathon reported an infectious episode during the week following the race in comparison to only 2.2% of similarly experienced runners who had not participated in this event. Forty percent of the runners also reported at least one upper respiratory tract infection during the two-month winter period prior to the marathon. Nieman et al (1990a) calculated that the marathon participants were six times more likely to develop an upper respiratory tract infection than the non-participants. Furthermore, those training more than 96 kilometers per week were at double the risk for infection than those who trained less than 32 kilometers per week.

The idea that acute stress of running predisposes the athlete to infectious illness is a view supported by Heath et al (1991). These workers collected longitudinal data on upper respiratory tract infection symptoms in a population of 530 trained runners over a one-year period. It was found that the lower odds ratio for upper repiratory tract infection was found in those running less than 16 kilometers per week. The odds ratio more than doubled for those running more than 27 kilometers per week, demonstrating that total running distance for a year is a significant risk factor for upper respiratory tract infection among runners, with risk increasing as running distance rises.

These epidemiological studies suggest that heavy acute or chronic exercise is associated with an increased risk of upper respiratory tract infection. This risk appears to be high during the one- or two-week period following the marathon-type race events. These studies have also suggested that, amongst runners varying widely in training habits, the risks for upper respiratory tract infection is slightly elevated for the highest distance runners, but only when several confounding factors are controlled for.

However, all of these studies are limited by self-reporting of symptoms and the link between exercise, immunological changes and symptoms of upper respiratory tract infections remains unsubstantiated (Keast et al, 1988; MacKinnon and Tomasi, 1986; Nieman and Nehlson-Cannarella, 1991). It is also not clear whether the apparent increase in upper respiratory tract infection symptoms after competitive sports events can be general or local impairment of defences.

2.7. Summary

The evidence to date shows that while exercise at maximal capacity is generally immunosuppressive, conflicting results have been obtained with moderate exercise protocols. There is no doubt that exercise immunology is a complex subject where results can be potentially influenced by many biological and technical variables that are unrelated to exercise.

Evidence has accumulated in the past decade that strenuous physical exercise is associated with an oxydative stress in the body. There is evidence that oxygen-free radical generation is the underlying mechanism for the exercise-induced oxydative damage. Enzymatic and non-enzymatic antioxidants play a vital role in protecting tissues from excessive oxidative stress during exercise. Because acute strenuous exercise and chronic

exercise training increase the consumption of various antioxidants, it is conceivable the supplementation of specific antioxidants during exercise or training would be beneficial.

Finally, from the overview of some of the pertinent literature and recent studies on ultra distance events, it can thus be concluded that participants in such events do possess a greater predisposition to infection during the two-week post-race period and that supplementation of the antioxidant vitamins appear to play a prophylactic role. At present, substantiative evidence exists only for ascorbic acid supplementation. Extensive, well controlled studies looking at the possible benefits of beta-carotene and L-tocopherol supplementation present an interesting area for future research.

CHAPTER THREE

METHODS

3.1. Experimental Design

An eight-week double-blind, randomized, placebo-controlled study was undertaken. The individuals in each group ingested the active agent or placebo for the six weeks prior to a 90 km ultra marathon footrace, and for a further two weeks after the event. A questionnaire was administered in order to obtain demographic data.

3.2. Subjects

The study group (N=120) comprised 60 distance runners of both genders who competed in the 1993 90km Comrades Marathon, and 60 non-running controls. All the athletes had completed the race on at least one previous occasion, had been running for more than two years and were recruited from a single athletic club. Each athlete selected a non-running partner with whom they were paired. This non-running control was of a similar age and was a member of the same household or otherwise closely associated with the runner. All subjects were instructed not to ingest any form of vitamin or mineral supplementation for at least two months prior to the study. Exclusion criteria were those with respiratory disorders, asthmatics, smokers, industrial workers, and those on prescription medication (excluding the oral contraceptive pill).

The runners were randomly assigned to one of 3 study groups. Group (A) received ascorbic acid 250 mg/day, Group (B) received beta-carotene 4.5 mg/day and Group (C) received the placebo. The non-running control with which the runner was paired received the identical supplement. Groups A (ascorbic acid) and B (beta-carotene) each comprised 15 runners and 15 controls, while Group C (placebo) consisted of 30 runners and 30 controls. The placebo was identical in form to the ascorbic acid and beta-carotene tablets but without the active ingredients.

3.3. Supplements

Both the ascorbic acid and beta-carotene supplements were bonded in a food complex (see Appendix I). The daily supplemental intake of 250 mg ascorbic acid provided 833% Recommended Daily Allowance while 4.5 mg beta-carotene provided 100% of the Recommended Daily Allowance for retinol.

3.4. Training diary and reporting of upper respiratory tract infection symptoms

During the eight-week experimental period, each runner kept a log book detailing their training and any physical, including upper respiratory tract infection symptoms they experienced. What constituted an upper respiratory tract infection symptom was carefully explained to each subject by the researcher at a gathering at the running club prior to the commencement of the project, and a comprehensive physical checklist was provided with their log books and questionnaire (Appendix II). If upper respiratory tract infection symptoms were severe enough, the subject was instructed to seek the attention of the researcher. The controls kept a

similar record, which obviously excluded training data. The detailed questionnaire also covered demographic, medical and psychological factors.

3.5. Data analysis

All the data obtained in this study was processed using the Lotus 1-2-3 computer program (Lotus Development Corporation, Boston). All data relating to the incidence and severity of upper respiratory tract infection in the various study groups was analysed using Chi-square. The relationship between training and lifestyle factors was determined using simple linear regression (Statgraphics, STSC, Rockville, U.S.A.)

CHAPTER FOUR

RESULTS

4.1. DEMOGRAPHIC DATA

TABLE 4.1 : NUMBER OF SUBJECTS IN EACH STUDY GROUP

	NO. OF RECRUITED RUNNERS	NO. OF RUNNERS COMPLETING STUDY	NO. OF RECRUITED NON-RUNNING CONTROLS	NO. OF NON-RUNNING CONTROLS COMPLETING STUDY
GROUP A: ASCORBIC ACID	15	13	15	11
GROUP B: BETA-CAROTENE	15	12	15	11
GROUP C: PLACEBO	30	19	30	19
TOTAL	60	44	60	41

Thirty five subjects (16 runners and 19 non-running controls), constituting 29% of the study population failed to complete the study. Fifteen subject (6 runners and 9 controls) elected to discontinue taking the supplement. Reasons given included psychological factors, flatulence (which impaired ability to train) and increased appetite. Fourteen subjects (8 runners and 6 controls) failed to complete their log books or questionnaires adequately during the study.

Six subjects (2 runners and 4 controls) lost all interest in participating in the study soon after the initial meeting with the researcher and after receiving their supplements. It is possible that they might have volunteered for other reasons unrelated to the desire to participate in a research study or did not understand what was required of them. They did not respond to any of the telephone calls made by the researcher. In total, 54 males and 31 females participated in the study.

TABLE 4.2. : DEMOGRAPHIC DATA - RUNNERS

	GROUP A Ascorbic acid	GROUP B B-carotene	GROUP C Placebo	TOTAL
Age (yrs)	36.92 +-7.70	35.46 +-7.8	35.84 +-6.7	36.02 +-7.4
Total mileage (km)	1588 +-597	1404 +-649	1626 +-842	1550 +-704
Marathon PB (hrs:mins)	3h17m +-27m	3h15m +-26m	3h08m +-35m	3h13m +-30m
Comrades finish.	9h02m +-1h38m	8h50m +-1h30m	8h47m +-1h43m	8h54m +-1h42m
Running exp. (yrs)	10.13 +-6.1	8.42 +-5.8	12.29 +-8.3	10.56 +-6.8
'Flu (units)	6.85 +-1.62	6.75 +-1.68	6.53 +-1.9	6.68 +-1.8
Stress (units)	1.83 +-1.4	2.08 +-0.9	1.71 +-0.9	1.84 +-1.1
Alcohol consumption*	3.67 +-3.1	4.77 +-3.0	4.10 +-3.1	4.18 +-3.0
Tobacco use+	1.83 +-1.5	1.08 +-0.3	1.16 +-0.5	1.32 +-0.5

Data expressed as means +- standard deviation

* Number of tots of alcohol per day

+ Number of cigarettes per day

TABLE 4.3. : DEMOGRAPHIC DATA - NON-RUNNING CONTROLS

	GROUP A Ascorbic acid	GROUP B B-carotene	GROUP C Placebo	TOTAL
Age (yrs)	**35.63** **+-8.3**	**38.09** **+-6.9**	**36.11** **+-6.6**	**36.5** **+-6.3**
'Flu (units)	**6.82** **+-1.5**	**6.50** **+-1.8**	**6.0** **+-2.2**	**6.35** **+-1.8**
Stress (units)	**1.23** **+-0.6**	**1.0** **+-0.8**	**1.63** **+-1.2**	**1.35** **+-0.9**
Alcohol consumption*	**1.9** **+-1.0**	**2.9** **+-1.5**	**1.84** **+-1.3**	**1.92** **+-1.3**
Tobacco use+	**2.8** +-2.6	1.55 +-1.0	1.26 +-0.7	1.75 +-1.5

Data expressed as means +- standard deviation

* Number of tots of alcohol per day

+ Number of cigarettes per day

Explanation of variables as measured in Tables 2 and 3

1. Age:

The subject's chronological age, recorded in years.

2. Total mileage (TM):
   The total distance run in the five months preceding the race (January 1 to May 31, 1993) was recorded in kilometers.
3. Personal Best time (PBT):
   The best running time ever achieved over 42.2 kilometers was recorded in hours and minutes.
4. Comrades finishing time (CFT):
   The finishing time in the 1993 Comrades Marathon was recorded in hours and minutes.
5. Running experience (RE):
   The number of years the subject had been competing in distance running races.
6. 'Flu susceptibility rating:
   The subject's resistance to influenza was weighted on a scale from 1 to 10 with 1 = weak resistance and 10 = very strong resistance. These ratings were based on the individual's perception of factors such as the number of influenza episodes experienced per annum, the severity thereof and the recovery rate (see Appendix II, questions 7-10).
7. Stress:
   Each subject's perceived stress experience was also weighted on a scale from 1 to 10 with 1 = very low stress level and 10 = very high stress level. The individual's stress ratings were based on the response to the questions in Appendix II, part E, which included factors such as lifestyle and family relations.
8. Alcohol consumption:
   The alcohol consumption was weighted on a scale from 1 to 10 where 1 = no alcohol consumption and 10 = very heavy drinker, based on the response to questions on alcohol use included in Appendix II, part B. Heavy drinking implied either four or more beers per day or two to three tots of whisky, brandy or spirits per day.
9. Tobacco use:
   Tobacco use ratings were allocated in the same way as for alcohol use with 1 = non-smoker and 10 = very heavy smoker, based on the response to questions on tobacco use in Appendix II, part B. Heavy smoking implied 20 or more cigarettes per day.

Appendix III contains the raw data for each of the variables listed above.

4.2. THE INCIDENCE AND SEVERITY OF UPPER RESPIRATORY TRACT INFECTIONS (URTI) AND THE EFFECT OF ANTI-OXIDANT SUPPLEMENTATION

TABLE 4.4. : NUMBER OF SUBJECTS WHO REPORTED UPPER RESPIRATORY TRACT INFECTION SYMPTOMS

	Runner	Runner	Runner		Control	Control	Control	
SYMPTOM	GRP A	GRP B	GRP C	TOTAL	GRP A	GRP B	GRP C	TOTAL
None	9	7	6	22	6	6	7	19
*Mild	3	4	5	12	4	3	8	15
**Mod	0	0	0	0	1	2	0	3
*** Severe	1	1	8	10	0	0	4	4
Total	13	12	19	44	11	11	19	41

*Mild: cold and allergy symptoms (running nose, sore throat, cough, itchy eyes or congested nose)

**Mod: above symptoms including headache

***Severe: above symptoms and headache, with fever, myalgia and joint pain.

GROUP A : Ascorbic acid supplementation

GROUP B : Beta-carotene supplementation

GROUP C : Placebo supplementation

TABLE 4.5. : THE TOTAL INCIDENCE OF URTIS IN RUNNERS AND NON-RUNNING CONTROLS

	NO URTI	URTI	LEVEL OF SIGNIFICANCE
RUNNERS	22 (50%)	22 (50%)	
NON-RUNNING CONTROLS	19 (47%)	22 (53%)	p = 0.736

The data is divided simply into those runners and controls who had experienced no symptoms versus those who had, be they mild, moderate or severe (URTI). There are no differences between runners and non-running controls in the post race incidence of URTIs ($p > 0.05$). Half of the runners, and 53% of the non-running controls developed URTIs during the two-week post-race period.

TABLE 4.6. : THE SEVERITY OF URTI's EXPERIENCED BY RUNNERS AND NON-RUNNING CONTROLS

	MILD URTI	MODERATE URTI	SEVERE URTI	LEVEL OF SIGNIFI-CANCE
RUNNERS	12 (54.5%)	0	10 (45.5%)	
NON-RUNNING CONTROLS	15 (68.2%)	3 (13.6%)	4 (18.2%)	p = 0.002

There was a significant difference (p = 0.01) in the severity of the URTI's experienced by the runners compared to the controls. Significantly more runners (45%) experienced severe URTI's compared to the non-running controls (18.2%) (Table 4.6.)

Of importance is that more runners than controls had severe URTI's. The data does not support the idea that runners were more sick, only that more runners were severely ill, compared to the controls.

TABLE 4.7. : THE INCIDENCE OF URTI's IN THE THREE GROUPS OF RUNNERS AND NON-RUNNING CONTROLS

		ASCORBIC ACID	BETA-CAROTENE	PLACEBO	LEVEL OF SIGNI-FICANCE
RUNNERS	NO URTI	9	7	6	
RUNNERS	URTI	4	5	13	p = 0.15
CONTROLS	NO URTI	6	6	7	
CONTROLS	URTI	5	5	12	p = 0.27

There was no significant difference in the incidence of URTI's experienced by the runners or controls in each of the three study groups, namely ascorbic acid, beta-carotene and placebo supplementation (Table 4.7).

TABLE 4.8. : THE EFFECT OF ANTI-OXIDANT VERSUS PLACEBO SUPPLEMENTATION ON THE INCIDENCE OF URTIS IN THE RUNNERS AND THE NON-RUNNING CONTROLS

		NO URTI	URTI	LEVEL OF SIGNIFI-CANCE
RUNNERS	ANTI-OXIDANT	16	9	
RUNNERS	PLACEBO	6	13	p = 0.033
CONTROLS	ANTI-OXIDANT	12	10	
CONTROLS	PLACEBO	7	12	p = 0.257

However, when the data for Group A (ascorbic acid) and Group B (beta-carotene) were pooled to form one anti-oxidant supplemented group, and compared to the placebo group, a significant difference emerged in the running group. That is, those athletes who had taken either 600 mg ascorbic acid or 4.5 mg beta-carotene experienced significantly fewer ($p < 0.05$) URTIs in the two-week post-race period. There was no significant relationship in the non-running controls.

TABLE 4.9. : THE EFFECT OF ANTI-OXIDANT VERSUS PLACEBO SUPPLEMENTATION ON THE SEVERITY OF URTIs EXPERIENCED BY THE RUNNERS AND THE NON-RUNNING CONTROLS

		MILD	MODERATE	SEVERE	LEVEL OF SIGNIFI-CANCE
RUNNERS	ANTI-OXIDANTS	7	0	2	
RUNNERS	PLACEBO	5	0	8	p = 0.0003
CONTROLS	ANTI-OXIDANTS	7	3	0	
CONTROLS	PLACEBO	8	0	4	p = 0.002

Anti-oxidant supplementation did not affect the incidence of mild URTIs in the runners or controls. However, in both study groups, there was a significant difference ($p < 0.01$) in the incidence of severe URTI's according to the type of supplementation. That is, 80% of the runners and 100% of the controls with severe URTI's were on placebo medication.

For the non-running controls, there was a less marked effect, but anti-oxidant supplementation also significantly decreased ($p = 0.01$) the incidence of severe URTI's (0% of those on anti-oxidants, versus 33.3% on placebo experienced severe URTI's).

TABLE 4.10. : THE EFFECT OF THE TWO TYPES OF ANTI-OXIDANT SUPPLEMENT ON THE INCIDENCE OF URTI's EXPERIENCED BY THE RUNNERS AND THE NON-RUNNING CONTROLS

		NO URTI	URTI	LEVEL OF SIGNIFI-CANCE
RUNNERS	ASCORBIC ACID	9	4	
RUNNERS	BETA-CAROTENE	7	5	p = 0.571
CONTROLS	ASCORBIC ACID	6	5	
CONTROLS	BETA-CAROTENE	6	5	p = 0.0

Therefore, there was no significant difference between ascorbic acid or beta-carotene supplementation on the incidence of URTI's in either the runners or controls. That is, neither anti-oxidant was more or less effective in preventing URTI's in either study group.

TABLE 4.11. : THE EFFECT OF THE TYPE OF ANTI-OXIDANT SUPPLEMENT ON THE SEVERITY OF URTI's EXPERIENCED BY THE RUNNERS AND THE NON-RUNNING CONTROLS

		MILD	MODERATE	SEVERE	LEVEL OF SIGNIFI-CANCE
RUNNERS	ASCORBIC ACID	3	0	1	
RUNNERS	BETA-CAROTENE	4	0	1	p = 0.056
CONTROLS	ASCORBIC ACID	4	1	0	
CONTROLS	BETA-CAROTENE	3	2	0	p = 0.036

There was a significant difference ($p < 0.05$) in the severity of URTI's experienced in the non-running control but not in the running group. However, this was not attributable to the type of anti-oxidant supplementation, as in both groups almost all subjects experienced mild URTI's regardless of what form of anti-oxidant they were using. That is, in neither the runners nor the non-running controls could ascorbic acid or beta-carotene be considered more effective in decreasing severity of URTI's.

4.3. Running, training and lifestyle factors and the incidence and severity of URTI's

All the running, training and lifestyle variables listed in Tables 4.2 and 4.3 were examined using the simple linear regression (Statgraphics, STSC, Rockville, U.S.A.) in order to establish whether there was any relationship between these and the severity of URTI's experienced in both study groups.

TABLE 4.12. : CORRELATION* BETWEEN LIFESTYLE AND TRAINING VARIABLES AND INCIDENCE OF URTI'S IN THE STUDY GROUPS

VARIABLE	CORRELATION RUNNERS (n = 44)	CO-EFFICIENT (r) CONTROLS (n = 41)
Total mileage (km)	0.015	-
Marathon PB (hr:mins)	0.019	-
Comrades finishing time (hr:mins)	0.061	-
Running experience (yrs)	0.151	-
'Flu susceptibility	0.008	0.092
Stress experience	0.032	0.045

Alcohol consumption	0.234	0.070
Tobacco use	0.072	0.062

***** r 0.05 = 0.257

The analysis of the data obtained showed that there was no significant correlation ($p > 0.05$) between any of the variables measured, and the severity of URTI's experienced for either the runners or the non-running control group.

CHAPTER FIVE

DISCUSSION

The purpose of this study was to determine whether anti-oxidant supplementation had any effect on the incidence and severity of upper respiratory tract infections experienced by distance runners in the two-week period after competing in an ultra-marathon running event.

The results show that there was:

i) no difference between the runners and controls in the incidence of post-race URTI's (Table 4.5), although

ii) significantly more runners than controls experienced severe URTI's (45% and 18% respectively) ($p < 0.01$) (Table 4.6).

iii) As there was no difference in the rate or severity of infection between the ascorbic acid and beta-carotene supplemented groups (Tables 4.4, 4.10 and 4.11), the data from these groups was combined. Hence

iv) athletes, but not controls on anti-oxidant supplementation (600 mg ascorbic acid or 4.5 mg beta-carotene) experienced significantly fewer URTIs than those on placebo supplementation ($p < 0.05$)(Table 4.8), although

v) all of the non-running controls (100%) and 80% of the athletes who developed severe URTI's were on placebo medication (Tables 4.4 and 4.9).

vi) There was no correlation between any of the lifestyle or demographic variables measured and the incidence of post-race URTI in any of the study groups.

That exercise has both immunostimulatory and immunosuppressive effects has been acknowledged for at least the last century. Athletes commonly believe that they are more susceptible to certain illnesses during intense training and major competition. On the other hand, there is also the widespread perception that those who exercise regularly are less susceptible to certain illnesses, such as upper respiratory tract infections. Current evidence therefore points to a dual effect of exercise: intense exercise increases illness susceptibility, while moderate exercise does the opposite.

Nieman (1994) has modelled the relationship between physical activity and URTI in the form of a "J" curve. This model suggests that while the risk of URTI may decrease below that of a sedentary individual when one engages in moderate exercise training, risk may rise above average during periods of excessive amounts of exercise.

Heavy exertion is a form of physiological stress that causes large increases in circulating epiniphrine and cortisol, hormones that have been consistently associated with a suppression of immune function, and rapid disturbance in the circulating leukocytes and lymphocytes.

Psychological factors which vary according to the intensity and duration of the training programme and the competitiveness of the athlete may also play an important role in the relationship between exercise and URTI.

There are relatively few studies that have explored the relationship between physical activity and the incidence of URTI's. Of the twelve published to date (Nieman 1994), 80% were epidemiological in design, evenly divided between prospective and retrospective, while 20% employed a randomised, controlled experimental design.

Several of the epidemiological studies suggest that athletes engaging in marathon-type events and/or very heavy training are at increased risk of URTI. Peters and Bateman (1983) were the first South African researchers to quantify rates of illness post-race in ultramarathon runners. They found that those athletes who ran the faster times, and trained the highest mileages were more likely than the slower, less well trained runners and the sedentary control subjects to develop post-race URTI's. Subsequent studies by Peters et al (1993, 1996) on Comrades Marathon runners have not entirely supported the idea that it is the more competitive athlete who is more likely to develop post-race URTI's. In ultramarathon events, under-trained athletes who finish in slow times are also at increased risk of post-race URTI's (Peters et al, 1996).

Nieman et al (1990a) and Linde (1987) have further supported the idea that runners experience increased risk of URTI during heavy training or following a marathon race event. Nieman et al (1990a) researched the incidence of URTI in 2311 marathon runners who varied widely in running ability and training habits. Of those who participated in the marathon, 12.9% reported symptoms consistent with an infectious episode during the week following the race. Only 2.2% of similarly experienced runners who had applied for but did not participate in the race became ill.

Linde (1987) documented upper respiratory tract infection rates in a group of 44 Danish elite orienteers to be 2.5 episodes and that of the non-athletic control subjects to be 1.7 during a one-year period. One third of the controls reported no upper respiratory tract infection episodes during the year-long study, but this was the case for only 10% of the orienteers.

In this study, there was no difference between the runners and controls in the incidence of post-race URTI's (Table 4.5), although significantly more runners than controls experienced severe URTI's (45% and 18% respectively) ($p < 0.01$) (Table 4.6). Their symptoms, in addition to sore throats and nasal congestion, included headaches, fever, myalgia and joint pains. In 80% of the affected runners the symptoms lasted for more than three days, suggesting an infective origin. Both these findings are contrary to those of previous studies (Peters, et al 1993, 1996; Peters and Bateman 1983; Nieman, et al 1989). A possible explanation is that the non-running control for each athlete was a member of the same household or otherwise closely associated with the runner. Living in close physical proximity could increase the likelihood of either the runner or control infecting the other, if one were to develop a URTI.

In this study significantly more runners than controls experienced severe URTI's (45% and 18% respectively)($p < 0.01$) (Table 4.6). This suggests that, although the risk of infection was the same for both groups, ultramarathon running is an additional stress which contributed to the decrease in illness immunity.

This could be attributed to one or both of the following factors: i) the impairment of general host resistance to infection, resulting from the extreme stress and fatigue or running an ultramarathon; or, ii) the physical effects of cold and dry air on local mucosal defensives (Peters and Bateman, 1983).

Acute stress is recognised as a cause of increased susceptibility to oropharyngeal infection. Normal oral flora may become invasive and herpes simplex virus may be reactivated during stress. The observed immunological effects of stress in man include a decreased T-cell response to mitogens, impaired lymphocyte cytotoxicity and impairment of function of neutrophils and cells of the macrophage-phagocytic series. Some of these changes may be mediated by the alterations in adrenal or pituitary hormone levels which are known to occur (Solomon and Armkraut, 1981).

Peters and Bateman (1983) supported the role of stress by their finding that the faster runners experienced more symptoms. These runners were subjected to greater stress arising from their own competitiveness and because running at a faster pace demanded a higher oxygen consumption per minute. Their subjection to greater physical stress was further reflected in the higher incidence of musculoskeletal pain and injury in this group.

There was no relationship in this study between total training distance, finishing time, number of years running experience or best marathon time and the incidence of URTI. This contrasts with the findings of Peters and Bateman (1983), Peters et al (1996) and Nieman et al (1989). For example, Peters and Bateman (1983) found the frequency of URTI symptoms to be inversely related to the time taken to complete a 56 km foot race, and a significant but weaker association between symptoms and high weekly training distance.

Nieman et al (1989) found that weekly training mileages of greater than 96 km or less than 32 km significantly increased the risk of post-marathon URTI. Peters et al (1996) found that, for an ultramarathon, low rather than high weekly mileage was a risk factor for URTI.

The lack of correlation between exercise variables and URTI risk in this study suggests that factors other than running stress per se contributed to the URTIs experienced by some runners. Although there is no data as such to support the psychoneuroimmunological model of exercise-associated infection, the relationship between physical and psychological stress, immune function and infection has been acknowledged in more recent studies (Linde, 1987).

An attempt to quantify life stress was made in this study . Each subject completed a questionnaire in which they were asked to indicate whether they had experienced a range of known stress situations in the past six months. These statements were derived from the well-validated Social Readjustment Rating Scale (Holmes and Rahe, 1967). In scoring the the responses, no weighting factors were applied, and one point was allocated for every life stress recently experienced by that individual. However, if a validated psychometric scale had been employed, a more substantial relationship between life stress and URTI rates may have been demonstrated.

MacKinnon (1994) has presented a concept of exercise, stress and illness as three points on a triangle, each having independent effects on the immune system. Each factor in the triangle can

also interact with the other two. For example, exercise may influence resistance to illness and presence of illness may influence the capacity for exercise. Similarly, stress is a known contributing factor to illness, and exercise may modulate the stress response.

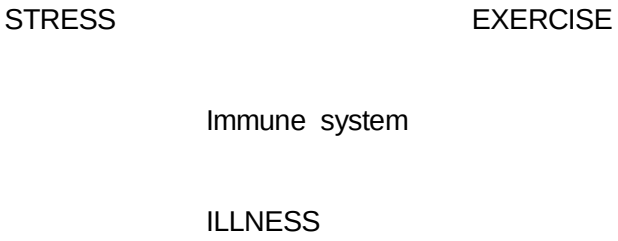

Fig. 5.1. Theoretical model of the interrelationships between stress, exercise, illness and the immune system (MacKinnon, 1994: 194)

Studies by Packer (1986) and Smith et al (1988) have shown that, during prolonged exercise, during which oxygen consumption is elevated eight to twelve times the basal levels, production of immunosuppressive oxygen radicals is enhanced. Indirect evidence thus exists that athletes participating in prolonged exercise need, in addition to extra caloric intake, to consume proportionately higher amounts of anti-oxidant vitamins such as ascorbic acid and beta-carotene to deactivate the free radicals (Anderson, 1984). However, exercise also induces a change in the distribution and metabolism of ascorbic acid, as well as increased rates of excretion.

Peters et al (1993; 1996) have shown that ascorbic acid supplementation may enhance resistance to upper respiratory tract infections that occur commonly in competitive ultramarathon runners. Other researchers (Marobia et al, 1989; Peters et al, 1992) have considered retinol supplementation both as an aid to running performance and to increase resistance to infection. While Marobia et al (1989) suggested that a diet poor in Vitamin A is associated with an increased risk of airway obstruction, Peters et al (1992) showed that supplementation of Vitamin A failed to result in a lowered percentage incidence of URTI's.

Neither anti-oxidant intakes from dietary sources or circulating anti-oxidant vitamin levels were quantified in this study. This may explain why there was no difference in the rate or severity of infection between the ascorbic acid and beta-carotene supplemented group (Tables 4.4, 4.10 and 4.11). When the data for the two supplemented groups was combined, the athletes, but not the controls, experienced significantly fewer URTI's than those on placebo supplementation ($p < 0.05$) (Table 4.8). Moreover, all of the non-running controls (100%) and 80% of the athletes who developed severe URTI's were on placebo medication (Tables 4.4 and 4.9). This strongly suggests that anti-oxidant supplementation is effective in decreasing the incidence and severity of URTI's in ultramarathon runners.

CHAPTER SIX

CONCLUSION

A relationship between physical and psychological stress, immune function and upper respiratory tract infection is well documented. There is a common belief among the general and athletic populations alike that regular exercise training decreases the risk of acquiring an upper respiratory tract infections, while severe exertion may increase the risk of URTI. Accordingly, the evidence to date suggests that while exercise at maximal capacity is generally immuno-suppressive, conflicting results have been obtained with moderate exercise protocols. One explanation for this dichotomy is the complexity of the immune system which is regulated by many variables that are unrelated to exercise, and difficult to quanitify.

Psychoneuroimmunology or behaviour immunology is a cross-disciplinary field that includes exercise science, psychology, immunology, physiology, neuroendocrinology and medicine. Models used to explain the immune response to exercise have neuroendocrine factors playing a pivotal role as it is now generally accepted that there is a two-way communication between the neuroendocrine and immune systems. Exercise can be considered a form of physical stress, since plasma concentrations of many of the stress hormones epinephrine and cortisol rise during exercise. Environmental conditions of a psychosocial or physical nature may influence the immune reactivity in proportion to the individual's evaluation of the psychological or physical stimulus. During prolonged exercise, production of immunosuppressive oxygen-free radicals is accelerated by a massively increased rate of oxygen consumption. It has been suggested that ascorbic acid and beta-carotene supplementation could decrease the rate of post-race illnesses.

This study showed that there was no difference between the runners and controls in the incidence of post-race URTI's, nor any correlation between the lifestyle or demographic variables measured and the incidence of post-race URTI's in any of the study groups. Significantly more runners than controls experienced severe URTI's (45% and 18% respectively). As there was no difference in the rate or severity of infection between the ascorbic acid and beta-carotene supplemented groups, the data from these groups were combined. Hence, athletes, but not controls, on anti-oxidant supplementation experienced significantly fewer URTI's than those on placebo supplementation. All of the controls (100%) and 80% of the athletes who developed severe URTI's were on placebo medication.

The results suggest that, while prolonged, strenuous exercise per se does not increase the risk of upper respiratory tract infection, post-race URTI's are common in distance runners. However, ingestion of supplemental anti-oxidant in the form of ascorbic acid or beta-carotene before and after a prolonged running event, significantly decreases the severity of post-race illness.

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APPENDICES

APPENDIX I

BIO-CONTROL PRODUCTS USED IN THE PROJECT

1.	BETA-CAROTENE	4.5 mg (100% RDA for Vitamin A)
	Energy Kj/cal	5.58/1.36
	Protein	60 mg
	Carbohydrate	280 mg
	Fat	8 mg
2.	ASCORBIC ACID	250 mg (833% RDA)
	Food complex	1 g
	Energy Kj/cal	10.2/2.42
	Protein	230 mg
	Carbohydrate	399 mg
	Fat	trace
	Other complexes	120 mg

APPENDIX II

QUESTIONNAIRE ADMINISTERED TO ALL STUDY SUBJECTS

PROJECT 93

Dear Runner,

Many thanks for taking part in "Project 93".

Title: "Ascorbic acid and beta-carotene in the prevention of post-race upper respiratory tract infections"

Investigator: Dr M.E. Moolla (Shorty)

Supervisor: Dr L.M. Weight (UCT)

Institution: MRC/UCT Bioenergetics of Exercise Research Unit, Department of Physiology, University of Cape Town Medical School, Observatory

Kindly fill in the attached questionnaire as best as you can. Please note that all the information is confidential and is for the sole use of "Project 93".

NOTE:

1. The questionnaire must be completed in detail by both the runner and the non-running control.
2. The runner and the non-running control must continue with the supplementation (A, B or C) up to two weeks after the Comrades Marathon.
3. During the supplementation period (8 weeks) if there are any problems (medical or otherwise) please contact me at 729449 (office hours) or 821632 (after hours).
4. At the end of the trial (+- 15.6.93) hand in your questionnaire to Jackie or George at the Savages office.
5. Which supplementation are you on: A, B or C (please tick)

CONSENT FORM

I, ... am a willing participant in "Project 93". The details of the Project have been explained to me.

At present I am not suffering from any major illness.

I understand that I can quit the Project at any stage.

I hereby indemnify the researcher, the sponsor, UCT or Savages Athletic Club against any illness or injury experienced during the course of the Project.

.....

SIGNATURE

[A] DEMOGRAPHIC DETAILS

NAME: .....
DATE OF BIRTH: ..... AGE AT COMRADES: ..... YRS
MALE/FEMALE: .....
MARRIED: YES/NO .....
OCCUPATION: .....
CHILDREN: NUMBER: ..... OLDEST: ..... YRS/YOUNGEST .....YRS
HEIGHT: ..... WEIGHT: .....

[B] HABITS

1. ALCOHOL USE:
   DO YOU DRINK? YES/NO .....
   IF YES - TYPE: .....
   DAILY: .....
   WEEKLY: .....
   OCCASIONAL: .....
   NO. OF YEARS DRINKING: .....

2. TOBACCO USE:
   DO YOU SMOKE? YES/NO .....
   NO. OF CIGARETTES PER DAY: .....
   NO. OF YEARS SMOKING: .....

[C] HISTORY OF ILLNESS/INJURIES

1. PLEASE RECORD ANY ILLNESS/INJURIES ENCOUNTERED DURING THE TRIAL PERIOD. ESPECIALLY NOTE EACH DAY WHETHER YOU HAVE ANY OF THE FOLLOWING SYMPTOMS:-
   COLD (RUNNY NOSE, SORE THROAT, OR COUGH)
   ALLERGY (ITCHY EYES OR STUFFY NOSE)
   HEADACHES
   FEVER (IF POSSIBLE RECORD TEMPERATURE AT THIS TIME)
   NAUSEA/VOMITING/DIARRHOEA
   FATIGUE/TIREDNESS
   MUSCLE/JOINT/BONE PROBLEM INJURY
   MENSTRUAL CRAMPS

2. ONCE A WEEK UP TO COMRADES, PLEASE TAKE YOUR WAKING PULSE
   WEEK 6 ..... BEATS/MIN
   WEEK 5 ..... "
   WEEK 4 ..... "
   WEEK 3 ..... "
   WEEK 2 ..... "
   WEEK 1 ..... "
   COMRADES MORNING ..... "
   1 WEEK AFTER ..... "
   2 WEEKS AFTER ..... "

RECORD YOUR SYMPTOMS (AS DISCUSSED IN [C] 1. BELOW AND AT BACK OF THIS PAGE IF NECESSARY.

3. ARE YOU AT PRESENT ON ANY MEDICATION? YES/NO
   IF YES: STATE WHAT:

4. ARE YOU ON ANY DIETARY SUPPLEMENT? YES/NO

IF YES: STATE WHAT:

5. ARE YOU ON ANY VITAMINS TO AUGMENT YOUR TRAINING? YES/NO
IF YES: STATE WHAT:

6. DO THESE SUPPLEMENTS IN YOUR OPINION HELP YOUR PERFORMANCE? YES/NO
IF YES: STATE HOW:

7. HOW OFTEN DO YOU GET A FLU/COLD YEARLY?
1, 2, 3, 4 TIMES OR MORE

8. IS YOUR RECOVERY QUICK? YES/NO
1, 2, 3, 4, 5 DAYS OR MORE

9. HOW DOES A COLD OR FLU AFFECT YOUR TRAINING?
DO YOU STOP TRAINING? ..... IF SO, FOR WHAT PERIOD
3, 5, 8, 10 DAYS OR MORE

10. DO YOU OFTEN GET 'FLU-LIKE SYMPTOMS A FEW DAYS AFTER A MARATHON? YES/NO
DO THOSE SYMPTOMS PRESENT WHEN YOUR TRAINING MILEAGE INCREASES?
YES/NO

[D] CURRENT AND PAST RUNNING PRACTICE

1. NUMBER OF YEARS RUNNING: .....
2. AVERAGE/WEEK AT PRESENT: .....
WEEKLY MILEAGE (IN SEASON) .....
WEEKLY MILEAGE (OUT OF SEASON) .....
3. LONGEST DISTANCE YOU HAVE EVER COVERED IN A SINGLE RUNNING EVENT:
4. PERSONAL BEST FOR: 10 KM ..... DATE: .....
21.1 KM ..... DATE: .....
42.2 KM ..... DATE: .....
56 KM ..... DATE: .....
COMRADES ..... DATE: .....
OR OTHER ..... DATE: .....

5. HOW MANY DAYS PER WEEK DO YOU TRAIN AT PRESENT?

6. AVERAGE FOR THREE MONTHS PRIOR TO COMRADES?
MARCH: ....
APRIL: ....
MAY: .....
7. TOTAL MILEAGE: JANUARY TO MAY: +- .....

[E] STRESS (NOTE: TRAINING FOR COMRADES IS ONE STRESS)

1. IN THE PAST SIX MONTHS WERE THERE ANY MAJOR CHANGES IN YOUR LIFE? PLEASE TICK AGAINST THE RELEVANT FACTOR
PREGNANCY
CHANGE OF JOB
ADDITION TO FAMILY (ANOTHER CHILD)

LOSS OF EARNING
DEATH IN FAMILY OR CLOSE FRIEND
MAJOR ILLNESS/INJURY TO SELF OR FAMILY MEMBER
DIVORCED/SEPARATED/MARRIAGE
TROUBLE WITH THE LAW
VICTIM OF VIOLENT CRIME
TAKING ON ADDITIONAL WORK OR STUDY LOAD
DOES YOUR JOB INVOLVE FREQUENT TRAVEL?

2. DO YOU EAT BREAKFAST REGULARLY?

3. APPROXIMATELY NUMBER OF HOURS YOU SLEEP:

4. NUMBER OF PEOPLE IN THE HOUSEHOLD:

5. DO YOU LIVE ALONE? YES/NO

6. NUMBER OF DAYS MISSED WORK/SCHOOL BECAUSE OF ILLNESS OR INJURY SINCE JANUARY 1993:

NOTE: DURING SUPPLEMENTATION PLEASE RECORD BELOW OR AT BACK OF THIS PAGE:

A. INJURIES
B. CHANGE IN PERSONAL HEALTH
C. CHANGE IN HEALTH OF FAMILY