THE ROLE OF ANTI-OXIDANTS IN THE PREVENTION OF POST-RACE UPPER RESPIRATORY TRACT INFECTIONS

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DECLARATION

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ABSTRACT

Several epidemiological reports suggest that athletes engaging in marathon-type running events are at increased risk of symptoms of upper respiratory tract infections (URTI). A possible explanation for this increased susceptibility is that during prolonged, strenuous exercise, production of immunosuppressive oxygen free radicals is increased. The purpose of this study therefore was to examine the effect of anti-oxidant vitamin supplementation on the incidence and severity of post-race symptoms of URTI's among athletes competing in a 90 kilometer ultramarathon footrace.

A double blind, randomised, placebo controlled study design was employed. Eighty five subjects were divided into three experimental and three control groups. 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. The experimental and control groups were divided into those ingesting 250 mg/day of ascorbic acid (n = 13 runners, 11 non-running controls), or 4.5 mg/day of beta-carotene (n = 12 runners, 11 non-running controls) or placebo (n = 19 runners and 19 non-running controls). All groups commenced supplementation six weeks before the ultramarathon and continued for two weeks after the race.

The runners and non-running controls experienced the same incidence of symptoms of upper respiratory tract infections during the study period (50% and 53% respectively) but significantly more runners than non-running controls experienced severe symptoms of upper respiratory tract infections of infective origin (45% and 18% respectively, $p < 0.01$). Of the runners, 30.8% on supplemental ascorbic acid, 41.7% on beta-carotene and 68% on placebo developed symptoms of URTI's. The comparative figures for non-running controls were 45.5%, 45.5% and 63% respectively. All of the non-running controls (100%) and 80% of the athletes who developed severe symptoms of URTIs were on placebo medication.

Although post-race symptoms of URTI's are common in distance runners, prolonged, strenuous exercise itself is only one of a number of risk factors for symptoms of URTI. However, ingestion of supplemental anti-oxidant in the form of ascorbic acid or beta-carotene for an eight-week period before and after an endurance running event significantly decreases the severity of athletes' symptoms of upper respiratory tract infections.

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LIST OF ABBREVIATIONS

g	grams
mg	milligrams
ug	micrograms
l	litre
dl	decilitre
ml	millilitre
mmol	millimole
hr	hour
I.U.	International Units
m	metre
km	kilometres
RDA	Recommended Daily Allowance
VO_2 max.	maximal oxygen uptake

In this thesis the vitamins have been referred to by their chemical and not their common names. Hence,

Ascorbic acid	Vitamin C
Retinol	Vitamin A
Tocopherol	Vitamin E

CHAPTER ONE

GENERAL INTRODUCTION

The effect 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). 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 (URTI's) (MacKinnon and Tomasi, 1986).

That exercise has both immunostimulatory and immunosuppressive effects has been acknowledged for at least the last century. This suggests a dualistic effect in that intense exercise may increase illness susceptibility, while moderate exercise does the opposite. Nieman (1994) has modelled this relationship between physical activity and URTI's in the form of a "J-shaped" 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 training.

Several 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) 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 participate in this event for reasons other than illness. 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. Nieman et al (1989)

found that among recreational runners 25% of those running 25 km or more 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 that 25 km per week.

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 endurance 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.

Also of current research interest is the role of anti-oxidant supplementation on URTI rates in athletes. The possible protective effect of free radical supplementation is thought to be due to two main factors: Exercise increases the production of free oxygen radicals (Dreosti, 1988) which in turn may inhibit leukocyte chemotaxis. Anti-oxidant requirements may therefore be increased in order to counteract these free radicals. However, exercise also changes the distribution, metabolism, and excretion of ascorbic acid via urine and sweat.

Peters et al (1993, 1994) for example have shown that ascorbic acid but not vitamin A 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 aim of this study was therefore to determine whether eight weeks of anti-oxidant supplementation in the form of 250 mg/day ascorbic acid or 4.5 mg/day beta-carotene had any effect on the incidence and severity of symptoms of upper respiratory tract infection experienced by distance runners in the two week period after competing in an ultra-marathon running event.

CHAPTER TWO

REVIEW OF LITERATURE

2.1. Overview of the Immune System

The human immune system is a diverse and complex network of interacting cellular and humoral components. Its principal purpose is to provide 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. These nonspecific immune mechanisms are not affected chronically by a prior infection.

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, complement activation and the increased synthesis and release into the circulation of a variety of hepatic acute-phase proteins are the predominant features of this response (MacKinnon, 1992).

The dual limbs of the adaptive 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-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.

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 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 necessitating 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.

2.1.1. The concept of psychoneuroimmunology

The immune system does not operate in isolation, but interacts reciprocally with the 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, epinephrine 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 (Keast et al, 1988; MacKinnon, 1992; McCarthy and Dale, 1988). Environmental conditions of a psychosocial or physical nature may also 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 (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 as a consequence of a variety of essential biochemical reactions, such as cell oxygen metabolism, phagocytosis and lipid peroxidation. In this way about 98% of the oxygen that enters the body through breathing is converted to water in the process of normal respiration, while about 2% is converted to toxic free radicals (Smith et al, 1988).

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. Oxidases 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. Some of the endogenous free radical sources are both generated and active intracellularly, others are released into the surrounding tissue (Machlin and Bendich, 1987; Machlin, 1992).

There are many exogenous sources of free radicals, but the principle one is 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 radical load (Machlin and Bendich, 1987; Machlin 1992).

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. 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.

The production of reactive oxygen species is a normal process in the life of aerobic organisms. Under physiological conditions, these deleterious species are removed effectively by the cellular anti-oxidant systems, including anti-oxidant vitamins, glutathione and sulfhydryls, and anti-oxidant enzymes. Existing data show that

anti-oxidant defences are not perfect and the anti-oxidant reserve capacity in most tissues is rather marginal. Therefore, an increased production of reactive oxygen species or a weakening of the anti-oxidant systems, or both, can subject the organisms to oxidative stress and tissue damage (Ji, 1995).

Heavy physical exercise is associated with the remarkable increase in oxygen consumption, and hence a challenge to the anti-oxidant systems. Anti-oxidant enzymes provide the first line of defence. Free radical species that escape the anti-oxidant enzymes are quenched by the chain-breaking anti-oxidant vitamin E. Similarly, each anti-oxidant plays a unique role in protecting the tissues from exercise-induced oxidative damage. Deficiency of an anti-oxidant nutrient can severly hamper the corresponding anti-oxidant system during exercise (Ji, 1995). Cigarette smoke is an intense source of oxidative stress, and some of the adverse effects of smoking on the respiratory tract may be mediated by free radicals and other oxidants. Plasma levels of anti-oxidant nutrients, including beta-carotene and vitamin C, are characteristically lower in smokers than in non-smokers. This may reflect the destruction of these anti-oxidants during neutralisation of smoke-mediated oxidative stress (Van Antwerpen et al, 1995). Moreover, anti-oxidants have a relatively weak effect upon neutrophil-derived reactive oxygen species in situations such as cigarette smoking.

The impact of diet on free radical production and oxidative damage has been best illustrated in experimental animals with anti-oxidant nutrient deficiencies. For example, a diet deficient in selenium, a trace mineral essential for the synthesis of glutathione peroxidase, is known to cause major disturbances in anti-oxidant function at the cell, organ and the whole body levels. This has actually been demonstrated in humans by an epidemic in Northern China (a region with selenium-poor soil) called Keshan Disease, which is characterised by cardiac myopathy and a high mortality rate (Ji et al, 1992).

Although several studies have shown that vitamin E or a mixture of anti-oxidant vitamins (E, C and beta-carotene) can reduce the increase in indirect indicators of free-radical generation, other studies have failed to demonstrate this effect. It is possible that anti-oxidants may work in concert with each other.

However, studies on the effects of anti-oxidant supplementation have many limitations. Principally, the side effects of high doses of dietary supplementation and the lack of accurate methods of assessing the free radical and anti-oxidant systems interaction. Possible side effects of the anti-oxidant vitamin C would be gastric irritation, gastric disturbance as mild diarrhea, increased risk of urinary oxalate stone formation, possibility of excessive iron absorption and possible lowering of blood levels of vitamin

B_{12}. Possible side effects of the anti-oxidant beta-carotene would be that supplementation with large amounts may lower blood levels of other carotenoids or possibly lower blood levels of vitamin E.

2.3. The anti-oxidant vitamins

Oxygen, while being vital to life, can also be destructive (Dreosti, 1988). Hence there are a series of co-operative 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. 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 dietary sources (Machlin and Bendich, 1987).

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, as yet, no case for massive anti-oxidant supplementation, except possibly in the prevention and treatment of specific degenerative diseases. Moreover the role of multi-vitamin

and mineral supplementation in enhancing immune functioning has not been adequately addressed (Van den Beek, 1985; 1991).

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 to deactivate the free radicals (Anderson, 1984).

2.3.1. Ascorbic acid

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 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 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 authors suggest that anti-oxidants countered the immuno-suppressive effects of free radicals.

2.3.2. Beta-carotene

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 (Bloem et al, 1990). Retinol is essential to the integrity and function of mucosal and epithelial surfaces, so a deficiency thereof results in abnormalities in the respiratory epithelium potentiating bacterial colonisation 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 (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 infection 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

L-tocopherol is the most important lipid-soluble anti-oxidant. Its unique membrane-borne cellular location enhances its efficiency to quench the free radicals originating 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. 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). For example, following an 8 km running event plasma zinc levels were significantly reduced for two hours post exercise. 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 exercise-associated changes in susceptibility to infection provides some support to these observations (MacKinnon, 1982). Independently of exercise, psychological stress also exerts an immunosuppressive effect (Smith, 1994). Hence athletes undertaking strenuous training and under psychological stress may be at high risk, especially for primary infections.

Intense exercise is generally immunosuppressive, 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. 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, and the logistics of sampling and assay techniques.

The dualistic effects of exercise on immunity may be related to the intensity-dependent release of stress hormones, some of which have potent regulatory effects (MacKinnon, 1992). For example, high circulating levels of immuno-enhancing growth hormone, are found at low exercise intensity. In contrast, when workload intensity exceeds 60% VO_2 max, the immunosuppressive hormones cortisol and epinephrine are activated (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 directly proportional to the intensity and duration of exercise, and inversely proportional to the level of fitness of the individual. 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 neutrophils 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). In addition to increasing the number of polymorphonuclear neutrophils in the blood, exercise may also activate polymorphoneuclear neutrophils.

2.4.2. The effect of exercise on leukocyte function

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 is associated with increased circulating levels of cytokines, for example IL-1 (Eichner, 1993). It is at present unclear to what extent these may mediate immune function during and after prolonged exercise. Increased IL-1 and IL-6 levels have been recorded after exercise lasting more than three hours (Weight et al, 1991). However, 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

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.

However, 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. If this could be verified, it could be a useful tool in athlete management (Keast et al, 1988).

2.6. Exercise and upper respiratory tract infections

Most athletes believe that regular exercise will produce health benefits, among these improved resistance to infection, resulting in fewer upper respiratory tract infections (MacKinnon and Tomasi, 1986). However, epidemiological studies suggest that acute

exercise stress increases 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 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.

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 participation in either a 5-km, 10-km or 21.1-km race, 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 prolonged strenuous exercise is generally immunosuppressive, the effect of moderate exercise on immune function is less precise. One of the reasons for this variability is that exercise immunology is a complex subject where *in vivo* and *in vitro* measurements can be potentially influenced by many biological and technical factors that are unrelated to exercise.

Strenuous physical exercise is associated with oxidative stress and oxygen-free radical generation. 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, in terms of immune functioning.

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 are predisposed 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. Demographic data was obtained by questionnaire. All subjects were required to keep a detailed log book, in which they recorded any URTI symptoms during the study period.

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. This information was then submitted to the researcher on the questionnaire forms provided (see Appendix II). What constituted an upper respiratory tract infection symptom was carefully explained to each subject by the researcher prior to the commencement of the study, and comprehensive physical checklists were provided with their log books and questionnaires. 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. Explanation of demographic variables

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. URTI susceptibility rating:

The subject's resistance to URTI's 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 URTI episodes experienced per annum, the severity thereof and the recovery rate (see Appendix II, questions 7-10).

7. Stress:

Each subject's perceived stress 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 qustions on alcohol use included in Appendix II, part B. Heavy drinking implied either four or more beers per day or two or 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.

3.6. Data analysis

All the data obtained in this study was processed using Lotus 1-2-3 (Lotus Development Corporation, Boston). All data relating to the incidence and severity of symptoms of upper respiratory tract infection in the various study groups was analysed using Chi-square. The Kruskal-Wallis one-way ANOVA and the Kolmogonov (Siegel, 1956) were used to determine whether there were any significant differences between the study groups with regard to the severity of the URTI symptoms experienced.

CHAPTER FOUR

RESULTS

4.1. DEMOGRAPHIC DATA

TABLE 4.1 NUMBER OF SUBJECTS IN EACH STUDY GROUP

	NO.OF RUNNERS RECRUITED	NO.OF RUNNERS COMPLETING STUDY	NO.OF NON-RUNNERS RECRUITED	NO.OF NON-RUNNERS 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 subjects (6 runners and 9 non-running 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 non-running controls) failed to complete their log books or

questionnaires adequately during the study.

Six subjects (2 runners and 4 non-running 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 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 (n = 13)	GROUP B BETA-CAROTENE (n = 12)	GROUP C PLACEBO (n = 19)	TOTAL (n = 44)
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 time	9h02m +-1h38m	8h50m +-1h30m	8h47m +-1h43m	8h54m +-1h42m
Running experience (yrs)	10.13 +-6.1	8.42 +-5.8	12.29 +-8.3	10.56 +-6.8
"URTI rating" (units)	6.85 +-1.62	6.75 +-1.68	6.53 +-1.9	6.68 +-1.8
Stress experience (units)	1.83 +-1.4	2.08 +-0.9	1.71 +-0.9	1.84 +-1.1
Alcohol intake	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

There were no significant differences in any variable, between the the groups as determined by the Kruskal-Wallis one-way ANOVA (Siegel, 1956)

TABLE 4.3. DEMOGRAPHIC DATA - NON-RUNNING CONTROLS

	GROUP A ASCORBIC ACID (n = 11)	GROUP B BETA-CAROTENE (n = 11)	GROUP C PLACEBO (n = 19)	TOTAL (n = 41)
Age (yrs)	35.63 +-8.3	38.09 +-6.9	36.11 +-6.6	36.5 +-6.3
"URTI rating" (units)	6.82 +-1.5	6.50 +-1.8	6.0 +-2.2	6.35 +-1.8
Stress experience (units)	1.23 +-0.6	1.0 +-0.8	1.63 +-1.2	1.35 +-0.9
Alcohol intake	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

The above represents the demographic data of the non-running controls from the three groups.

There are no significant differences between the groups.

4.2. THE INCIDENCE AND SEVERITY OF SYMPTOMS OF URTI AND THE EFFECT OF ANTI-OXIDANT SUPPLEMENTATION

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

	NONE	*MILD	**MOD	***SEVERE	TOTAL
RUNNER GROUP A	9	3	0	1	13
RUNNER GROUP B	7	4	0	1	12
RUNNER GROUP C	6	5	0	8	19
TOTAL	22	12	0	10	44
NON-RUNNER GROUP A	6	4	1	0	11
NON-RUNNER GROUP B	6	3	2	0	11
NON-RUNNER GROUP C	7	8	0	4	19
TOTAL	19	15	3	4	41

*Mild: (Rating scale 2) : cold and allergy symptoms (running and/or congested nasal passage, sore throat, cough, itchy eyes)

**Mod: (Rating scale 3) : all of the above symptoms including headache ("head cold")

***Severe: (Rating scale 4) : all of the above symptoms and headache, with fever, myalgia and joint pain, anorexia, nausea and vomiting.

GROUP A : Ascorbic acid supplementation

GROUP B : Beta-carotene supplementation

GROUP C : Placebo supplementation

The upper respiratory tract infection symptoms and specific clinical signs were correlated using the upper respiratory tract infection range classified by Crompton and Haslett (Crompton and Haslett, 1995). The range covers the basic URTI symptoms, primarily centred around the nasal passages, to the situation where the whole body is affected with the associated joint and muscle pain and accompanying fever. This was practical from the point of view of self-reporting of symptoms of upper respiratory tract infections. It was not possible to have every subject medically examined at various stages.

TABLE 4.5. THE TOTAL INCIDENCE OF SYMPTOMS OF URTI's IN RUNNERS AND NON-RUNNING CONTROLS

	NO URTI	URTI	TOTAL	LEVEL OF SIGNIFI-CANCE
RUNNERS	22 (50%)	22 (50%)	44 (100%)	
NON-RUNNERS	19 (47%)	22 (53%)	41 (100%)	$p = 0.736$

The data are 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 symptoms of URTIs ($p > 0.05$). Half of the runners, and 53% of the non-running controls developed symptoms of URTIs during the two-week post-race period.

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

	MILD URTI	MODERATE URTI	SEVERE URTI	TOTAL	LEVEL OF SIGNIFI-CANCE
RUNNERS	12 (54.5%)	0	10 (45.5%)	22 (100%)	
NON-RUNNERS	15 (68.2%)	3 (13.6%)	4 (18.2%)	22 (100%)	$p = 0.002$

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

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

		ASCORBIC ACID	BETA-CAROTENE	PLACEBO	LEVEL OF SIGNIFI-CANCE
RUNNERS	NO URTI	9 (69.2%)	7 (58.3%)	6 (32%)	
RUNNERS	URTI	4 (30.8%)	5 (41.7%)	13 (68%)	p = 0.15
TOTAL		13 (100%)	12 (100%)	19 (100%)	
NON-RUNNERS	NO URTI	6 (54.5%)	6 (54.5%)	7 (37%)	
NON-RUNNERS	URTI	5 (45.5%)	5 (45.5%)	12 (63%)	p = 0.27
TOTAL		11 (100%)	11 (100%)	19 (100%)	

There was no significant difference in the incidence of symptoms of URTI's experienced by the runners or non-running controls in each of the three study groups, namely ascorbic acid, beta-carotene or placebo supplementation.

TABLE 4.8. THE EFFECT OF THE TYPE OF ANTI-OXIDANT SUPPLEMENT ON THE SEVERITY OF SYMPTOMS OF URTI's EXPERIENCED BY THE RUNNERS AND THE NON-RUNNING CONTROLS

		MILD	MODE-RATE	SEVERE	TOTAL	LEVEL OF SIGNI-FICANCE
RUNNERS	ASCOR-BIC ACID	3 (75%)	0 (0%)	1 (25%)	4 (100%)	
RUNNERS	BETA-CARO-TENE	4 (80%)	0 (0%)	1 (20%)	5 (100%)	p = 0.056
NON-RUNNERS	ASCOR-BIC ACID	4 (80%)	1 (20%)	0 (0%)	5 (100%)	
NON-RUNNERS	BETA-CARO-TENE	3 (60%)	2 (40%)	0 (0%)	5 (100%)	p = 0.036

There was a significant difference ($p < 0.05$) in the severity of symptoms 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, but to the fact that in both groups almost all subjects experienced mild as opposed to severe 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 symptoms of URTI's.

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

The following four tables illustrate runners and controls divided into either three sub-groups (URTI rating 1, 2 and 4) (Tables 4.9 and 4.10) or simply as no URTI symptoms vs URTI symptoms present (Tables 4.11 and 4.12). There are no differences between the groups (means +- standard deviation). For the controls' URTI ratings 3 and 4 were combined as one group. Statistical analysis was not necessary.

URTI rating:

Rating scale: (1) no URTI symptoms

(2) mild URTI symptoms

(3) moderate URTI symptoms

(4) severe URTI symptoms

TABLE 4.9. DEMOGRAPHIC VARIABLES AND URTI SYMPTOMS RATING FOR RUNNERS (I)

There are no significant differences between the groups.

VARIABLE		URTI RATING	
	1 (n = 22)	2 (n = 12)	4 (n = 10)
Total mileage	1579	1444	1660
	+-996	+-263	+-545
Comrades finish time (hr)	8.94	9.26	8.87
	+-1.55	+-1.78	+-1.44
Run experience (yrs)	9.41	11.0	12.55
	+-6.36	+-6.44	+-9.41
'Flu susceptibility	6.61	6.86	6.57
	+-1.73	+-1.77	+-1.91
Stress rating	1.81	1.46	2.05
	+-1.11	+-0.5	+-1.04
Alcohol intake	3.91	3.1	5.7
	+-3.19	+-3.0	+-2.21
Tobacco intake	1.27	1.58	1.1
	+-0.9	+-1.24	+-0.32

Data presented as means +- standard deviation

TABLE 4.10 : DEMOGRAPHIC VARIABLES AND URTI SYMPTOM RATING FOR RUNNERS (II)

There are no significant differences between the groups.

VARIABLE	NO URTI SYMPTOMS	POST-RACE URTI SYMPTOMS
	(n = 22)	(n = 22)
Total mileage (km)	1633	1543
	+-952	+-252
Comrades finish time (hr)	8.69	9.00
	+-1.56	+-1.61
Run experience (yrs)	9.41	11.7
	+-6.37	+-7.77
'Flu susceptiblity	6.61	6.73
	+-1.56	+-1.61
Stress rating	1.82	1.73
	+-1.11	+-0.83
Alcohol intake	3.91	4.45
	+-3.19	+-2.86
Tobacco intake	1.27	1.36
	+-0.9	+-0.95

TABLE 4.11 DEMOGRAPHIC DATA AND URTI RATINGS FOR CONTROLS (I)

There are no significant differences between the groups.

VARIABLE		URTI RATING	
	1 (n = 19)	2 (n = 15)	4 (n = 7)
'Flu susceptibility	6.53	6.07	6.14
	+-1.01	+-9.91	+-1.68
Stress rating	1.39	1.47	1.14
	+-1.21	+-0.85	+-0.41
Alcohol intake	2.16	1.6	2.14
	+-1.58	+-0.91	+-0.90
Tobacco intake	1.79	1.27	2.43
	+-1.9	+-0.59	+-2.49

Data presented as means +- standard deviation.

TABLE 4.12 DEMOGRAPHIC DATA URTI SYMPTOM RATINGS FOR CONTROLS (II)

There are no significant differences between the groups.

VARIABLE	NO URTI SYMPTOMS	POST-RACE URTI SYMPTOMS
	(n = 19)	(n = 22)
'Flu susceptibility	6.53	6.09
	+-1.01	+-1.8
Stress rating	1.39	1.36
	+-1.21	+-0.73
Alcohol intake	2.16	1.77
	+-1.58	+-0.92
Tobacco intake	1.79	1.64
	+-1.9	+-1.21

Data presented as means +- standard deviation.

The analysis of the data obtained showed that there was no significant difference ($p > 0.05$) between the study groups with respect to the severity of symptoms of URTI's experienced for either the runners or the non-running control group.

The results of this study show that there was:

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

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

iii) There was no difference in the rate or severity of infection between the ascorbic acid and beta-carotene supplemented groups (Table 4.7)

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

CHAPTER FIVE

DISCUSSION

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

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, 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 non-running controls in the incidence of post-race symptoms of URTI's (Table 4.5). Significantly more runners than non-running controls experienced severe symptoms of 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 lasting for more than three days, suggestive of an infectious origin is contrary to the findings of previous studies that both runners and non-runners experienced the same incidence of URTI (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 symptoms of URTI. The finding that significantly more runners than non-running controls experienced severe symptoms of URTI's 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 of 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) implicated stress in explaining their finding that the faster runners experienced more symptoms. These runners were subjected to both greater psychological 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.

It is commonly perceived that factors other than running stress per se contributed to the symptoms of URTI's 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).

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.

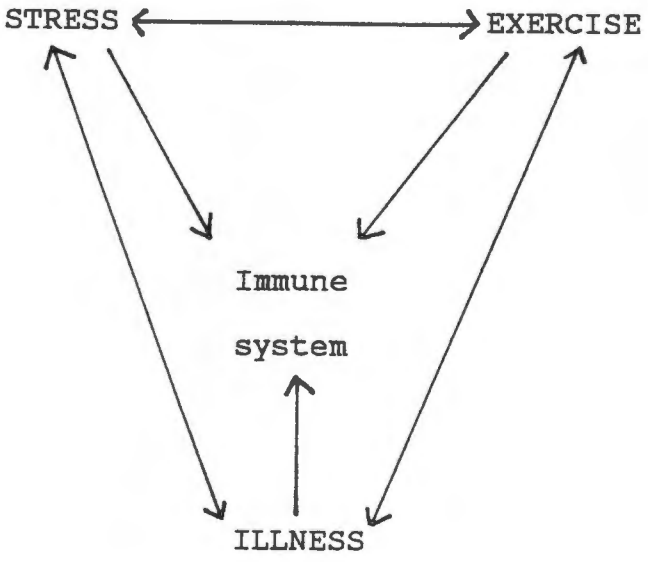

Fig. 5.1. Theoretical model of the interrelationships between stress, exercise, illness and the immune system (MacKinnon, 1994: 194)

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 responses, no weighting factors were applied, and one point was allocated for every life stress 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.

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 nor circulating anti-oxidant vitamin levels were quantified in this study. This may explain why there was no difference in the rate or severity of symptoms of infection between the ascorbic acid and beta-carotene supplemented groups. Moreover, all of the non-running controls (100%) and 80% of the athletes who developed severe symptoms of URTI's were on placebo medication (Table 4.4). This strongly suggests that anti-oxidant supplementation is effective in decreasing the severity of post-race symptoms 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 infection, while severe exertion may increase the risk of URTI. 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 and the difficulties inherent in quantifying the factors that regulate it.

It is now generally accepted that there is a two-way communication between the neuroendocrine and immune systems, and the models used to explain the immune response to exercise have neuroendocrine factors playing a pivotal role. Exercise can be considered a form of physical stress, since plasma concentrations of epinephrine and cortisol rise during exercise. Environmental conditions of a psychosocial or physical nature may influence immune reactivity, in proportion to the individual's evaluation of the psychological or physical stimulus. Moreover, during prolonged exercise, production

of immunosuppressive oxygen free radicals is accelerated by a massively increased rate of oxygen consumption. Hence athletes participating in prolonged, strenuous exercise may be more susceptible to URTI's after the competitive event. There is evidence however that anti-oxidant supplementation could decrease the risk of post-race illness.

This study showed that there was no difference between the runners and controls in the incidence of post-race symptoms of URTI's. Significantly more runners than controls experienced severe symptoms of URTI's (45% and 18% respectively). There was no difference in the rate or severity of infection between the ascorbic acid and beta-carotene supplemented groups. All of the controls (100%) and 80% of the athletes who developed severe symptoms of URTI's were on placebo medication.

The results suggest that, while prolonged, strenuous exercise per se does not increase the risk of symptoms of upper respiratory tract infection, post-race symptoms of 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, strenuous running event significantly decreases the severity of symptoms of post-race illness.

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APPENDICES

APPENDIX I

BIO-CONTROL PRODUCTS USED IN THE PROJECT

1.	BETA-CAROTENE (bonded and in a food complex)	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 (bonded and in a food complex)	250 mg (833% RDA)
	Energy Kj/cal	10.2/2.42
	Protein	230 mg
	Carbohydrate	399 mg
	Fat	trace
	Other complexes	120 mg

3. PLACEBO (in identical form to the ascorbic acid and beta-carotene tablets without the active ingredients)

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. <u>ALCOHOL USE:</u> DO YOU DRINK? YES/NO .....

IF YES - TYPE: .....

DAILY: .....

WEEKLY: .....

OCCASIONAL: .....

NO. OF YEARS DRINKING: .....

2. <u>TOBACCO USE:</u> 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? e.g.

2, 4, 6, 8, 10, 14 DAYS

OR

DO THOSE SYMPTOMS PRESENT WHEN YOUR TRAINING MILEAGE INCREASES?

[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? e.g.

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 PAGE:

A. INJURIES

B. CHANGE IN PERSONAL HEALTH

C. CHANGE IN HEALTH OF FAMILY

WOULD YOU BE PREPARED TO UNDERGO A BLOOD TEST FOR BIOLOGICAL MARKERS IN THE DAYS FOLLOWING THE COMRADES MARATHON? YES/NO
(NOTE THIS IS NOT ESSENTIAL TO THE PROJECT)

WOULD YOU BE PREPARED TO TAKE PART IN FUTURE PROJECTS?

(25)

PROJECT 93

EAR RUNNER,

ANY THANKS FOR TAKING PART IN "PROJECT 93".

ITLE: "ASCORBIC ACID AND BETACAROTENE IN THE PREVENTION OF POST RACE UPPER RESPIRATORY TRACT INFECTIONS"

NVESTIGATOR: DR. M.E. MOOLLA (SHORTY)

UPERVISOR: DR. L.M. WEIGHT (UCT)

NSTITUTION: (MCR/UCT BIOENERGETICS OF EXERCISE RESEARCH UNIT, DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF CAPE TOWN MEDICAL SCHOOL, OBSERVATORY.)

INDLY FILL IN THE ATTACHED QUESTIONNAIRE AS BEST AS YOU CAN. LEASE NOTE THAT ALL THE INFORMATION IS CONFIDENTIAL AND IS FOR HE SOLE USE OF "PROJECT 93".

TE:

THE QUESTIONNAIRE MUST BE FILLED IN DETAIL BY BOTH THE RUNNER AND THE NON-RUNNING CONTROL.

THE RUNNER AND THE NON-RUNNING CONTROL MUST CONTINUE WITH THE SUPLEMENTATION (A,B,C,OR D) UP TO 2 WEEKS AFTER THE COMRADES MARATHON.

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).

AT THE END OF THE TRIAL (+ 15/06/93) HAND IN YOUR QUESTIONNAIRE TO JACKIE OR GEORGE AT THE SAVAGES OFFICE.

WHICH SUPPLEMENTATION ARE YOU ON: A B C (D) (PLEASE TICK).

CONSENT FORM

I BERNARD BISCHOFF 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 ENDEMNIFY THE RESEARCHER, THE SPONSOR, UCT, OR SAVAGES ATHLETIC CLUB AGAINST ANY ILLNESS OR INJURY EXPERIENCED DURING PROJECT.

[A] DEMOGRAPHIC DETAILS

NAME: H.B. BISCHOFF

DATE OF BIRTH: 3-2-52 AGE AT COMRADES: 41 YRS.

MALE/FEMALE: MALE

MARRIED: (YES) / NO

OCCUPATION: FINANCIAL CONSULTANT.

CHILDREN: NUMBER 3 OLDEST 12 YRS. / YOUNGEST 4 YRS.

HEIGHT: 190 cm

WEIGHT: 91 kg.

[B] HABITS

1. ALCOHAL USE: DO YOU DRINK? (YES) / NO

IF YES - TYPE: BEER + WHISKY

DAILY 10

WEEKLY 5

OCCASIONAL ✓ 2

NO OF YEARS DRINKING 20

2. TOBACCO USE: DO YOU SMOKE? YES/NO NO

NO OF CIGARRETS 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:-

(1) COLD (RUNNY ROSE, SORE THROAT, OR COUGH)
(2) ALLERGY (ITCHY EYES OR STUFFY NOSE)
(3) HEADACHES
(4) FEVER (IF POSSIBLE RECORD TEMPERATURE AT THIS TIME)
(5) NAUSEA / VOMITING / DIARRHOEA
(6) FATIGUE / TIREDNESS
(7) MUSCLE / JOINT / BONE PROBLEM INJURY
(8) MENSTRUAL CRAMPS

2. ONCE A WEEK UP TO COMRADES PLEASE TAKE YOUR WAKING PULSE:

WEEK 6		BEATS/ MIN
" 5		" DID NOT MEASURE.
" 4		"
" 3	48	"
" 2	48	"
" 1	46	"
COMRADES MORNING	60	"
ONE WEEK AFTER	48	"
TWO WEEKS AFTER	48	"

RECORD YOUR SYMPTOMS (AS DISCUSSED IN C(1)) BELOW + AT BACK OF THIS PAGE IF NECESSARY.

(1). RIGHT HAMSTRING SPASMS ONE WEEK BEFORE COMRADES.

(2). SINUS ATTACK - LASTED TWO DAYS TWO WEEKS BEFORE COMRADES.

ARE YOU AT PRESENT ON ANY MEDICATION? YES (NO)
IF YES: STATE WHAT:

ARE YOU ON ANY DIETARY SUPPLEMENT? (YES) NO
IF YES: STATE WHAT:
LEPPIN CARBO BOOSTER - 3 DAYS BEFORE COMRADE
LEPPIN ENERGY SACHETS - ON COMRADES DAY.

ARE YOU ON ANY VITAMINS TO AUGMENT YOUR TRAINING (YES) NO
IF YES: STATE WHAT MAGNESIUM - SLOW MAG

DO THESE SUPPLEMENTS IN YOUR OPINION HELP YOUR PERFORMANCE?
(YES) NO
IF YES: STATE HOW
PREVENTS CRAMPS ON COMRADES DAY.

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

IS YOUR RECOVERY QUICK? (YES) NO → GENERALLY QUICK. BUT IT VARIES FROM TIME TO TIME.
1, 2, 3, 4, 5 DAYS OR MORE

HOW DOES A COLD OR FLU AFFECT YOUR TRAINING?
DO YOU STOP TRAINING? YES: IF SO, FOR WHAT PERIOD
3, (5,) 8, 10 DAYS OR MORE
→ AT LEAST.

DO YOU OFTEN GET FLU LIKE SYMPTOMS A FEW DAYS AFTER A MARATHON? EG.
2 4 6 8 10 14 DAYS
NO.

OR

DO THOSE SYMPTOMS PRESENT WHEN YOUR TRAINING MILAGE INCREASES ?
YES
NO
ONLY WHEN I DO NOT SUPPLEMENT. WITH VITAMINS & BETA CAROTENE & GARLIC & PARSLEY.

5

[D] CURRENT AND PAST RUNNINNG PRACTICE

1. NUMBER OF YEARS RUNNING: 12

2. AVERAGE / WEEK AT PRESENT 80 kms

   WEEKLY MILAGE (IN SEASON) 80 - 100 kms

   WEEKLY MILAGE (OUT OF SEASON) 50 - 60 kms

3. LONGEST DISTANCE YOU HAVE EVER COVERED IN A SINGLE RUNNING EVENT: COMRADES.

4. PERSONAL BEST FOR

10 KM	43 MINS	DATE:	1981
21,1 KM	94 MINS	DATE:	1985
42,2 KM	3 HR 30	DATE:	1992
56 KM	4 HR 50	DATE:	1986
COMRADES	8 HR 46	DATE:	31/5/86
OR OTHER		DATE:	

5. HOW MANY DAYS PER WEEK DO YOU TRAIN AT PRESENT?
   5 - 6 DAYS PER WEEK.

6. AVERAGE FOR 3 MONTHS PRIOR TO COMRADES? MARCH: 332.

   APRIL: 326.

   MAY : 272.

7. TOTAL MILAGE JANUARY TO MAY ± 1260

[E] STRESS (NOTE: TRAINING FOR COMRADES IS ONE STRESS) 2

1. IN THE PAST 6 MONTHS WERE THERE ANY MAJOR CHANGES IN YOUR LIFE? EG.

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 2
DIVORCED / SEPERATED / MARRIAGE 2
TROUBLE WITH THE LAW
VICTIM OF VIOLENT CRIME
TAKING ON ADDITIONAL WORK OR STUDY LOAD
DOES YOUR JOB INVOLVE FREQUENT TRAVEL

ONLY TRAINING FOR COMRADES.

. DO YOU EAT BREAKFAST REGURLARLY?

YES - EVERYDAY.

. APPROXIMATELY NO OF HOURS YOU SLEEP: 8 Hours PER DAY.

. NUMBER OF PEOPLE IN THE HOUSE-HOLD : 3.

. DO YOU LIVE ALONE? YES / (NO)

. NO OF DAYS MISSED WORK/SCHOOL BECAUSE OF ILLNESS OR INJURY SINCE JANUARY 1993:

NIL.

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

A) INJURIES

B) CHANGE IN PERSONAL HEALTH

C) CHANGE IN HEALTH OF FAMILY.

A. RIGHT HAMSTRING SPASM - 7 DAYS BEFORE COMRADES.

B. SINUS ATTACK - LASTED TWO DAYS 2 WEEKS BEFORE COMRADES.

C. WIFE HAD A COLD - 3 WEEKS BEFORE COMRADES

WOULD YOU BE PREPARED TO UNDERGO A BLOOD TEST FOR BIOLOGICAL MARKERS IN THE DAYS FOLLOWING THE COMRADES MARATHON? YES/NO
(NOTE THIS IS NOT ESSENTIAL TO THE PROJECT)

WOULD YOU BE PREPARED TO TAKE PART IN FUTURE PROJECTS? YES/NO

PROJECT 93

EAR RUNNER,

ANY THANKS FOR TAKING PART IN "PROJECT 93".

ITLE: "ASCORBIC ACID AND BETACAROTENE IN THE PREVENTION OF POST RACE UPPER RESPIRATORY TRACT INFECTIONS"

NVESTIGATOR: DR. M.E. MOOLLA (SHORTY)

UPERVISOR: DR. L.M. WEIGHT (UCT)

NSTITUTION: (MCR/UCT BIOENERGETICS OF EXERCISE RESEARCH UNIT, DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF CAPE TOWN MEDICAL SCHOOL, OBSERVATORY.)

INDLY FILL IN THE ATTACHED QUESTIONNAIRE AS BEST AS YOU CAN. LEASE NOTE THAT ALL THE INFORMATION IS CONFIDENTIAL AND IS FOR HE SOLE USE OF "PROJECT 93".

)TE:

THE QUESTIONNAIRE MUST BE FILLED IN DETAIL BY BOTH THE RUNNER AND THE NON-RUNNING CONTROL.

THE RUNNER AND THE NON-RUNNING CONTROL MUST CONTINUE WITH THE SUPLEMENTATION (A,B,C,OR D) UP TO 2 WEEKS AFTER THE COMRADES MARATHON.

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).

AT THE END OF THE TRIAL (+ 15/06/93) HAND IN YOUR QUESTIONNAIRE TO JACKIE OR GEORGE AT THE SAVAGES OFFICE.

WHICH SUPPLEMENTATION ARE YOU ON: A B C (D) (PLEASE TICK).

Non-Runner

CONSENT FORM

I Anna-Mari E. Bischoff 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 ENDEMNIFY THE RESEARCHER, THE SPONSOR, UCT, OR SAVAGES ATHLETIC CLUB AGAINST ANY ILLNESS OR INJURY EXPERIENCED DURING THE COURSE OF THE PROJECT.

Signed by candidate

SIGNATURE

[A] DEMOGRAPHIC DETAILS

NAME: Anna-Marie Bischoff

DATE OF BIRTH; 13.2.1963 AGE AT COMRADES: 30 YRS.

MALE/FEMALE: Female

MARRIED: YES/NO Yes

OCCUPATION: Housewife

CHILDREN: NUMBER 1 OLDEST 4 YRS. / YOUNGEST ____ YRS.

HEIGHT: 1,65

WEIGHT: 86 kg

[B] HABITS

1. ALCOHAL USE: DO YOU DRINK? (YES)/NO
   IF YES - TYPE: Cinzano
   DAILY ____
   WEEKLY ____
   OCCASIONAL #
   NO OF YEARS DRINKING 10

2. TOBACCO USE: DO YOU SMOKE? YES/NO No
   NO OF CIGARRETS 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 ROSE, SORE THROAT, OR COUGH) 3 weeks before Comrades
   ALLERGY (ITCHY EYES OR STUFFY NOSE)
   HEADACHES so as result of cold
   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

" 5 _____ "

" 4 _____ "

" 3 _____ "

" 2 _____ "

" 1 _____ "

COMRADES MORNING 70 "

ONE WEEK AFTER 68 "

TWO WEEKS AFTER 68 "

RECORD YOUR SYMPTOMS (AS DISCUSSED IN C(1)) BELOW + AT BACK OF THIS PAGE IF NECESSARY.

3. ARE YOU AT PRESENT ON ANY MEDICATION? (YES)/NO
IF YES: STATE WHAT:
Tegretol - ~~450mg~~ 200mg in morning and evening.

Convulex - 450mg in morning and evening

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

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

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

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

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

. DO YOU OFTEN GET FLU LIKE SYMPTOMS A FEW DAYS AFTER A MARATHON? EG.
2 4 6 8 10 14 DAYS

OR

DO THOSE SYMPTOMS PRESENT WHEN YOUR TRAINING MILAGE INCREASES ?

Non-Runner

[D] CURRENT AND PAST RUNNINNG PRACTICE

1. NUMBER OF YEARS RUNNING:_____

2. AVERAGE / WEEK AT PRESENT_____

   WEEKLY MILAGE (IN SEASON)_____

   WEEKLY MILAGE (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 3 MONTHS PRIOR TO COMRADES? MARCH: _____

   APRIL: _____

   MAY : _____

7. TOTAL MILAGE JANUARY TO MAY ± _____

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

1. IN THE PAST 6 MONTHS WERE THERE ANY MAJOR CHANGES IN YOUR LIFE? EG.

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 / SEPERATED / MARRIAGE
TROUBLE WITH THE LAW
VICTIM OF VIOLENT CRIME
TAKING ON ADDITIONAL WORK OR STUDY LOAD
DOES YOUR JOB INVOLVE FREQUENT TRAVEL

. DO YOU EAT BREAKFAST REGURLARLY?

No

. APPROXIMATELY NO OF HOURS YOU SLEEP: 10 hours

. NUMBER OF PEOPLE IN THE HOUSE-HOLD : 3

. DO YOU LIVE ALONE? YES ~~NO~~

. NO OF DAYS MISSED WORK/SCHOOL BECAUSE OF ILLNESS OR INJURY SINCE JANUARY 1993: None

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

A) INJURIES

B) CHANGE IN PERSONAL HEALTH

C) CHANGE IN HEALTH OF FAMILY.

WOULD YOU BE PREPARED TO UNDERGO A BLOOD TEST FOR BIOLOGICAL MARKERS IN THE DAYS FOLLOWING THE COMRADES MARATHON? (YES)/NO
(NOTE THIS IS NOT ESSENTIAL TO THE PROJECT)

WOULD YOU BE PREPARED TO TAKE PART IN FUTURE PROJECTS? (YES)/NO

APPENDIX III

TABLE 1 : RUNNING, TRAINING AND LIFESTYLE DATA FOR RUNNERS SUPPLEMENTED WITH ASCORBIC ACID

N	URTI	TM	PBT	CFT	RE	FLU	ST	AL	TO	AGE	GE
1	1	1254	3.54	9.57	2.5	6.5	3	6	1	29	M
3	1	1124	3.45	8.88	9	5.25	1	3	1	29	M
5	2	1500	3.58	10.35	3	8.75	1.5	1	1	24	F
8	4	1600	2.8	7.12	10	8.75	1.5	6	1	35	M
15	2	1325	3.42	9.57	10	6.75	2.5	3	1	39	M
22	1	3100	2.72	6.37	5	5	2	6	1	26	F
25	1	1163	3.9	10.83	7	8.75	2.5	7	1	44	F
33	1	2200	2.73	7.15	4	5	2.5	2	1	31	M
35	1	1200	2.77	6.97	5	7.25	1	1	1	30	M
42	1	1250	3.75	10.67	5	3.75	4	2	1	39	F
43	2	950	3.42	9.97	18	8.75	2	6	2	47	M
45	1	1200	3.6	8.75	9	6.5	1	10	1	43	F
47	1	393	2.67	8.73	22	6.75	2	9	1	45	M

N : Number of the questionnaire filled in by the runner

URTI : Symptoms of URTI susceptibility rating

TM : Total mileage covered in training in the five months before race

PBT : Personal best marathon time

CFT : Comrades finishing time

RE : Running experience i.e. number of years competing

FLU : 'Flu history

ST : Stress experience

AL : Alcohol consumption

TO : Tobacco use

AGE : Age of runner

GE : Gender of runner

TABLE 2 : RUNNING, TRAINING AND LIFESTYLE DATA FOR RUNNERS SUPPLEMENTED WITH BETA-CAROTENE

N	URTI	TM	PBT	CFT	RE	FLU	ST	AL	TO	AGE	GE
2	1	1260	3.5	9.95	12	7.75	1	3	1	41	M
4	1	1209	3.85	10.07	5.5	5.67	6	6	1	48	M
6	1	1900	2.83	7.45	10	8.25	2	1	1	44	M
17	2	1700	3.25	7.85	13	4.5	1	3	1	31	F
20	2	2000	2.97	7.67	22	6.5	1	3	5	40	F
21	1	2940	2.78	6.87	3	8.75	1	1	1	28	M
32	2	1600	3.08	12	4	8	1.5	1	1	24	M
37	1	650	3.07	7.98	5	9.25	1.5	1	1	32	F
48	4	1400	3.23	10.08	14	6.5	2	6	1	46	M
55	2	1200	4.08	10.22	4	6.33	1.5	1	1	30	M
56	1	2100	2.83	7.65	18	6.75	2	9	4	38	M
59	1	1100	3.92	10.57	11	4	1.5	9	4	41	M

N : Number of the questionnaire filled in by the runner

URTI : Symptoms of URTI susceptibility rating

TM : Total mileage covered in training in the five months before race

PBT : Personal best marathon time

CFT : Comrades finishing time

RE : Running experience i.e. number of years competing

FLU : 'Flu history

ST : Stress experience

AL : Alcohol consumption

TO : Tobacco use

AGE : Age of runner

GE : Gender of runner

TABLE 3 : RUNNING, TRAINING AND LIFESTYLE DATA FOR RUNNERS SUPPLEMENTED WITH PLACEBO

N	URTI	TM	PBT	CFT	RE	FLU	ST	AL	TO	AGE	GE
7	4	1650	3.32	9.02	36	8.25	1.5	9	1	55	M
9	1	1400	3.67	10.63	7	6.75	1.5	1	1	31	M
10	4	950	4.3	10.88	4	9.25	2.5	6	1	26	M
11	1	2700	2.3	5.88	20	9	1	3	1	35	F
30	2	1300	4.33	12	4	7.5	1	9	1	44	M
36	1	900	3.18	8.72	4	4	1	1	1	33	M
40	4	1300	3.12	9.55	5	4	1	5	1	31	F
44	4	1760	2.82	7.25	9	7.75	4.5	2	1	33	M
57	4	1700	3.23	9.33	3.5	4.75	2.5	3	1	33	M
12	4	3100	2.6	6.78	15	7	1.5	5	1	33	F
16	1	1200	3.43	10.63	8	4.75	1.5	2	1	27	F
26	2	1600	2.57	6.97	18	9.75	1.5	1	1	41	M
27	1	4500	2.75	7.48	10	8.25	1.5	1	1	35	M
34	2	1500	2.4	6.65	12	6.25	2	3	1	33	F
39	2	1200	3.02	8.58	15	4	1	9	3	40	F
46	2	1400	3.02	9.58	9	5.25	1	1	1	36	F
49	1	1200	3.27	9.35	25	7.5	2.5	2	1	43	M
58	4	1900	3.33	8.38	15	5	1	9	2	38	M
60	4	1300	3.42	10.83	14	4.5	2.5	6	1	34	M

N : Number of the questionnaire filled in by the runner
URTI : Symptoms of URTI susceptibility rating
TM : Total mileage covered in training in the five months before the race
PBT : Personal best marathon time
CFT : Comrades finishing time
RE : Running experience
FLU : 'Flu history
ST : Stress experience
AL : Alcohol consumption
TO : Tobacco use
AGE : Age of runner
GE : Gender of runner

TABLE 4 : LIFESTYLE DATA FOR CONTROLS SUPPLEMENTED WITH ASCORBIC ACID

N	URTI	FLU	ST	AL	TO	AGE	GE
1	2	8	2	2	1	29	M
3	2	6	1	1	1	29	M
5	1	8	1	1	1	24	F
8	2	6	1	2	1	35	M
22	2	8	1	3	2	26	F
25	1	6	1.5	3	8	44	F
33	3	6	1	2	5	31	M
42	1	6	2	2	6	39	F
43	1	8	2	1	2	47	M
45	1	9	1	1	1	43	F
47	1	4	0	4	1	45	M

N : Number of questionnaire filled in by the control

URTI : URTI susceptibility rating

FLU : 'Flu history rating

ST : Stress experience rating

AL : Alcohol consumption rating

TO : Tobacco use rating

AGE : Age of control

GE : Gender of control

TABLE 5 : LIFESTYLE DATA FOR CONTROLS SUPPLEMENTED WITH BETA-CAROTENE

N	URTI	FLU	ST	AL	TO	AGE	GE
2	3	7	1	3	1	41	M
4	1	4	0	5	1	48	M
6	1	9	0	1	1	44	M
17	1	6	1	1	2	31	F
20	2	6	2	2	1	40	F
21	1	6	2	1	1	28	M
37	2	9	2	1	1	32	F
48	3	6	1	3	4	46	M
55	1	4	0	1	1	30	M
56	2	6	1	1	3	38	M
59	1	6	1	4	1	41	M

N : Number of the questionnaire filled in by the control

URTI : URTI susceptibility rating

FLU : 'Flu history rating

ST : Stress experience rating

AL : Alcohol consumption rating

TO : Tobacco use rating

AGE : Age of control

GE : Gender of control

TABLE 6 : LIFESTYLE DATA FOR CONTROLS SUPPLEMENTED WITH PLACEBO

N	URTI	FLU	ST	AL	TO	AGE	GEN
7	4	8	1	3	4	55	M
9	1	4	1	3	1	31	M
10	2	3	2	1	2	26	M
11	1	9	4	2	1	35	F
12	4	4	1	2	1	33	F
16	4	4	1	1	1	27	F
26	1	9	0	1	1	41	M
27	2	8	0	1	1	35	M
28	2	4	3	1	1	36	F
30	2	4	2	1	1	44	M
34	2	7	1	1	1	36	F
36	1	8	3	1	1	33	M
39	2	8	1	1	1	40	F
40	1	5	1	6	1	31	F
44	4	8	2	1	1	33	M
46	2	4	2	2	1	36	F
49	1	9	1	1	2	43	M
57	1	4	4	2	1	33	M
58	2	4	1	4	1	38	M

N : Number of the questionnaire filled in by the control

URTI : URTI susceptibility

FLU : 'Flu history rating

ST : Stress experience rating

AL : Alcohol consumption rating

TO : Tobacco consumption rating

AGE : Age of control

GE : Gender of control