Clinical and immunological factors associated with post-race Upper Respiratory Tract Symptoms (URTS) in Ironman triathletes

A dissertation prepared by Peter Baxter (BXTPET002)
in partial fulfilment of the requirements for the Master of Philosophy degree in Sports Medicine (MPhil Sports Medicine) from the University of Cape Town

September 2007

List of Figures

Abbreviations

AT	Anaerobic threshold
Cl^-	Chloride
CMI	Cell-mediated Immunity
EAC	Exercise-Associated Collapse
EAMC	Exercise-Associated Muscle Cramps
GIT	Gastrointestinal tract
HPA	Hypothalamic-Pituitary-Adrenocortico
Ig	Immunoglobulin
IL	Interleuken
K^+	Potassium
LRTS	Lower Respiratory Tract Symptoms
Na^+	Sodium
°C	Degrees Celsius
RTS	Respiratory Tract Symptoms
SAM	Sympatho-Adreno-Medullary system
SS	Systemic symptoms
URTI	Upper Respiratory Tract Infection
URTS	Upper Respiratory Tract Symptoms

Abstract

Background: Ultra-endurance events, in particular Ironman Triathlons, are physically very demanding for the competitors. There is a large body of evidence showing that Upper Respiratory Tract Symptoms (URTS) are very common in athletes in the 2-week period after such an event. However, there is no definitive explanation as to the exact cause or mechanism for the development of post-race URTS.

Objective: The aims of this study were: (1) to determine the incidence of post-race URTS in triathletes competing in an Ironman Triathlon; (2) to identify clinical and immunological factors that are associated with the development of post-race URTS in these triathletes.

Methods: In this prospective cohort study, 99 triathletes entering the 2006 South African Ironman Triathlon were recruited as subjects. All the subjects completed a validated questionnaire in the one to three days before the race (during registration). The questionnaire contained sections on demographics, training history and previous performances, common general medical conditions that they may have experienced, and a detailed section pertaining to respiratory tract symptoms (RTS) and allergies. At registration, each subject had a blood sample taken for analysis of cytokines representing mainly a TH1 response (IL-2, and IL-12) (cell mediated immunity) and a TH2 response (IL-4, IL-6, IL-10) (humoral immunity), as well as a saliva sample (for salivary α-amylase, cortisol and IgA concentrations). Collection of blood and saliva samples was repeated immediately post-race. Data regarding race performance was collected within one week after completion of the race.

Subjects who completed the race (n=85) were then followed over a 14 day period after the race, and those who developed URTS (symptomatic group=12) were re-assessed. The remaining subjects were asymptomatic and acted as a Control group (n=73). Upon presentation with URTS, symptomatic subjects as well as a smaller matched control sub-group (n=11) were examined clinically and blood and saliva samples were repeated at the time of the post-race consultation.

Results: The main findings of the study were that the incidence of post-race URTS in this cohort of triathletes was 7%, and that factors associated with the development of these post-race URTS were (1) pre-race URTS in the 6- and 1-week periods prior to the race; (2) a higher pre-race salivary α-amylase concentration; and (3) a greater change in salivary α-amylase concentration from pre- to post-race and consultation. Other findings were that triathletes who developed post-race URTS tended to be a lower calibre of triathlete and that their actual race time was slower relative to their pre-race predicted time. In triathletes who developed post-race URTS, there was no evidence of up-regulation of TH2 or down-regulation of TH1 responses.

Conclusion: A recent history of URTS (pre-race) and a high pre-race salivary α-amylase concentration appears to predispose triathletes to the development of post-race URTS. There is no association between the development of post-race URTS and changes in TH1 or TH2 responses, nor changes in salivary IgA concentrations in these athletes.

Keywords: respiratory tract symptoms, upper respiratory tract infections, triathletes, salivary α-amylase , salivary IgA , TH1, TH2 responses, allergies

Chapter 1

Introduction and scope of the thesis

The South African Ironman Triathlon, which was held in March 2006 in Port Elizabeth, South Africa, is an ultra-endurance triathlon which has steadily grown in popularity, with 1136 triathletes registering to participate in 2006. The event comprises a 3.8km surf swim (2 laps of 1.9km each), 180km cycle (3 laps of 60km each), and finally a 42.2km run (3 laps of 14km each) which all have to be completed within the cut-off time of 17 hours.

This event places significant physical and mental stress on the triathlete and thus, there is the potential that medical complications may occur before, during, or after the event. These may range from injuries to various medical conditions. Some of the more common medical conditions which occur in Ironman triathletes are the development of Exercise-Associated Muscle Cramps (EAMC), Exercise-Associated Collapse (EAC), and abnormalities of hydration serum electrolytes (notably dysnatraemias) during and after the race.

It is particularly the development of upper respiratory tract symptoms (URTS) in endurance athletes in the 14 days after such an event that has captured the interest of many researchers working in this field. Whilst much research has been done in this area in an attempt to understand this common problem, the

underlying pathophysiology of this condition remains unclear. It is thought that the development of these upper respiratory tract symptoms might be due to immune suppression leading to infection, or to allergy. Of particular interest is the hypothesis that an endurance event, such as the Ironman Triathlon, may alter the T helper 1 and T helper 2 response. Salivary IgA and other salivary markers of the response to stress may also play a role in the pathophysiology of post-race URTS. However, these parameters have not been investigated as factors associated with post-race URTS in endurance athletes. There is a substantial body of scientific literature on which these hypotheses are based, and this body evidence will be reviewed in Chapter 2 of this dissertation.

In Chapter 3 the details of an original investigation designed to identify factors that are associated with the development of post-race URTS in Ironman triathletes will be presented. The main findings and practical clinical applications of these findings will be summarised in Chapter 4 of this dissertation.

Chapter 2

Post-race Respiratory Tract Symptoms (RTS) in Ironman triathletes: A review

2.1. Introduction

It has been well established that regular participation in physical exercise is an important component of a healthy lifestyle. Indeed, participation in regular physical activity is beneficial in the management and control of risk factors that are associated with poor health [1-3], including high blood pressure [4;5], increased body weight [6], impaired glucose tolerance [7] and elevated blood cholesterol concentrations [2]. As a result, there is an increasing trend for greater participation of all members of the population in recreational and competitive sporting activities.

Whilst there are many different forms of exercise in which people participate, endurance exercise has become increasingly popular. In South Africa, this is particularly evident as numbers of participants in ultra-endurance events including ultra marathons, cycling events, and triathlons (Ironman) are increasing. The Ironman ultra-triathlon is a particularly strenuous event that comprises a 3.8km surf swim, followed by a 180km cycle, and is completed by a 42,2km run. The participation in the Ironman ultra-triathlon in South Africa has increased from 500 participants in 2001 to 1500 participants in 2007.

This event places extreme physical and mental stress on the triathlete, and therefore there is the potential for medical complications occurring before, during, or after the event [8-13]. The prevalence of pre-race medical conditions is an area that has not been thoroughly studied in the endurance athlete, and, as such, has not been extensively reported [9;12;14]. Some of the more common medical complaints in Ironman triathletes are the development of Exercise-Associated Muscle Cramps (EAMC), Exercise-Associated Collapse (EAC)[15], abnormalities of hydration status and serum electrolyte concentrations (notably dysnatraemias) during and after the race [9;10;12;13;16;17] and respiratory tract symptoms (RTS) [8]. At present, it is well recognised that an athlete presenting with RTS may have symptoms that are localised to the upper airways ('blocked nose', 'runny nose', sore throat, swollen glands) or symptoms localised to the lower airways (cough, wheeze, chest pain) [18].

In previous research conducted at the UCT/MRC Research Unit for Exercise and Sports Medicine of the University of Cape Town, it was noted that 49,2% of Ironman triathletes developed respiratory tract symptoms before or after the race [8]. Post-race respiratory tract symptoms have also been documented in a number of other ultra endurance events [14;19;20]. It is evident that the precise mechanism(s) responsible for the development of post race symptoms has not been well documented. The principle hypothesis for the development of post-race URTS is infection [18;19;21] as a result of immunosuppression [22-24], but this hypothesis has not yet been proven [25]. This hypothesis and other possible hypotheses will be reviewed in Section 2.3.4. The focus of this dissertation

and this review will be on factors that may be associated with the development of URTS in the post-event period. In this review, the particular focus is on the development of upper respiratory tract symptoms in endurance athletes with specific reference to ultra-triathletes.

2.2. Respiratory tract symptoms (RTS) in endurance athletes, with specific reference to triathletes

There is a general perception amongst athletes, trainers and sports physicians that athletes are susceptible to infectious illnesses during intensive training and major competition [26;27]. Indeed, upper respiratory tract symptoms (URTS) are the most common group of medical symptoms affecting elite athletes [28]. More specifically, endurance athletes have been shown to have an increased incidence of URTS [29]. As this is an extremely common condition, it is important to have an understanding of the causes of these URTS. Therefore the various hypotheses resulting in URTS will be discussed in the next section.

2.2.1. Terminology and definitions

The terminology used to describe respiratory tract symptoms is extensive, yet inconsistent. Athletes can describe a variety of symptoms when presenting with respiratory tract illness. These symptoms can include a 'blocked' nose, 'runny nose', sore throat, swollen glands (upper respiratory tract), or cough, wheeze and chest pain (lower respiratory tract). Furthermore, the athlete may

present with additional systemic symptoms including fever, headache, muscle aches, joint pains and general fatigue. In the past, the terminology 'flu-like' illness has been used to describe the syndrome of both local and systemic symptoms [25].

In a number of studies where respiratory tract symptoms in athletes have been documented, the symptoms have been self-reported and without objective evidence that the symptoms were associated with an actual infection [25]. Thus the use of the term Upper Respiratory Tract Infections (URTI), as has been used in many reports, is incorrect. Indeed, there is some evidence that these post-race upper respiratory symptoms are, in fact, not due to infection [30].

The clinical significance of the above finding is that different medical advice and return-to-play recommendations could be given to an athlete presenting with RTS localised to the upper airways (nose and orophraynx), compared to an athlete presenting with RTS below the level of the orophraynx (cough, wheeze, chest pain). This clinical advice may also change further when the athlete has accompanying systemic symptoms, including fever, muscle aches, joint pains and general fatigue [18]. Therefore terminology that takes these clinical implications into account is required, and thus the use of the terms Upper Respiratory Tract Symptoms (URTS) ('blocked' nose, 'runny nose', sore throat, swollen glands), Lower Respiratory Tract Symptoms (LRTS) (cough, wheeze, chest pain) and systemic symptoms (SS) (fever, muscle

aches, joint pains, general fatigue) to describe these clinical presentations is therefore more appropriate.

For the purposes of this dissertation, the following terminology will be used:

- **Upper Respiratory Tract Symptoms (URTS)** will refer to the presence of respiratory symptoms that are localised to the nose and pharynx ('blocked' nose, 'runny nose', sore throat),
- **Lower respiratory Tract Symptoms (LRTS)** will refer to the presence of respiratory symptoms below the level of the pharynx (cough, wheeze, chest pain),
- **Respiratory Tract Symptoms (RTS)** will refer to the presence of any respiratory symptoms involving either upper or lower respiratory tract,
- **Systemic symptoms (SS)** will refer to symptoms associated with infection including fever, muscle aches, joint pain and generalised fatigue.

It is important to note that RTS in athletes could also be due to many other cardiorespiratory conditions. For example, asthma is a common respiratory condition in athletes that could give rise to RTS. However, for the purpose of this dissertation, the discussions regarding RTS will be those related to infections, and the main focus of the thesis will be on URTS. Furthermore, it is well recognised that the systemic symptoms (SS) that are listed above can also occur as a result of many other infections (not only those affecting the respiratory tract) and other systemic conditions.

2.2.2. Epidemiology of RTS in endurance athletes

The incidence of RTS in the general (non-athletic) population is high. Indeed, respiratory tract illness which causes RTS is the most common of all acute illness in humans responsible for some 75-80% of all acute presentations. The majority of RTS originate from the upper respiratory tract [31].

For endurance athletes this pattern is no different. Symptoms of upper respiratory tract illness is also the leading cause of acute illness (during training) in endurance athletes from various sports [31], including runners [14;19;32-34], rowers[35], swimmers[36;37] and cross country skiers[38]. Therefore, the incidence of symptoms of URT illness is high in both the general population, and in endurance athletes.

A number of studies have been conducted to investigate the pattern of URTS in endurance athletes. Some of the important findings of these studies can be summarized as follows:

- The incidence of URTS is twice as high in ultra-distance athletes compared with sedentary controls in the 2-week post-race period [14],
- In general, faster athletes are more susceptible to post-race URTS than slower athletes [14;19;39],
- Increased intensity and duration of training, especially high mileage, is associated with a higher risk of the development of URTS [32;40;41],

- A number of other factors appear to be associated with an increased risk of developing URTS in endurance athletes. These include perceived increased stress, sleep deprivation [41], poor nutritional knowledge and diet [41], decreased Vitamin C intake [19], and decreased carbohydrate ingestion during exercise [42].

The relationship between differing intensities of exercise and the development of URTS has also been widely researched. In general, it has been shown that moderate-intensity exercise is associated with a reduced risk of URTS [43-47], whilst both inactivity [48] and high-intensity, prolonged exercise [32;40;41;49] have been associated with increased risk of URTS. However, these findings have not been confirmed in all studies [50;51].

2.2.3. Aetiology and pathophysiology of RTS in endurance athletes

The precise aetiology of RTS in endurance athletes in not well understood. The most common hypothesis for the development of URTS in endurance athletes is that the symptoms result from a respiratory tract infection due to "immune suppression" (infective hypothesis). This hypothesis is based on the observation that immune function is suppressed during the so-called "open window" period in the 3-72 hour post intense and prolonged exercise period [52-57]. Other contributing factors that have been suggested as factors that will increase the risk of post-race URTS are deficiencies of carbohydrate intake[58] and vitamin C[33;34;59-61] which may contribute to the immune suppression during this period.

More recently, other hypotheses for the development of RTS have been proposed. These hypotheses include the roles of allergy and physical or chemical irritants that may cause RTS. Evidence in support for each of these hypotheses these will now be briefly reviewed.

2.2.3.1. Evidence for the "infective hypothesis" for URTS in athletes

There is substantial evidence to suggest that changes in immune function follow acute exercise [25;53;56;62-66]. Although most researchers have suggested that there is a relationship between these immune changes and the development of URTS, to date a direct causal relationship between the changes in immune parameters and the development of URTS remains tenuous. It is important to note that no consistent relationship has been documented between specific changes in immune markers and acute exercise [62;65] despite the fact that this has been examined extensively [36;67-73].

Nutritional supplementation, as a means to enhance the immune system and thereby reduce the risk of developing URTS, has also been extensively studied but to date, no single supplement has been consistently shown to prevent URTS in athletes [33;42;74-76]. It is of interest to note that very few studies have yielded positive results. Peters et al. [19], in a study focusing on competitive ultra-marathoners, found that those athletes who supplemented with Vitamin C had a 33% incidence of post-race URTS, whereas the placebo group had an incidence of 60%. He concluded that Vitamin C supplementation

reduces the incidence of post-race URTS in athletes. Carbohydrate supplementation has been shown to reduce immune suppression during acute exercise [42;77]. The role of nutritional strategies to counter stress to the immune system after intense exercise has been studied. These studies show that the suppression in function in both the innate and acquired immune systems can to some extent be attenuated by carbohydrate supplementation during exercise. In particular, carbohydrate supplementation resulted in the attenuation of the increase in blood neutrophil counts, stress hormones and inflammatory cytokine response, indicating that carbohydrate supplementation was a partial countermeasure[77]. This finding is supported by findings from previous work in which it was suggested that carbohydrate supplementation results in diminished physiologic stress and inflammation [42].

In summary, many studies have been conducted to examine the relationship between URTS and changes in immune function following exercise; yet no strong causal relationship between these two factors has been shown to exist in athletes. Furthermore, there is no definitive evidence by means of bacterial or viral culture to substantiate the hypothesis of an infective cause for URTS[28].

2.2.3.2. Evidence for the "allergic" hypothesis for URTS in athletes

The second hypothesis for the development of URTS in athletes is that of allergy. Allergies are very common worldwide, and the prevalence is increasing in the general population [78;79]. Allergic conditions that may affect

the respiratory tract of athletes include allergic rhinitis, allergic rhinoconjunctivitis, allergic sinusitis and allergic asthma [79-82]. It appears that the prevalence of both allergic rhinitis and asthma in athletes is increasing [78-80].

As the clinical presentation of allergy in the respiratory tract may be very similar to that of an infection in the URT (blocked or runny nose, post nasal drip, headache, malaise and fatigue), it could be hypothesised that URTS in athletes may be, in fact, due to allergy rather than infection.

The prevalence of allergic conditions appears to be related to the sports type. It has been shown that aquatic athletes (swimmers, divers and rowers) have a higher incidence of atopy compared to non-aquatic athletes, with equestrian athletes having a low prevalence [82]. In two studies[45;83], the prevalence of atopy, in particular allergic rhinitis, was reported to be higher in endurance athletes than in other subgroups of athletes.

Allergy must therefore be considered as a plausible causative mechanism of URTS in endurance athletes due to (1) the high incidence of atopy in endurance athletes, which appears to involve predominantly the URT, and (2) the observed changes in the immune system in response to intense exercise which could have an affect on atopic predisposition in these athletes. In a recently completed study among Ironman triathletes[8], it was documented that pre-race URTS in triathletes is associated with a history of allergies.

In summary, there is currently no strong evidence for a direct causal relationship to support either the infective or the allergic hypotheses for the development of RTS in athletes. It is therefore important to consider other non-allergic/non-infective hypotheses for the development of these symptoms.

2.2.3.3. Other hypotheses for URTS in athletes

Another possible cause of URTS in athletes is the irritation of the respiratory tract mucosa by physical factors and/or irritants. During exercise, a high ventilation rate (>30l/min) especially in the presence of cold, dry air, has the tendency to cause mouth-breathing. Mouth-breathing can, in turn, result in an increased exposure to inhaled irritants (physical or chemical) and allergens[83]. Some of these physical irritants that can have an impact on health are sulphur dioxide, photochemical smog (ozone and nitrous oxide), and airborne particulates [84]. Furthermore, the inhalation of cold dry air can result in an inflammatory process in the URT [85;86]. The relationship between this inflammatory response and the development of URTS requires further investigation.

2.2.3.4. Summary: Hypotheses for URTS in athletes

The precise aetiology and pathogenesis of URTS in endurance athletes during training and post-event, is unclear. The traditional view has been that strenuous prolonged exercise causes changes in the immune system that predispose athletes to infections, despite the fact that evidence for these

infections have never been demonstrated through culture or by serology. Thus, there is no clear cause-effect relationship between the change in immune functioning and subsequent infection.

It has also been noted that there is an increasing incidence in the general population of atopic illnesses, and that allergies are particularly common in endurance athletes. Furthermore, symptoms of URT allergy and infections are very similar, and URTS seen in these athletes may in fact be due to allergy. Finally, other factors, such as physical and chemical irritants, may also be a cause for URTS in endurance athletes, and this hypothesis warrants further investigation.

2.2.4. Clinical implications of URTS on the triathlete

In general, the effect of URTS on training and exercise performance has not been well investigated. The main reason for this is probably that the aetiology of URTS in athletes has not been well established. The effects of both infective and allergic conditions of the respiratory tract on training and exercise performance will now be briefly discussed.

2.2.4.1. The effects of URTS in athletes on training and performance

The effect of URTS on training and exercise performance has not been well investigated and as such, is not well understood. However, there is anecdotal evidence to suggest that athletes who have recovered from URTS due to

infections often complain of a residual decrease in performance. Although this may be due to the effects of a period of detraining during the recovery period, there is a possibility that there may be residual negative effects resulting from the infection itself. This has never been investigated well in a scientific study. In one pilot study, athletes were followed during recovery from an URT infection and later during an equivalent period of detraining [87]. The results of this study showed that there is a measurable decrease in exercise performance (treadmill running time) which lasts for 2-4 days after full clinical recovery from an URTI when compared with detraining alone. The practical suggestion resulting from this study is that athletes may experience a decline in performance for a few days following full clinical recovery from an URT infection. However, this is an area that requires further scientific study.

The most important clinical consideration in athletes who present with URT infection, and who wish to continue training, is the risk of sudden death as a result of myocarditis. It is known that some of the infective agents which cause URTS due to infection can cause more severe pathology, including myocarditis [31;88-90], which, in turn, can result in sudden death during exercise [89;90]. Currently accepted guidelines with respect to URTS and exercise suggest that athletes with URTS in the presence of any possible symptoms of systemic illness (fever, myalgia, arthralgia), including clinical features suggestive of myocarditis (chest pain, dyspnoea, resting tachycardia), should not participate in any physical exercise until they are asymptomatic, in order to minimise the risk of sudden cardiac death [31].

2.2.4.2. The effects of allergy on training and performance in athletes

The potential negative effects of chronic allergy on exercise performance have not been well studied. There are, however, anecdotal reports, that Olympic athletes with severe exacerbations of atopic illnesses have sub-optimal exercise performances [91] .These observations have not, however, been confirmed by well-conducted scientific studies.

In the non-athletic population, allergic rhinitis has been associated with an altered sleep pattern, probably due to nasal obstruction, rhinorrhoea and increased sinus pressure [92]. Sleep deprivation can result in chronic tiredness and subsequently, athletes may have sub-optimal exercise performance [83]. Athletes with allergic rhinitis have been shown to have depressed reaction time, attention span and vigilance when participating in cognitive processing tests after having been exposed to pollens [78], and this may, in turn, have a negative impact on performance.

2.2.4.3. Summary: RTS and exercise performance

The potential negative effects of respiratory tract infections or allergy on exercise performance has not been well studied. However, anecdotal reports and data from pilot studies indicate that both respiratory tract infections and allergies can, indeed, have a negative effect on athletic performance.

2.3. Immune function in endurance athletes

2.3.1. Introduction to immune function

The understanding of the immune system and its functioning is essential before the changes that occur in response to exercise can be considered. However, a detailed discussion of the immune system is beyond the scope of this review and therefore a brief overview of the immune system follows.

Immunity can be defined as the body's ability to resist almost all types of organisms or toxins which may cause damage to the tissues and organs of the body [93]. The immune system has a number of components. The first component is innate immunity, otherwise known as the non-specific or natural component of the immune system. The innate immune system includes the macrophages, natural killer cells, polymorphonuclear cells and the T cytotoxic cells [94;95]. These cells "attack" any foreign material after the rapid recognition of their molecular patterns [96]. The innate system is also involved in the subsequent activation of the acquired system and as such provides the first line of defence before the more specific system is activated [95].

The second component of the immune system is the acquired component. Acquired immunity refers to the specific component of the immune system which provides a more targeted anti-microbial response through both cellular and humoral responses, thus providing powerful specific immunity. T and B lymphocytes are included in this system, with the T lymphocytes being closely

associated with cell-mediated immunity (CMI), and the B lymphocytes with humoral immunity. The major function of the CMI is the destruction of intracellular pathogens, while the humoral response produces antibodies to antigens [97]

A third, and very important component, of the immune system are the cytokines. Cytokines, which are soluble glycoproteins [98], can be considered as "emergency communication and signalling" molecules that are produced by a variety of immune cells, including macrophages, lymphocytes, as well as other cells, such as fibroblasts and endothelial cells. Cytokines are not produced and then stored, but rather are synthesised in response to a challenge to the immune and inflammatory systems [99].

Cytokines fulfil a number of functions which may be broadly defined as pro- or anti-inflammatory, and are important in the coordination of the body's immune/inflammatory response [53;98]. To date, more than 100 cytokines have been identified [93]. A detailed discussion of each of these cytokines is beyond the scope of this review. However, where appropriate for the purposes of this research study (described in Chapter 3), specific cytokines and their functions will be discussed.

In summary, the immune system is important in maintaining the body's internal homeostasis. It comprises an innate or non-specific system and an acquired or specific system, which is mediated by T and B lymphocytes producing CMI and humoral immunity respectively. A third and important part

of this system is the cytokines or "messengers" which can activate or inhibit the body's inflammatory responses.

2.3.2. Immune function – TH1 and TH2 responses

There are the two types of acquired immune responses – the humoral response and the CMI response. CMI is mediated through the T lymphocyte series of cells, most notably the T-helper (TH) cells [97]. Recently, it has been shown that the TH cells can be divided into two subsets of cells, the TH1 and TH2 lymphocytes, each with different functions [100-102]. In general, TH1 cells have been associated with CMI, while TH2 cells have been associated with humoral immunity, and also function in the body's normal response to trauma or infection [94;95;100;103] (Figure 2.1.).

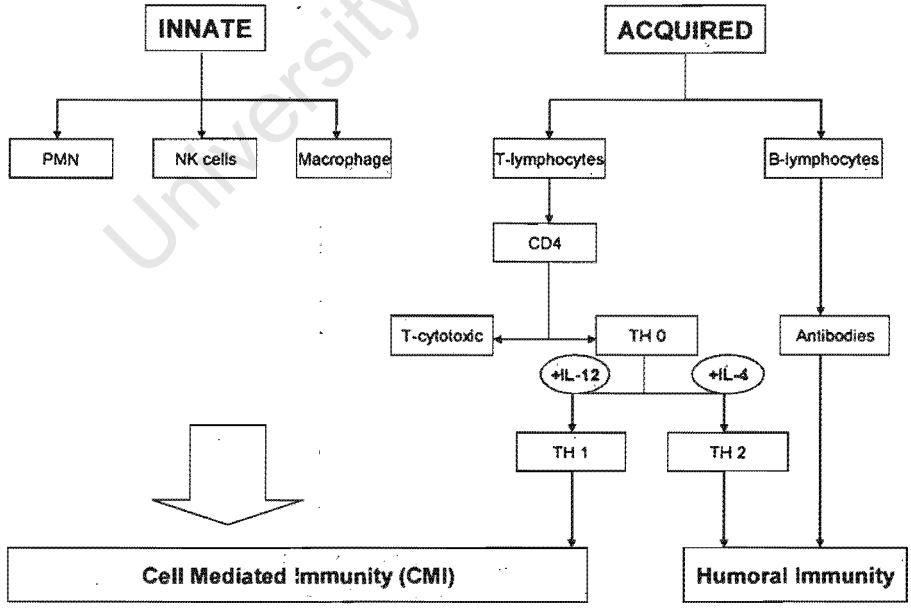

Figure 2.1.: Innate and acquired immune systems (Adapted from [53]).

The development of these subsets of T cells is from an intermediate group of cells known as the TH0 lymphocytes. TH0 lymphocytes develop from naïve CD4+ T cells, which then differentiate into TH1 or TH2 cells depending on the type of stimulus. Stimuli can include severity of injury, concentration of antibody, and the type of cytokine response [97;104]. It has also been suggested that there may be "switching" from TH1 to TH2, but not from TH2 back to TH1 - the reason for which is not well understood [100].

A predominantly TH1 lymphocyte response would favour the phagocytic-dependent CMI, while decreased activation of the TH1 response would render the body more susceptible to infection. Failure of the activation of TH1 has also been associated with multiple organ death following secondary infections [105]. Furthermore, it has been shown that a sustained up-regulation of TH1 cells is associated with some auto-immune illnesses [104].

A predominantly TH2 lymphocyte response is more closely related to B lymphocyte function. A TH2 response would therefore favour humoral immunity, and is non-phagocytic-dependent. A further function of the TH2 response is to down-regulate the TH1 response, which, if excessive, may result in decreased protection for the body [100], and therefore greater susceptibility to infection.

The role of cytokines in the TH1 and TH2 responses is that the differentiation of TH0 to either TH1 or TH2 is affected by the action of various cytokines. Interleukins (IL) are cytokines that can affect the TH1 and TH2 responses.

The change from TH0 to TH1 is largely under the influence of IL-12 (which is essential), IL-2 and IFNgamma. The change from TH0 to TH2 is influenced by IL-6, IL-10 and IL-4. Furthermore, IL-12 is also involved in the inhibition of the TH2 response, while IL-4 and IL-10 are inhibitors of the TH1 response [94;100;103;105].

In summary, TH1 and TH2 cells differentiate from THO cells and this process is under the influence of various cytokines (interleukins). The differentiation from TH0 results in predominance of either TH1 or TH2 subset of T cells, and the result of this process is an up-regulation of CMI or humoral immunity respectively.

2.3.3. Immune function: The effects of exercise on changes in the TH1 and TH2 response

In recent years, there has been considerable interest in the effects of exercise on immune function. A detailed review of these responses is beyond the scope of this dissertation. However, of particular importance to this dissertation is the role of exercise on the functioning of the immune system as it relates to the TH1 or TH2 response.

More specifically, this research is focused on whether post-exercise URTS in athletes are related to a predominantly TH1 or a TH2 response.

Participation in ultra-endurance exercise results in tissue trauma, with a subsequent inflammatory response. Part of this inflammatory response is the production of cytokines, which are communication or signalling molecules for the immune system. As previously mentioned, cytokines fulfil an important function, namely, to protect the body from infections, toxins, and damage. The effect of these cytokines (IL-4, IL-10), which are produced by the innate immune system [106], is to favour the up-regulation of the TH2 subset of T cells from THO cells. This up-regulation is enhanced by the exercise-induced increase in circulating cortisol, catecholamines, and prostaglandin E2, all of which have the effect of further up-regulating the TH2 response. In response to exercise, the TH1/TH2 balance is further shifted in favour of TH2 by the down-regulation of TH1 by TH2. As a result, the increased TH2 response, and the decreased TH1 response effectively results in a depression of CMI and this may theoretically increase susceptibility to infection [100].

The cytokine response to a marathon has previously been described [53]. In this study, blood samples were taken before and 1.5hrs after a marathon from 50 volunteers, and the cytokine responses were analysed. The overall post-marathon cytokine pattern was suggestive of a TH2 response, with a significant increase in IL-10, and a lack of elevation of IL-12 (markers of TH2 and TH1 respectively, as described earlier). Interestingly, in the 2 weeks after the marathon, only 7 of these athletes developed any URTS according to a self-reported daily log. However, it is not known whether the cytokine parameters in the symptomatic athletes continued to show a TH2 response pattern in the 2-week post-race period [53].

In summary, there are very few studies in which the effects of exercise on the TH1 and TH2 responses have been documented, or how these may be associated with the development of URTS. It appears that strenuous exercise may result in a switching to a predominantly TH2 or humoral response, thereby increasing the susceptibility to infection post race. This hypothesis does require further investigation. It is possible to determine if up-regulation of the TH2 response occurs, by measuring cytokine markers for each of the responses, namely IL-2, IL-12 and IFN gamma as markers for the TH1 response, and IL-4, IL-6, and IL-10 as markers for the TH2 response. However, the specific effects of the intensity, duration and frequency of exercise bouts on these markers require further investigation.

2.4. The role of salivary glands in post-exercise RTS

Salivary glands are tubulo-alveolar structures that contain fluid-generating acini and have a branching system of ducts. Salivary glands produce saliva, which is translocated to the oral cavity, usually in response to neural stimulation [93]. The composition of saliva is mainly water (99%) [107], but it also contains electrolytes (Na^+, K^+, Cl^-), hormones (testosterone, cortisol), organic materials (maltase, albumin, lactate, vitamin C), gases, and immunoglobulins (IgA, IgM, IgG) [107]. The function of the salivary glands is under the control of the autonomic nervous system [108], and catecholamines may be involved in the control of salivary electrolytes and protein [109]. Parasympathetic stimulation results in the production and secretion of copious amounts of saliva that is

high in fluid and low in organic and inorganic substances [108;110]. Sympathetic stimulation, on the other hand, results in a lower volume of saliva which is high in organic substances, notably the protein alpha-amylase [108;111;112].

Salivary IgA, (as a marker of mucosal protection), cortisol (as a marker of the hypothalamic-pituitary-adrenocortical (HPA) axis), and alpha-amylase (as a marker of the sympatho-adrenomedullary system) (SAM) have been used in research studies to investigate changes in these systems in response to exercise. These markers can be used to study responses to exercise and will therefore now be reviewed.

2.4.1. Changes in salivary IgA in response to exercise

Salivary IgA has an important function and is one the body's first lines of defence against potentially pathogenic viruses [113;114] related to URT infections. Salivary IgA has the capacity to inhibit the colonisation of pathogens [115], bind antigens for transport across the epithelial barrier, and neutralise viruses [116;117].

It has been shown that an acute exercise bout, as well as regular exercise training, can affect the salivary concentrations of IgA. Exercise variables that appear to alter the response to salivary IgA concentrations include exercise intensity, intermittent versus continuous exercise, and exercise duration. It has been shown that intense exercise [118] results in a decrease in salivary IgA concentrations for up to 60 minutes after the cessation of the exercise bout,

after which the concentrations return to normal [118;119]. As salivary IgA is important in mucosal protection, the decrease in salivary IgA concentration has been implicated in the development of URTS in athletes [27;29;118;120]. It has been noted that intense training over many years may in fact result in chronic suppression of salivary immunoglobulin levels [118]. On the other hand, moderate-intensity exercise training [training protocols within the guidelines recommended by the American College of Sports Medicine(ACSM)] does not appear to alter salivary IgA concentrations [44;121;122]. This finding supports the hypothesis that intense exercise increases [120;123] and moderate exercise decreases the athlete's susceptibility to illness [118].

It has also been documented that intermittent exercise protocols do not suppress salivary IgA concentrations but continuous exercise protocols performed at the same overall work rate in fact decrease salivary IgA concentrations [123]. However, salivary IgA responses to strenuous intermittent exercise during a rugby game did not lead to altered salivary IgA concentrations. [124]. Finally, it has been documented that the production of salivary IgA decreased following a prolonged endurance event (marathon) and that this was not influenced by age, gender or carbohydrate ingestion [77;125].

In summary, it is clear that prolonged exercise performed at a high intensity may result in alterations in salivary IgA secretion. As salivary IgA is one of the body's first lines of defence against possible URT infections, this change

(decrease in salivary IgA concentration) may have a significant role to play in the development of post-race URTS in endurance athletes.

2.4.2. Changes in salivary cortisol in response to exercise

It is well established that there are two primary physiological systems involved in the body's stress response. The first of these two primary systems is the hypothalamic-pituitary-adrenocortical (HPA) axis, of which plasma and salivary cortisol is a marker, and the second is the sympatho-adrenomedullary system (SAM), of which salivary α-amylase is a marker[126]. In this section, the hypothalamic-pituitary-adrenocortical (HPA) axis and cortisol response will be discussed first, followed by a discussion of the sympatho-adrenomedullary system (SAM) and the salivery α-amylase response.

It has been shown that salivary cortisol concentrations are a good indicator of the adrenocortical response to stress (and exercise), as salivary cortisol concentrations closely reflect plasma cortisol concentrations [127]. In addition, measurement of salivary cortisol is a technically easier measurement than the determination of plasma concentrations [128-130]. Therefore salivary cortisol concentrations can be used as an indicator of the glucocorticoid response to exercise [128;131], as plasma and salivary cortisol concentrations are very similar during exercise [128;130;132].

Both the salivary and plasma cortisol concentrations rise in a linear fashion [133] during graded exercise until the athlete reaches higher intensity exercise

(anaerobic threshold) when the levels lose their linearity. This exponential increase in cortisol concentrations may be as a result of the marked increase in sympathetic activity during high-intensity exercise, or due to the increase in circulating blood catecholamine concentrations seen in exercise intensities above the anaerobic threshold [125;127]. Furthermore, it has also been suggested that as exercise intensity increases the accumulation of intramuscular lactate activates chemorecptors in the muscles, possibly resulting in stimulation in the HPA axis and subsequent increased cortisol production [134;135].

In summary, cortisol is a marker of the HPA axis' response to exercise and is readily measurable in the saliva where the salivary concentrations closely follow plasma concentrations. A linear increase in salivary cortisol concentrations can be expected during exercise, although this relationship may end once higher intensity exercise (anaerobic threshold) is reached.

2.4.3. Changes in salivary α-amylase response to exercise

In the previous section, the hypothalamic-pituitary-adrenocortical (HPA) axis and cortisol response was discussed. The discussion will now focus on the second of the two primary physiological systems involved in the body's stress response, namely, the sympatho-adrenomedullary system (SAM) and the α-amylase response to stress and exercise.

An acute bout of intense and prolonged exercise has been shown to result in an increased adrenergic response which, in turn, results in an increase in protein concentration in the saliva. One important protein in the saliva which is part of this adrenergic response is α-amylase. It has been shown that salivary α-amylase concentrations increase in response to an exercise bout, probably as a result of the increased β-sympathetic stimulation of the salivary glands [136]. The elevation in α-amylase concentrations in response to an exercise bout may also be due to the increase in the circulating catecholamines associated with exercise [119;136;137]. The concentration of α-amylase in the saliva in response to exercise can therefore be regarded as an indicator of adrenergic response to the stress of the bout of exercise [138], and is considered a useful tool in the evaluation of the SAM system [138;139].

It has been shown that during a progressive exercise test to exhaustion, salivary α-amylase concentrations initially decrease until the intensity of exercise reached the anaerobic threshold (AT), at which point the concentrations then increase back to basal levels [119]. This was attributed to an increase in sympathetic activity at higher intensity exercise (anaerobic threshold). It was concluded in this study that changes in salivary α-amylase concentration in response to exercise may, in fact be used as a valid new method for determining the exercise intensity (anaerobic threshold) [119].

The discussion thus far has centred on the response of salivary α-amylase to the stressor of exercise. Investigations have also been done to evaluate the salivary α-amylase response to psychological and non-exercise stressors.

Findings include that the circadian rhythm fluctuations in salivary α-amylase activity were much smaller than those induced by exercise, and that salivary α-amylase concentration was an excellent indicator of the changes in sympathetic nervous activity [140]. This validates the findings of a previous study by Takai et al. [126] where the salivary cortisol and α-amylase responses to viewing a stressful video were compared to a soothing video. The results of this study showed that there was a rapid and significant increase in the salivary α-amylase concentration when viewing the stressful video [126].

In conclusion, it has been shown that salivary α-amylase concentration is a good marker that can be used in the evaluation of the SAM system during exercise. In response to an exercise bout, the salivary α-amylase concentration initially decreases, but then increases when the level of exercise intensity reaches the anaerobic threshold.

2.5. Summary: Immunological and salivary markers during exercise

It is clear that there are immunological and salivary markers that, when measured, will provide insight into the possible causes of post-race URTS in the ultra-endurance athlete. However, there are very few studies that have examined these markers during ultra-endurance events, and there are no studies that have determined if there is an association between these markers and the development of post-race URTS in endurance athletes.

2.6. Summary and conclusions

- URTS is a common medical condition seen in endurance athletes, particularly during intense training and immediately after racing
- Alterations in immune parameters in athletes undergoing intense training and competition has not been well studied
- In spite of the common assumption that URTS in endurance athletes are as a result of infections due to alterations in immune parameters, there are no studies directly linking alterations in immune parameters in response to training, nor is there documented evidence of infections in athletes
- Allergic conditions, in particular allergic rhinitis, are also common in endurance athletes
- The symptoms of URT infections and allergic rhinitis show considerable overlap
- Other possible non-infective, non-allergic causes of URTS in athletes require further investigation and consideration
- Current clinical guidelines for the management of URTS in athletes are mainly based on the assumption that URTS in athletes are only as a result of an infective cause
- If other causes for URTS in athletes are documented, these guidelines may require modification
- The TH1 response mediates a CMI response and the TH2 a humoral response
- Cytokines are messengers which influence the development of either a TH1 or TH2 response

- IL-2 and IL-12 are markers of the TH1 response, and IL-4, IL-6, and IL-10 are markers of the TH2 response
- In response to exercise, cytokine production may result in the up-regulation of the TH2 response and thus cause a decrease in CMI – this may increase susceptibility to infection
- Salivary IgA is important as the first line of mucosal defence
- Salivary IgA concentrations have been shown to decrease with endurance exercise, potentially making the athlete more susceptible to infection
- Salivary cortisol concentration appears to be a good marker of the adreno-cortico response to exercise, and this is a linear increase
- Salivary α-amylase concentration appears to be a good marker of the SAM system
- In response to exercise, the increased adrenergic response results in increased circulating catecholamines and an increase in salivary α-amylase concentration
- There are no studies that have studied the association between the development of post-race URTS in ultra-endurance athletes and the TH1/TH2 response, or changes in the salivary cortisol, IgA, and α-amylase concentrations

Chapter 3

Clinical and immunological factors associated with post-race Upper Respiratory Tract Symptoms (URTS) in Ironman triathletes: A prospective cohort study

3.1. Introduction

It has been well established that regular participation in physical exercise is an important component of a healthy lifestyle. As a result, there is an increasing trend for greater participation in recreational and competitive sporting activities.

Indeed, endurance exercise has become increasingly popular. In South Africa, this is particularly evident as numbers of participants in ultra-endurance events, including ultra-marathons, cycling events, and triathlons are increasing. The Ironman ultra-triathlon is a particularly strenuous event that comprises a 3.8km surf swim, followed by a 180km cycle, and is completed by a 42,2km run.

Previous research has shown that 49,2% of Ironman triathletes developed upper respiratory tract symptoms (URTS) before or after the race [8]. Post-race respiratory tract symptoms have also been documented in a number of other

ultra-endurance events [14;19;20]. It is evident that the precise mechanism(s) responsible for the development of post race respiratory symptoms have not been well documented.

Whilst the main hypothesis for the development of post-race URTS is based on infection [18;19;21] following exercise-induced immunosuppression [22-24], this has not yet been proven [25]. To date, there are no prospective studies that have documented the clinical characteristics of ultra-triathletes who present with post-race URTS. Furthermore, to our knowledge there are no studies that have investigated whether (1) markers of the immune response, in particular the TH1 and TH2 responses, or (2) salivary markers of sympathetic and parasympathetic balance are related to the development of post-race URTS.

3.2. Aims of the study

The aims of this study were: (1) to determine the incidence of post-race (URTS) in triathletes competing in an Ironman Triathlon; (2) to identify the clinical and immunological factors that are associated with the development of post-race URTS in these triathletes.

3.3. Methods

3.3.1. Type of study

This study was conducted as a prospective cohort study.

3.3.2. Subjects

All the triathletes entering for the 2006 South African Ironman Triathlon, held in March 2006 in Port Elizabeth (South Africa) were potential subjects for this study. In order to facilitate the recruitment of triathletes, information about the study was posted on to the official race website (Appendix 1) 2 months prior to the event. This information included details about the study procedures (Appendix 2), the informed consent form (Appendix 3), and copies of the questionnaires to be completed (Appendix 4) as well as a service for triathletes to ask questions about the research by telephone or email.

Prior to the study, the protocol was approved by the Research Ethics Committee of the University of Cape Town (REC ref no. 425/2005) (Appendix 5), as well as the general organising committee and the medical sub-committee of the 2006 South African Ironman Triathlon.

Further recruitment of triathletes as subjects for the study took place at the registration area during the 1-3 days prior to the event. A team of researchers was based within the registration complex where a designated research area was established in close proximity to the registration desk. As triathletes reported to the registration desk, they were again reminded and informed about the nature of the study, and were afforded the opportunity to volunteer to take part in the study. In order to be included in the study, the triathlete had to reside in a specific geographical area of South Africa (the Pretoria/Johannesburg area in the province of Gauteng). This was important

as subjects were required to report to designated researchers residing in this geographical area in the 2-week period after the race for consultation and repeat sample collection should the need arise. Those triathletes that resided in this area, and who agreed to participate in the study, then reported to the research staff. The procedure and protocol was explained, and any questions were answered. Thereafter the triathletes gave written informed consent to participate in the study. Subjects were then requested to complete the comprehensive pre-race questionnaire.

Of the 1136 triathletes who registered for the event, 992 (87.2%) started the race. Of those 992 triathletes that started the race, 99 (10 %) completed the pre-race questionnaire, and agreed to be research subjects for this study (Figure 3.1.).

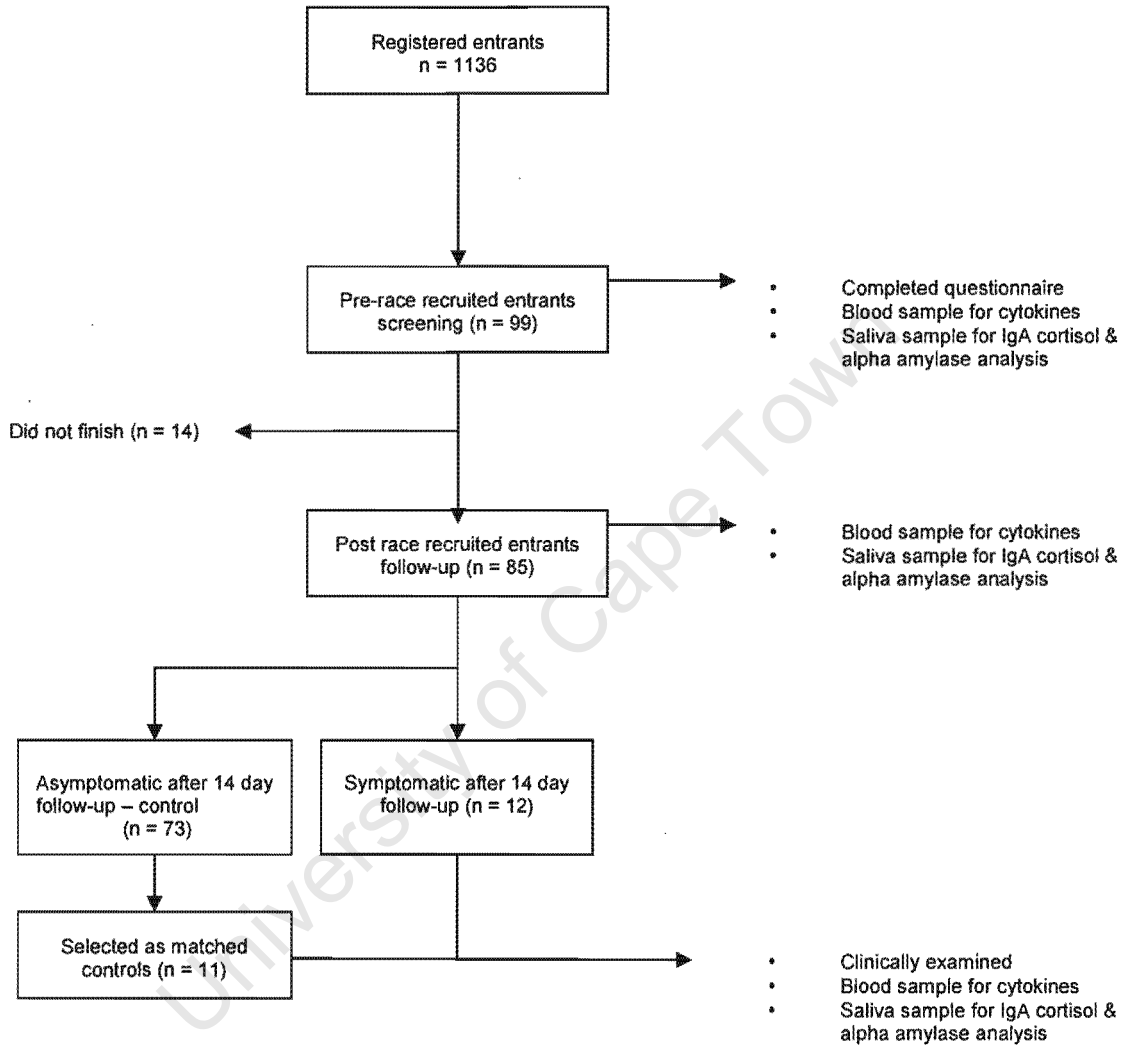

Figure 3.1.: Flow diagram representing methodology time line.

3.3.3. Pre-race data collection

3.3.3.1. Questionnaire

The questionnaire used in this study was a modified version of a previously validated pre-race questionnaire [15;45;141]. The format and content of the questionnaire was modified following input from a sample of triathletes that were not part of the research study. These triathletes were requested to read the questionnaire and assess its ease of administration, relevance and understanding. The independent comments made were then used to compile the final questionnaire which was used in the study.

Triathletes were encouraged to complete the questionnaire whilst remaining in the research area and the majority of volunteers complied. Alternatively, triathletes were allowed to take the questionnaire with them and return it the next day or on the morning of the race (<10% of questionnaires were returned in this way). Once this initial phase of the study was completed, the volunteers reported to researchers who were involved in the collection of blood and saliva samples.

3.3.3.2. Saliva sample collection

Saliva samples were collected prior to blood collection. The subjects were asked to lean slightly forward and tilt their heads downwards for a period of one minute in order to accumulate saliva in the floor of the mouth. At the end of the minute the saliva was swallowed and subjects were then asked to

accumulate saliva for a further four minutes in the same position. During these four minutes they could allow the saliva to passively drool into a pre-weighed plastic tube (50ml, Falcon Tube) at any time. After collection, the weight of the tube was measured and the tubes were then frozen at -80° until analysis. The weight of the saliva was used to calculate salivary flow rate, expressed in mg of saliva per min (mg/min). On the day of analysis, the saliva samples were allowed to thaw at room temperature. They were then centrifuged at 3000rpm for 15min and the supernatant was used for the analysis of cortisol, α-amylase, and salivary secretory (s)IgA.

3.3.3.3. Blood sample collection

Venous blood samples were drawn from athletes' upper limb veins following the saliva collection. A tourniquet was applied to the arm, and blood withdrawn into two 5ml blood sample tubes via a needle and syringe. Once the samples were obtained, the needle was withdrawn and pressure applied to the puncture wound site to prevent bruising.

The blood vials were first left to stand for 30min (on ice) and then spun down at 4000rpm for 10min. The supernatant was pipetted into 1.5ml microfuge tubes and immediately frozen. Blood samples were couriered to Ampath for serum cytokine (IL-2, IL-4, IL-6, IL-10, IL-12) concentration determination. The remainder of the samples were frozen at -20°C and transported to Pretoria for further analysis.

3.3.4. Immediate post-race data collection

At the time of the pre-race data collection, triathletes were also requested to report to a designated area in the medical facility on completion of the race. In order to ensure maximum compliance, a designated research area was established in close proximity to the finishing area. This area was in the main thoroughfare for the triathletes (all triathletes finishing had to pass the research area). For the purposes of easy identification, all subjects who volunteered for the study were supplied with an identification sticker which was placed on their race numbers. This enabled the researchers to easily identify the subjects as they passed the research area in the finishing tent.

On completion of the race, subjects reported to this area, and repeat blood and saliva samples were collected using the identical procedures as described above. A total of 70 of the initial 99 subjects that were recruited for the study, reported to the research facility after the event for immediate post-race data collection.

Once saliva and blood samples were collected, each triathlete was then given a self-assessment form containing details regarding the development of any respiratory tract symptoms in the 2 weeks following the race (Appendix 6). Subjects were reminded to complete the form on a daily basis. In addition, subjects were asked to report to the research team close to their residential area should they develop two or more of the symptoms on the list: Fever, chills, malaise (tiredness/fatigue), watery or itchy eyes, sneezing, nasal

discharge, blocked nose, earache, sore throat, laryngitis (hoarseness), headache, cough, joint ache, or muscle aches. A follow-up consultation was arranged with one of the medical staff if the triathlete developed any two of the abovementioned URT symptoms during the 14-day follow-up period.

3.3.5. Post-race follow-up consultation

The final phase of data collection involved the 2-week post-race period. As mentioned, subjects were given self-assessment forms to complete on a daily basis. To facilitate completion of these forms and to ensure greater compliance, each of the 70 triathletes who had completed the Ironman Triathlon and who had given the second samples, was contacted telephonically every third day during this period. All those triathletes who developed two or more URTS were then advised to report for a medical assessment, and for further blood and saliva sample collection. Blood and saliva sample collection was conducted in an identical fashion to the pre-race collection procedures.

A total of 12 subjects reported post-race URTS, and this group formed the "Symptomatic" group for this study. For the purpose of the questionnaire analysis, 73 subjects who completed the pre-race questionnaire, and who did not develop post-race symptoms formed the "Control" group. A further sub-group of asymptomatic triathletes (n=11) were matched as closely as possible by race time to triathletes who developed symptoms. This sub-group of asymptomatic triathletes were also requested to report for blood and saliva

sample collection in the 2-week post-race period on days similar to the Symptomatic group. This sub-group formed the "Matched control sub-group" for this study.

Both the Symptomatic group and the Matched control sub-group of triathletes also underwent a physical examination which was designed to assess clinical signs within the respiratory tract (Appendix 7). Clinical signs were assessed as absent or present, and a subjective classification of severity of signs (mild, moderate or severe) was used based on experience by the examining clinician (Peter Baxter).

3.3.6. Environmental conditions on race day

The South African Weather Service provided details of the weather conditions on race day. The average temperature during the race was 20°C, with a maximum temperature of 21°C and minimum temperature of 19°C. The average relative humidity during the race was 70%, with the average wind speed 37km/h. The sea temperature during the swim component was recorded as 19.2°C.

3.3.7. Sample analysis

3.3.7.1. Saliva

3.3.7.1.1. Salivary α-amylase

Samples were assayed for α-amylase using a commercially available kinetic reaction assay (Salimetrics, State College, PA). The assay employs a chromagenic substrate, 2-chloro-p-nitrophenol, linked to maltotriose. The enzymatic action of α-amylase on this substrate yields 2-chloro-*p*-nitrophenol, which can be spectrophotometrically measured at 405nm, using a standard laboratory plate reader. The amount of α-amylase activity present in the sample is directly proportional to the increase (over a 2 minute period) in absorbance at 405nm. Results are computed in units per millilitre of α-amylase using a formula: [Absorbance difference per minute X total assay volume (328ml) X dilution factor (200)] / [millimolar absorptivity of 2 –chloro-*p*-nitrophenol (12.9) X sample volume (0.008ml) X light path (0.97)]. Intra-assay variation (CV) computed for the mean of 30 replication tests was less than 7.5%. Inter-assay variation computed for the mean of average duplicates for 16 separate runs was less than 6%.

3.3.7.1.2. Salivary cortisol

All samples were assayed for salivary cortisol using a highly sensitive enzyme immunoassay US FDA (510k) cleared for use as an in vitro diagnostic

measure of adrenal function (Salimetrics, State College,PA). The test used 25μl of saliva (for singlet determinations), had a lower limit of sensitivity of 0.007μl/dl, range of sensitivity from 0.007 to 1.8μg/dl, and average intra-and inter-assay coefficients of variation of less than 5% and 10%.

3.3.7.1.3. Salivary secretory immunoglobulin A (sIgA)

Salivary sIgA was determined using an indirect enzyme immunoassay kit (Salimetrics, State College, USA). The concentration of saliva was expressed as salivary sIgA secretion rate (sIgA) (μg sIgA $\cdot min^{-1}$), or the total amount of sIgA appearing on the mucosal surface per time unit. The sIgA secretion rate was calculated by multiplying absolute sIgA concentration by saliva flow rate ($ml \cdot min^{-1}$). Saliva flow rate was calculated by dividing the total amount of saliva obtained in each sample (ml) by the time taken to produce the sample (4min). All samples were analysed in duplicate with the inter- and intra-assay coefficients of variation lower than 3.5% and 3.7%, respectively.

3.3.7.2. Cytokine analysis

The Bio-Plex human cytokine immunoassay (Bio-Rad Laboratories Inc., Hercules, CA, USA) was used for simultaneous quantification of five different cytokines (IL-2, IL-4, IL-6, IL-10 and IL-12). The assays were run according to the recommended procedure. In brief, the premixed standards were reconstituted in 0.5ml of culture medium, generating a stock concentration of $50,000pg \cdot ml^{-1}$ for each molecule been measured. The standard stock was

serially diluted in the same culture medium to generate 8 points for the standard curve. The assay was performed in a 96-well filtration plate supplied with the assay kit. Premixed beads (50µl) coated with target capture antibodies were transferred to each well of the filter plate (5000 beads per well per cytokine) and washed twice with Bio-Plex wash buffer. Premixed standards or samples (50µl) were added to each well containing washed beads. The samples were used directly without further dilution. The plate was shaken for 30sec and then incubated at room temperature for 30min with low-speed shaking (300rpm). After incubation and washing, premixed detection antibodies (50µl, final concentration of 2µg·ml^{-1}) were added to each well. The incubation was terminated after shaking for 10min at room temperature. After 3 washes, the beads were re-suspended in 125µl of Bio-Plex assay buffer. Beads were read on the Bio-Plex suspension array system, and the data were analysed using Bio-Plex Manager™ software (v 3.0) with 5PL curve fitting.

3.3.8. Statistical analysis of data

All the data from the questionnaires, as well as the results from the blood and saliva analyses, was entered on to an Excel spreadsheet (Microsoft 2003). Data was analysed using the Statistica 7.0 (Stat-soft Inc, Tulsa, Oklahoma, USA) and GraphPad InStat 2.05a (GraphPad Software, San Diego, California, USA) statistical programs. All normally distributed numerical data is represented by the mean ± standard deviation, with the number of subjects in parenthesis and a one-way analysis of variance (ANOVA) was used to determine any significant differences between groups. Blood and saliva data,

which was not normally distributed, is represented by a median with inter-quartile range in parentheses, together with the number of subjects, and a Mann-Whitney U test was used to determine any significant differences between groups. Categorical data are expressed as frequencies, and significant differences between groups were analysed using the Pearson's chi-square or Fisher's exact tests. A repeated-measures ANOVA was used to investigate differences in the pre-race, post-race and the follow-up consultation salivary and blood cytokine levels between the Symptomatic group and the Matched Control sub-group. Since these values were not normally distributed, they were log-transformed prior to the repeated-measures ANOVA. Statistical significance was accepted when $p<0.05$.

3.4. Results

3.4.1. General characteristics of the study population

The general characteristics of the Ironman study population are depicted in Table 3.1. There were no significant differences between the Symptomatic versus Matched Control or Symptomatic versus Control groups of triathletes who completed the 2006 South African Ironman Triathlon with respect to age, height, weight, BMI and gender.

Table 3.1.: General characteristics of the Symptomatic, Control and Matched Control sub-groups of triathletes who completed the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	**Matched Control sub-group** (n=11)	**p-value**	**Control group** (n=73)	**p-value**
Age (years)	36.9 ± 7.5 (12)	37.8 ± 8.1 (11)	0.80	37.3 ± 8.5 (73)	0.88
Height (cm)	179.1 ± 8.5 (11)	173.4± 6.3 (8)	0.13	177.9 ± 8.2 (49)	0.67
Weight (kg) [a]	78.3 ± 10.4 (12)	74.8 ± 4.6 (8)	0.38	77.2 ± 10.7 (50)	0.74
BMI (kg/m^2) [b]	24.3 ± 2.2 (11)	24.9 ± 1.9 (8)	0.49	24.2 ± 2.6 (48)	0.94
Gender (% males)	83.33 (10)	100 (11)	0.22	91.78 (67)	0.31
Questionnaire completed (%)	100 (12)	61.54 (8)	0.39	76.71 (56)	0.11

Except for gender, which is expressed as a frequency (%), values are expressed as average ± standard deviation. The number of subjects (n) is in parentheses.
[a] Weight is the athletes self-reported normal weight.
[b] Body mass index (BMI) is calculated as weight (kg) divided by height (m) squared.

3.4.2. Training and performance characteristics of the study population

Triathlon (sprint, standard, half-Ironman and Ironman) and road running (5km, 10km, 21.1km, 42.2km and ultra-marathon) personal best times (PB) and best times achieved over the preceding 15 weeks for the road running events, and 12 months for the triathlon events prior to the race of the Symptomatic and Control groups, and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon are depicted in Table 3.2.

There was a tendency for the personal best times in the Ironman Triathlon over the past 12 months to be faster in the Control group (740.1 ± 79.3

minutes, n=16) than the Symptomatic group (811.3 ± 84.0 minutes, n=7, p=0.07). Similarly, there was a tendency for the Control group (47.1 ± 5.3 minutes, n=20) to be faster than the Symptomatic group (51.8 ± 5.8 minutes, n=6, p=0.07), over a 10km run in the 15 weeks prior to the Ironman Triathlon event, with the Matched Control sub-group (39.7 ± 1.5 minutes, n=3) being significantly faster (p=0.01). In the sprint triathlon, the Matched Control sub-group (65.5 ± 5.4 minutes, n=6) tended to be faster than the Symptomatic group (74.7 ± 10.0 minutes, n=10, p=0.06). The triathletes' personal best times in the sprint triathlon over the 12 months prior to the Ironman, showed the Matched Control sub-group (70.0 ± 5.9 minutes, n=4) tended to be faster than the Symptomatic group (70.0 ± 5.9 minutes, n=4, p=0.07). The personal best times in the 10km run shows that there was a tendency for the Matched Control sub-group (38.4 ± 4.2 minutes, n=7) to be faster than the Symptomatic group (45.1 ± 8.3 minutes, n=7, p=0.08). The personal best times in the half marathon (21.1km) run shows that the Matched Control sub-group (89.8 ± 8.6 minutes, n=6) was faster than the Symptomatic group (105.9 ± 17.4 minutes, n=11, p=0.05).

Table 3.2.: Triathlon (sprint, standard, half-Ironman and Ironman) and road running (5km, 10km, 21.1km, 42.2km and ultra-marathons) personal best times (PB) and best times achieved over the last 12 months or 15 weeks of the Symptomatic and Control groups, and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	**Matched Control sub-group** (n=11)	**p-value**	**Control group** (n=73)	**p-value**
Sprint PB (min)	74.7 ± 10.0 (10)	65.5 ± 5.4 (6)	0.06	70.0 ± 13.1 (31)	0.30
Standard PB (min)	152.1 ± 22.2 (7)	134.5 ± 6.2 (4)	0.16	154.6 ± 29.2 (23)	0.84
Half Ironman PB (min)	341.3 ± 40.0 (12)	316.9 ± 40.1 (7)	0.22	339.2 ± 44.4 (43)	0.88
Ironman PB (min)	811.3 ± 84.0 (7)	808.5 ± 84.3 (4)	0.96	755.2 ± 96.9 (21)	0.18
Sprint 12 Months PB (min)	70.0 ± 5.9 (4)	70.0 ± 5.9 (4)	0.07	71.7 ± 18.9 (15)	0.44
Standard12 Months PB (min)	163.3 ± 40.4 (4)	138.7 ± 2.1 (3)	0.35	164.8 ± 32.6 (13)	0.94
Half Ironman 12 Months PB (min)	338.7 ± 35.4 (10)	329.7 ± 49.7 (6)	0.68	347.5 ± 47.0 (36)	0.59
Ironman 12 Months PB (min)	839.0 ± 78.8 (3)	855.5 ± 53.0 (2)	0.82	740.1 ± 79.3 (16)	0.07
5km PB (min)	20.5 ± 2.1 (6)	19.0 ± 2.2 (7)	0.24	19.5 ± 1.9 (26)	0.29
10km PB (min)	45.1 ± 8.3 (7)	38.4 ± 4.2 (7)	0.08	42.4 ± 5.5 (42)	0.27
21.1km PB (min)	105.9 ± 17.4 (11)	89.8 ± 8.6 (6)	0.05	97.5 ± 14.2 (46)	0.10
42.2km PB (min)	238.3 ± 47.3 (4)	202.0 ± 31.5 (6)	0.18	213.8 ± 30.1 (39)	0.15
Two Oceans PB (min)	335.0 ± 67.9 (2)	283.3 ± 32.4 (4)	0.25	318.4 ± 53.7 (21)	0.68
Comrades PB (min)	565.0 ± 77.8 (2)	478.5 ± 44.3 (4)	0.14	564.6 ± 83.8 (30)	0..99
5km 15 weeks PB (min)	26.0 ± 3.6 (3)	21.0 ± 3.0 (3)	0.14	21.9 ± 3.9 (15)	0.12
10km 15 weeks PB (min)	51.8 ± 5.8 (6)	39.7 ± 1.5 (3)	0.01	47.1 ± 5.3 (20)	0.07
21.1km 15 weeks PB (min)	110.3 ± 11.9 (8)	101.5 ± 13.6 (6)	0.22	112.0 ± 16.9 (31)	0.79
42.2km 15 weeks PB (min)	259.5 ± 41.7 (2)	242.0 ± 53.1 (3)	0.72	239.1 ± 36.3 (11)	0.49

Values are expressed as average ± standard deviation, with the number of subjects (n) in parentheses.
PB - personal best time; Comrades - the annual Comrades 89 km ultra-marathon run between Pietermaritzburg and Durban in South Africa; Two Oceans - 56 km ultra-marathon run in Cape Town, South Africa.

The training history of the Symptomatic, Control, and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon is depicted in Table 3.3.

Table 3.3.: The swimming, cycling, running and/or total training frequency, distances and durations for the 1- and 15-week period prior to the 2006 South African Ironman Triathlon of the Symptomatic and Control groups, and Matched Control sub-group

	Symptomatic group (n=12)	**Matched Control sub-group** (n=11)	**p-value**	**Control group** (n=73)	**p-value**
Training frequency (days/wk)	5.8 ± 0.8 (12)	5.6 ± 0.9 (5)	0.66	5.7 ± 0.9 (50)	0.80
15wk:					
Swim time (min/wk)	201.4 ± 80.2 (12)	213.8 ± 98.1 (8)	0.76	182.8 ± 75.5 (52)	0.45
Cycle time (min/wk)	516.7 ± 114.8 (12)	386.3 ± 139.3 (8)	0.03	454.6 ± 193.5 (51)	0.29
Run time (min/wk)	321.8 ± 125.9 (12)	265.7 ± 146.4 (8)	0.40	286.8 ± 113 (48)	0.37
Swim dist(km/wk)	7.0 ± 3.1 (12)	5.8 ± 2.1 (8)	0.31	5.8 ± 2.6 (53)	0.16
Cycle dist (km/wk)	211.3 ± 48.2 (12)	171.3 ± 90.1 (8)	0.21	203.5 ± 97.1 (52)	0.79
Run dist(km/wk)	44.8 ± 13.2 (12)	42.5 ± 23.3 (8)	0.79	46.2 ± 17.1 (52)	0.78
1wk:					
Swim time(min/wk)	55.0 ± 33.4 (12)	32.5 ± (8)	0.22	62.7 ± 49.1 (53)	0.61
Cycle time(min/wk)	109.6 ± 81.3 (12)	90.0 ± 78.6 (8)	0.61	134.7± 99.8 (52)	0.44
Run time(min/wk)	51.7 ± 54.4 (12)	48.0 ± 42.7 (8)	0.88	73.3 ± 60.4 (51)	0.26
Swim dist(km/wk)	1.8 ± 1.1 (12)	1,0 ± 1.3 (8)	0.14	2.4 ± 2.5 (54)	0.43
Cycle dist(km/wk)	42.7 ± 33.7 (12)	36.0 ± 38.4 (8)	0.69	56.4 ± 43 (53)	0.31
Run dist(km/wk)	8.8 ± 8.3 (12)	9.3 ± 9.1 (8)	0.90	14 ± 12.6 (51)	0.17

Values are expressed as average ± standard deviation, with the number of subjects (n) in parentheses.

The Symptomatic group of triathletes (516.7 ± 114.8 minutes, n=12), spent significantly more time in cycling training in the 15 weeks prior to the Ironman Triathlon than the Matched Control sub-group of triathletes (386.3 ± 139.3 minutes, n=8, p=0.03). All other training parameters (distance and time) revealed no differences between the Symptomatic and Control groups, or Symptomatic group and Matched Control sub-group of triathletes.

The predicted and actual times of the Symptomatic, Control, and Matched Control sub-group of triathletes is depicted in Table 3.4. The Symptomatic group (80.4 ± 18.9 minutes, n=12) tended to predict a faster swim time compared to the Control group (80.4 ± 18.9 minutes, n=12, p=0.07). The Matched Control sub-group performed significantly better in the swim component compared to their predicted time (95.4 ± 11.9 % of predicted, n=7) than the Symptomatic group (109.5 ± 15.5 % of predicted n=12, p=0.05). Overall, the Control group (105.3 ± 6.9 % of predicted, n=50) was significantly closer to their predicted time than the Symptomatic group (111.7 ± 12.9 % of predicted, n=11, p=0.02).

3.4.3. Self-reported medical and respiratory symptoms of the study population

The self-reported symptoms of general medical conditions of the Symptomatic, Control groups and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon is depicted in Table 3.5. There were no significant differences in the frequency of reported medical conditions between any of the groups.

Table 3.4.: The predicted (as reported in the pre-race questionnaire), and actual performance times of the Symptomatic and Control groups, and the Matched Control sub-group of triathletes during the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	**Matched Control sub-group** (n=11)	**p-value**	**Control group** (n=72)	**p-value**
Predicted Swim Time (min)	80.4 ± 18.9 (12)	95.0 ± 22.9 (7)	0.15	90.9 ± 17.8 (54)	0.07
Predicted Cycle Time (min)	374.6 ± 32.2 (12)	389.3 ± 44.8 (7)	0.42	397.2 ± 49.9 (54)	0.14
Predicted Run Time (min)	301.7 ± 46.2 (12)	287.1 ± 45.4 (7)	0.52	285.9 ± 47.5 (54)	0.28
Predicted Overall Time (min)	747.7 ± 74.7 (11)	774.0 ± 49.3 (5)	0.49	779.5 ± 98.8 (51)	0.32
Actual Swim Time (min)	86.7 ± 16.7 (12)	88.4 ± 14.5 (11)	0.78	93.8 ±16.8 (72)	0.18
Actual Cycle Time (min)	415.9 ± 33.6 (12)	425.4 ± 42.5 (11)	0.54	422.1± 41.3 (71)	0.63
Actual Run Time (min)	331.9 ± 75.9 (12)	297.7 ± 55.5 (11)	0.21	307.7 ± 53.1 (72)	0.17
Actual Overall Time (min)	834.5 ± 99.7 (12)	811.5 ± 91.2 (11)	0.55	822.4 ± 96.5 (72)	0.69
Swim Time (% Predicted) [b]	109.5 ± 15.5 (12)	95.4 ± 11.9 (7)	0.05	105.5 ± 14.5 (53)	0.39
Cycle Time (% Predicted) [b]	111.2 ± 5.4 (12)	109.5 ± 11.0 (7)	0.66	106.5 ± 8.5 (52)	0.07
Run Time (% Predicted) [b]	111 ± 23.6 (12)	101.6 ± 19.1 (7)	0.38	106.6 ± 13.3 (53)	0.38
Overall Time (% Predicted) [b]	111.7 ± 12.9 (11)	106.3 ± 6.8 (5)	0.40	105.3 ± 6.9 (50)	0.02

Values are expressed as average ± standard deviation, with the number of subjects (n) in parentheses..[b] Actual times expresses relative to the predicted split and overall times.

Table 3.5.: The general medical conditions of the Symptomatic and Control groups, and the Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	**Matched Control sub-group** (n=8)	**p-value**	**Control group** (n=54)	**p-value**
Respiratory tract symptoms (%) [b]	75.0 (9)	37.5 (3)	0.17	45.5 (25)	0.11
Medicines (%) [c]	16.7 (2)	12.5 (1)	1.00	27.3 (15)	0.72
Gastrointestinal Symptoms (%) [d]	50.0 (6)	37.5 (3)	0.67	45.5 (25)	1.00
Nervous system Symptoms (%)	16.7 (2)	25.0 (2)	1.00	21.8 (12)	1.00
Allergies (%)	58.3 (7)	37.5 (3)	0.65	38.9 (21)	0.33
Asthma (%)	8.3 (1)	0 (0)	1.00	12.7 (7)	1.00
Exercise-associated Collapse (%)	8.3 (1)	12.5 (1)	1.00	3.6 (2)	0.45

Values are expressed as a frequency (%) with the number of subjects (n) in parentheses.
[b] Six weeks before the race.
[c] Used medicines to treat injuries in the week before or during a race.
[d] During exercise.

The history of smoking, family and personal histories of allergy and asthma in the Symptomatic and Control groups are depicted in Table 3.6. There were no differences in any of the parameters between the groups.

Table 3.6.: The history of smoking, family and personal histories of allergy and asthma in the Symptomatic and Control groups of triathletes who completed 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	Matched Control subgroup (n=11)	p-value	Control group (n=55)	p-value
Smoking: never (%)	75.0 (9)	45.5 (5)		66.1 (37)	
: ex (%)	25.0 (3)	27.3 (3)	0.64	32.1 (18)	0.74
: current (%)	0 (0)	0 (0)		1.8 (1)	
Family History: Allergy (%)	41.7 (5)	36.4 (4)	0.10	43.4 (23)	1.0
: Asthma (%)	25.0 (3)	27.3 (3)	0.62	23.6 (13)	1.0
Personal History: Allergy (%)	58.3 (7)	27.3 (3)	0.65	38.9 (21)	0.33
: Asthma (%)	8.3 (1)	0 (0)	0.10	12.7 (7)	1.0

Values are expressed as percentage (%), with the number of subjects (n) in parentheses.

The presence of self-reported pre-race Respiratory Tract Symptoms (RTS), with or without Systemic Symptoms (SS), in the 6-week and 1-week periods prior to the race, in the Symptomatic, Control groups, and the Matched Control sub-group is depicted in Table 3.7. There was a higher self-reported incidence of RTS in the period 6 weeks prior to the event between the Symptomatic (66.7 %, n=8) and Control groups (32.9 %, n=23, p=0.02), and between the Symptomatic group (66.7 %, n=8) and Matched Control sub-group (27.3 %, n=3, p=0.04). In 1 week prior to the event, there was a higher incidence of self-reported RTS between the Symptomatic (58.3 %, n=7) and Control groups (10.0 %, n=7, p=0.02), and between the Symptomatic group (58.3 %, n=7) and Matched Control sub-group (9.1 %, n=1, p=0.03).

Table 3.7.: The presence of self-reported pre-race Respiratory Tract Symptoms (RTS), with or without Systemic Symptoms (SS) (in the 6- and 1-week periods prior to the race) of the Symptomatic and Control groups, and the Matched Control sub-group of triathletes who completed 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	**Matched Control subgroup** (n=11)	**p-value**	**Control group** (n=70)	**p-value**
6 wk pre-race: any RTS (%)	66.7 (8)	27.3 (3)	0.04	32.9 (23)	0.02
- without SS	33.3 (4)	27.3 (3)		18.6 (13)	
- with SS	33.3 (4)	0.0 (0)		14.3 (10)	
1 wk pre-race: any RTS (%)	58.3 (7)	9.1 (1)	0.03	10.0 (7)	0.02
- without SS	41.7 (5)	9.1 (1)		5.7 (4)	
- with SS	16.6 (2)	0		4.3 (3)	

Values are expressed as percentage (%), with the number of subjects (n) in parentheses.

3.4.4.: Clinical findings of the Ironman triathlete study population

The results of the clinical examination performed on the Symptomatic group and Matched Control sub-group in the 14-day post-race period is depicted in Tables 3.8(a) and (b).

Table 3.8(a).: General clinical findings in the Symptomatic group and Matched Control sub-group of triathletes in the 2-week period after completing the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	**Matched Control sub-group** (n=11)	**p-value**
Resting heart rate (beats/min)	65 ± 9 (12)	61 ± 4 (11)	0.19
SBP (mmHg)	127 ± 10 (12)	122 ± 7 (12)	0.21
DBP (mmHg)	77 ± 6 (12)	74 ± 6 (11)	0.25
RR (breaths/min)	13 ± 6 (12)	11 ± 2 (11)	0.04
Temp (°C)	36.7 ± 0.4 (12)	36.7± 0.3 (11)	0.66

SBP; systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, Temp: temperature

There was no difference between the two groups in any of the clinical parameters measured except that the respiratory rate in the Symptomatic group (13 ± 6 breaths/min, n=12) was significantly higher than in the Matched Control sub-group (11 ± 2 breaths/min, n=11, p=0.04).

Table 3.8(b).: Clinical upper respiratory tract findings at consultation of the Symptomatic group and Matched Control sub-group of triathletes in the 2-week period after completing the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	Matched Control sub-group (n=11)
Neck lymph nodes : absent	8.3 (1)	100 (11)
mild	33.3 (4)	
moderate	58.3 (7)	
severe	0 (0)	
Inflamed nasal mucosa : absent	83.3 (10)	100 (11)
mild	0 (0)	
moderate	16.7 (2)	
severe	0 (0)	
Post nasal drip : absent	0 (0)	100 (11)
mild	100 (12)	
moderate	0 (0)	
severe	0 (0)	
Inflamed pharynx : absent	0 (0)	100 (11)
mild	58.3 (7)	
moderate	41.7 (5)	
Severe	0 (0)	
Fluid in middle ear : absent	41.7 (5)	100 (11)
mild	50 (6)	
moderate	8.3 (1)	
severe	0	

Values are expressed as percentage (%), with the number of subjects (n) in parentheses

Clinical examination of the respiratory tract revealed that 58.3% (n=7) of the subjects in the Symptomatic group had a moderate neck lymphadenopathy, with 33.3% (n=4) having mild lymphadenopathy. This was absent in 8.3% (n=1) of the subjects.

An inflamed nasal mucosa was observed in only 16.7% (n=2) of the Symptomatic group, and this was found to be moderate in severity. All the subjects in the Symptomatic group had a mild post-nasal drip (100%, n=12).

The pharynx was found to be moderately inflamed in 41.7% (n=5), and mildly inflamed in 58.3% (n=7) of the subjects in the Symptomatic group.

Fluid in the middle ear was clinically absent in 41.7% (n=5) of the subjects in the Symptomatic group, with a mild degree of fluid in the middle ear in 50% (n=6) of the subjects and a moderate degree of fluid in the middle ear in 8.3% of the subjects.

Clinical evaluation did not reveal any positive findings in the case of the Matched Control sub-group.

3.4.5. Laboratory findings of the Ironman triathlete study population

The results of the markers of TH1 response (IL-2 and IL-12), which were measured pre-race, post-race, and at the follow-up consultation in the Symptomatic group and Matched Control sub-group are depicted in Table 3.9.

Table 3.9.: Markers of the TH1 response measured at pre-race registration, immediately post race, and at the post-race follow-up consultation of Symptomatic group and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	Matched Control sub-group (n=11)	p-value
Serum IL-2 (U/ml) :-			
pre-race	6.9 (5.1-8.3) (10)	7.9 (4.4-11.4) (7)	0.70
post-race	8.4 (7.1-11.6) (10)	7.6 (5.2-9.1) (8)	0.25
pre/post change	1.13 (-0.7-7.4) (9)	0.6 (-4.1-6.1) (7)	0.43
pre/post change %	16.1 (-8.9-110) (9)	7.6 (-33.9-183) (7)	0.43
consultation	9.5 (6.7-13.3) (12)	14.0 (4.5-17.5) (11)	0.67
pre/consult change	-4.0 (-6.1-3.8) (9)	-6.1 (-10.8-0.2) (7)	0.31
pre/consult change%	-51.6 (-147.9-46.1) (9)	-53.6 (-328-3.2) (7)	0.56
Serum IL-12 (U/ml) :-			
pre-race	15.9 (12-18.2) (10)	16.1 (14-23.3) (7)	0.46
post-race	16.9 (12.6-24.4) (10)	16.7 (15.8-18.8) (8)	0.93
pre/post change	4.7 (1.3-8.3) (9)	0.3 (-7.8-7.6) (6)	0.48
pre/post change %	30.3 (9.1-54.4) (9)	4.3 (-47.9-46.9) (6)	0.35
consultation	14.5 (8.8-20.1) (12)	19.6 (16.6-30.6) (11)	0.07
pre/consult change	-1.3 (-1.8-5.8) (9)	-5.6 (-15.5-1.4) (6)	0.35
pre/consult change%	-10.4 (-12.7-48.1) (9)	-36 (-66.6-6.6) (6)	0.41

Values are expressed as median with interquartile range in parentheses, with the number of subjects (n) in parentheses thereafter U/ml: units per millilitre

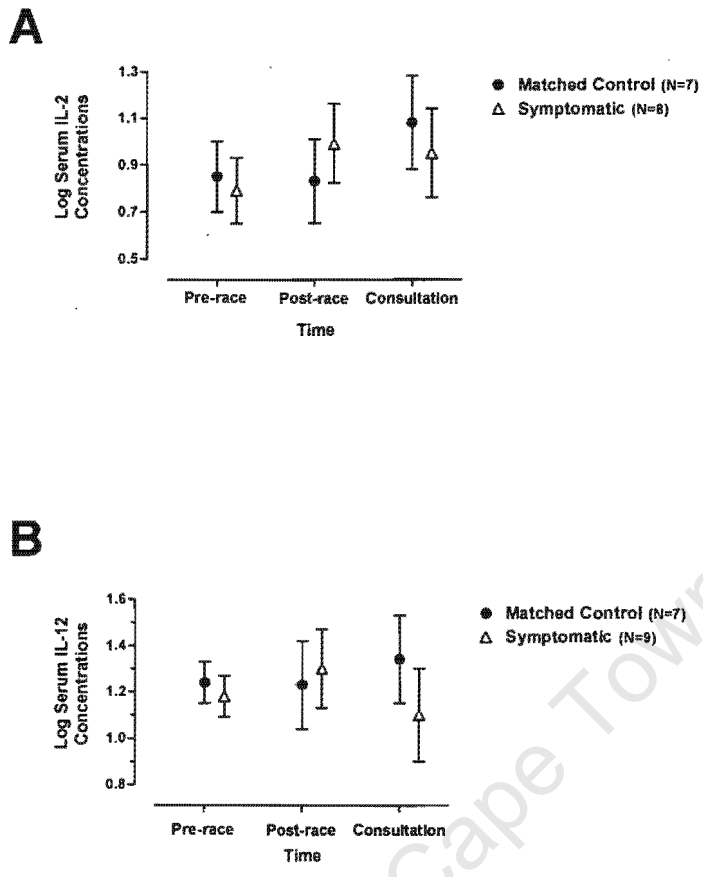

Figure 3.2.: Graph depicting (A) IL-2 and (B) IL-12 log-transformed data to show change in concentration over time

At the post-race consultation the Symptomatic group (14.5 (8.8-20.1) U/ml (n=12)) tended to have lower IL-12 concentrations compared with the Matched Control sub-group (19.6 (16.6-30.6) U/ml (n=11)) (p= 0.07). There was no significant group or time effects in the serum IL-2 and IL-12 concentrations (Figure 3.2.). The results of the markers of TH2 response (IL-4, IL-6, IL-10), which were measured pre-race, post-race, and at consultation, of the Symptomatic group and Matched Control sub-group are depicted in Table 3.10.

Table 3.10.: Markers of the TH2 response measured at pre-race registration, immediately post-race, and at the post race consultation of Symptomatic group and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	Matched Control sub-group (n=11)	p-value
Serum IL-4 level (U/ml):-			
pre-race	4.6 (4.1-4.9) (10)	4.7 (3.7-6.9) (7)	0.77
post-race	4.2 (4.0-4.8) (10)	4.4 (3.8-4.8) (8)	0.79
pre/post change	0.04 (-0.6-0.8) (9)	0.54 (-2.0-0.7) (7)	0.87
pre/post change %	1.0 (-12.8-18.5) (9)	10.0 (-28.8-19.8) (7)	0.96
consultation	4.2 (3.3-5.7) (12)	6.2 (3.5-8.0) (11)	0.24
pre/consult change	0.7 (-0.2-1.5) (9)	-2.4 (-3.2-0.1) (7)	0.12
pre/consult change%	17.2 (-6.2-30.0) (9)	-49.4 (-68.1-0.9) (7)	0.10
Serum IL-6 level (U/ml) :-			
pre-race	4.5 (2.9-8.2) (10)	4.8 (2.8-10.7) (7)	0.70
post-race	43.2 (23.2-75.0) (10)	56.8 (36.4-73) (8)	0.48
pre/post change	40.7 (19.2-69.7) (9)	45.9 (25.6-67.8) (7)	0.43
pre/post change %	875.7 (373-1311.7) (7)	717.6 (634.7-1061.1) (6)	1.00
consultation	11.0 (6.3-14.7) (12)	12.1 (6.0-23.3) (11)	0.54
pre/consult change	-8.2 (-14.9- -1.9) (9)	-12.1 (-19.9- -1.6) (7)	0.43
pre/consult change%	-64.8 (-208.1-45.0) (7)	-136.3 (-419.8- -54.6) (6)	0.39
Serum IL-10 level (U/ml):-			
pre-race	3.3 (3.0-5.4) (10)	4.3 (2.5-6.9) (7)	0.43
post-race	11.0 (6.3-25.8) (10)	13.6 (9.4-22.0) (8)	0.59
pre/post change	10.5 (3.7-22.8) (9)	10.6 (7.3-22.2) (7)	0.87
pre/post change %	544.1 (192.8-735.9) (9)	305.5 (246.9-608.6) (7)	0.96
consultation	5.8 (3.0-10.9) (12)	6.9 (3.7-11.6) (11)	0.58
pre/consult change	-3.8 (-6.5-0.7) (9)	-4.9 (-7.9- -2.0) (7)	0.79
pre/consult change%	-124 (-207.1-52.1) (9)	-131.1 (-249.5- -53,5) (7)	0.87

Values are expressed as median with interquartile range in parentheses, with the number of subjects (n) in parentheses thereafter
U/ml: units per millilitre

There were no significant differences between the Symptomatic group and the Matched Control sub-group with respect to any of the markers of TH2 response (serum concentrations of IL-4, IL-6 and IL-10), in the pre-race, post-race, and follow-up samples.

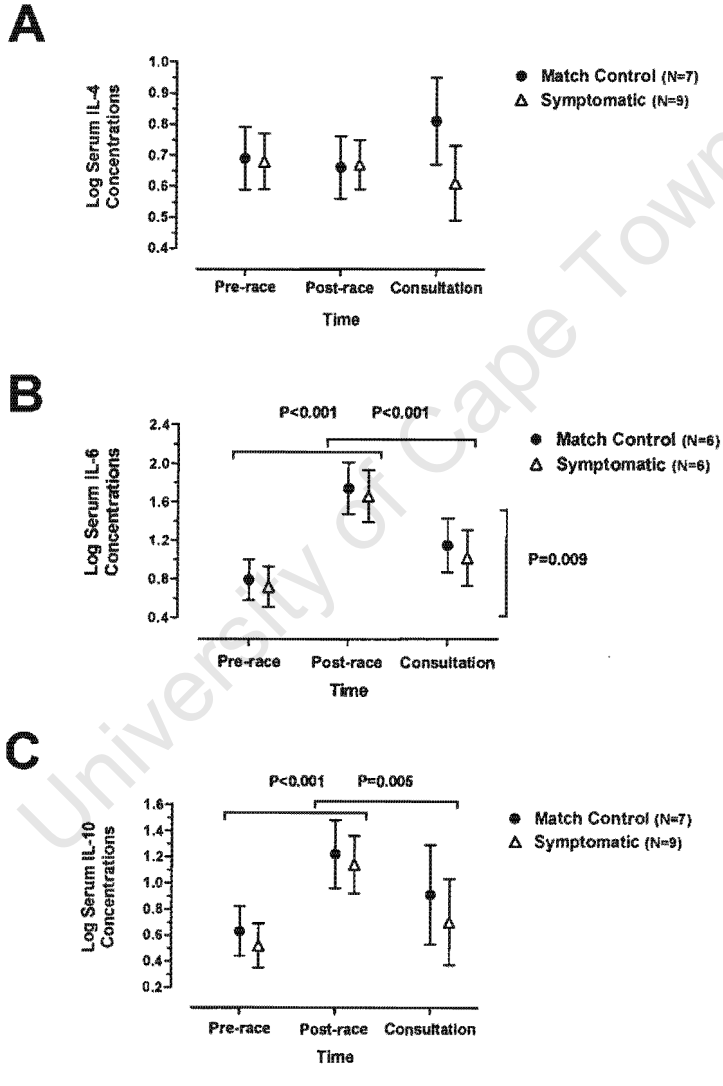

Figure 3.3.: Graph depicting (A) IL-4, (B) IL-6 and (C) IL-10 log-transformed data to show change in concentration over time

Figure 3.3. depicts the log-transformed data showing the change in IL-4, IL-6 and IL-10 concentration over time. There was a significant change over time in IL-6 concentration from pre-race to post-race ($p<0.001$) and from post-race to follow-up consultation ($p<0.001$). The follow-up consultation serum IL-6 levels were also significantly higher than the pre-race values ($P=0.009$). Similarly, there was a significant change over time for IL-10 concentration from pre-race to post-race ($p<0.001$) and from post-race to follow-up consultation ($p=0.005$).

The results of the saliva sample analyses (concentrations of IgA, cortisol and α-amylase), which were measured pre-race, post-race, and at the follow-up consultation, of the Symptomatic group and Matched Control sub-group are depicted in Table 3.11.

Table 3.11.: Saliva sample analyses measured at pre-race registration, immediately post-race, and at post-race follow-up consultation of the Symptomatic group and Matched Control sub-group of triathletes who completed the 2006 South African Ironman Triathlon

	Symptomatic group (n=12)	Matched Control sub-group (n=11)	p-value
IgA concentration (µg/min):-			
pre-race	158.9 (119.5-205.0) (12)	176.4 (78.3-258.5) (11)	0.90
post-race	139.4 (109.1-201.3) (10)	91.0 (83.0-109.5) (9)	0.09
pre/post change	-2.4 (-30.1-34.1) (10)	102.4 (12.9-155.0) (9)	0.19
pre/post change %	-1.5 (-20.5-18.4) (10)	48.3 (7.3-62.2) (9)	0.19
consultation	179.5 (163.1-259.4) (11)	207.4 (86.3-262.9) (11)	0.87
pre/consult change	-20.7 (-89.4-25.0) (10)	-24.4 (-105-67.2) (9)	0.82
pre/consult change%	-12.7 (-107.3-12.1) (11)	-20.1 (-151.0-31.7) (11)	0.82
Cortisol concentration (µg/dl):-			
pre-race	0.3 (0.2-0.6) (12)	0.3 (0.2-0.6) (11)	0.81
post-race	2.1 (1.2-2.9) (8)	2.0 (0.6-2.5) (5)	0.88
pre/post change	-1.73 (-2.1-0.83) (12)	-1.2 (-2.2- -0.14) (11)	0.66
pre/post change %	-286.7 (-876.3- -215.7) (8)	-157.1 (-681.3- -32.5) (5)	0.38
consultation	0.2 (0.1-0.4) (12)	0.2 (0.1-0.3) (11)	0.95
pre/consult change	0.08 (-0.06-0.47) (12)	0.05 (-0.2-0.5) (11)	0.81
pre/consult change%	38.1 (-32.0-73.4) (12)	23.0 (-89.3-68.7) (11)	0.95
Amylase concentration (U/ml):-			
pre-race	217.8 (114.7-255.0) (12)	125.3 (24.6-172.2) (9)	0.02
post-race	115.8 (76.9-189.7) (8)	189.9 (66.6-255.5) (7)	0.64
pre/post change	94.5 (21.6-141.4) (8)	-52.0 (-97.1-10.5) (6)	0.09
pre/post change %	45.7 (9.1-66.0) (8)	-32.8 (-56.7-42.7) (6)	0.09
consultation	155.1 (49.2-194.5) (11)	131.5 (76.8-221.7) (11)	0.77
pre/consult change	115.1 (-15.1-160.7) (11)	-6.2 (-64.0-13.8) (9)	0.05
pre/consult change%	42.9 (-8.0-78.8) (11)	-5.0 (-72.7-30.7) (9)	0.12

Values are expressed as median with interquartile range in parentheses, with the number of subjects (n) in parentheses thereafter
µg/min : micrograms per minute
U/ml : units per millilitre
µg/dl : micrograms per decilitre

There was a tendency for the immediate post-race salivary IgA concentrations to be higher in the Symptomatic group (139.4 (109.1-201.3) µg/min (n=10)) compared with the Matched Control sub-group (91.0 (83.0-109.5) µg/min (n=9), p=0.09). The remainder of the salivary IgA and salivary cortisol concentrations showed no difference between the groups.

There was a significantly higher pre-race salivary amylase concentration in the Symptomatic group (217.8 (114.7-255.0)U/ml (n=12)) compared with the Matched Control sub-group (125.3 (24.6-172.2)U/ml (n=9, p=0.02). Furthermore, the pre-, post-race change in salivary α-amylase concentration tended to be higher in the Symptomatic group (94.5 (21.6-141.4)U/ml (n=8)) when compared to the Matched Control sub-group (-52.0 (-97.1-10.5)U/ml (n=6, p=0.09). The change in α-amylase concentrations from pre-race to time of the follow-up consultation was significantly higher in the Symptomatic group (115.1 (-15.1-160.7)U/ml (n=11)) compared with the Matched Control sub-group (-6.2 (-64.0-13.8)U/ml (n=9, p=0.05).

Figure 3.4. shows that for salivary α-amylase and IgA concentrations there was no significant change over time. However, there was a time effect for salivary cortisol concentrations, with a significant increase over time from pre-race to post-race (p=0.004), and a significant decrease from post-race to follow up consultation (p<0.001).

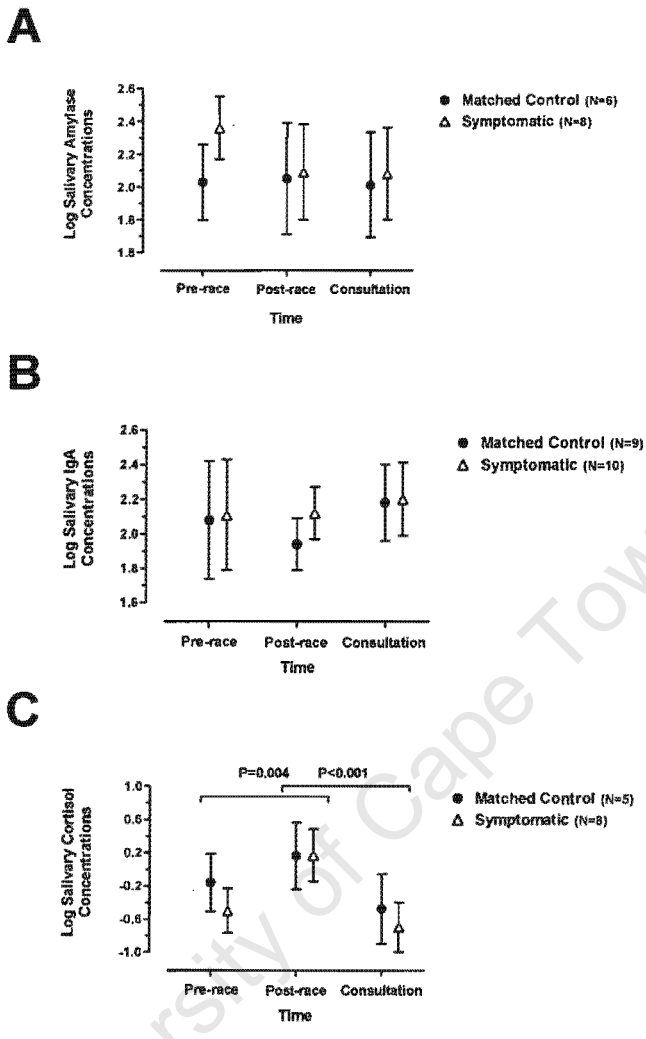

Figure 3.4.: Graph depicting (A) Salivary IgA, (B) cortisol and (C) α-amylase log-transformed data to show change in concentration over time

3.5. Discussion

In this prospective study, a cohort of triathletes was followed and those that developed URTS in the 2-week post-race period were compared to a Control group. The main aim was to determine which factors were associated with the development of post-race URTS in these triathletes. The focus was on the

following factors: (1) pre-race medical history, (2) post-race clinical assessment at the time of symptom presentation, (3) pre-post cytokine responses that were markers of the TH1 (cell-mediated immune) response and the TH2 (humoral immune) response, (4) salivary IgA (as a marker of mucosal protection), (5) salivary cortisol concentration (as a marker of the hypothalamic-pituitary-adrenocortical (HPA) axis), and (6) salivary α-amylase (as a marker of the sympatho-adrenomedullary system) (SAM).

From the outset the limitations to the present study must be acknowledged. One of the main limitations of this study is the fact that the data on RTS, training and allergy is self-reported, and is also based on recall over a period of weeks. Furthermore, the number of subjects in the cohort that developed URTS was smaller than has been previously reported. The reason for the low incidence of URTS in this group is not directly apparent. It is also important to recognise the limitation of the small sample size in this study which might affect statistical power in the present study.

Due to financial constraint, it was only possible to analyse the blood and saliva samples of these two smaller groups, and the blood and saliva samples of the larger Control group (both pre- and post-race) remained untested. It was also not possible to conduct any special tests to exclude infections as a cause of RTS in these athletes. Therefore our data have to be interpreted with these limitations in mind.

However, the strengths of the present study should also be recognised. These include; (1) the use of questionnaires that have been previously validated, (2) that except for 1 symptomatic athlete, all follow-up examinations were done by the primary researcher, (3) that there was good contact kept with the large sample group to ensure a high pick-up rate of those who developed URTS, and (4), the methodology (questionnaire survey) used did not differ from studies previously conducted in similar groups of athletes to document either URTS or allergies.

The main findings of the study were that the development of post-race URTS in the 2006 Ironman triathletes was associated with (1) a self-reported pre-race history of URTS in the 6- and 1-week periods prior to the race, (2) a higher pre-race salivary α-amylase concentration, and (3) a greater trend towards a change in pre- to post-race salivary α-amylase concentration. Furthermore, in triathletes who developed post-race URTS compared with those who remained asymptomatic , there was no evidence of: (1) up-regulation of the TH2 response, (2) down-regulation of the TH1 response, (3) changes in mucosal protection (salivary IgA) concentration, or (4) an altered response in the hypothalamic-pituitary-adrenocortical (HPA) axis response (salivary cortisol concentration). Other findings were that triathletes who developed post-race URTS tended to be a lower calibre of triathlete, and that their actual race time was slower relative to their pre-race predicted time.

It is of interest that there was an association between the prevalence of URTS in the triathletes for the period 6 weeks and 1 week prior to the race and the

development of post-race symptoms. Importantly, the general characteristics of each group showed no differences between the two groups with respect to age, gender, height and weight. Furthermore, there were no significant differences between the Symptomatic and Control groups with respect to frequency of reported general medical conditions. When comparing history of smoking, family and personal histories of allergy and asthma, there were no differences in any of these parameters between the groups. Analysis of the training history provided by the triathletes in the self-reported questionnaire showed that there was no difference between groups. The only different trend in training between the 2 groups was found in the time spent cycling in the 15 weeks before the event, with the Symptomatic group spending more time training. All other training parameters, including time spent and distances covered in each of the 3 disciplines, showed no differences.

Thus it is possible to conclude that the general profile of the triathlete who developed URTS is no different to those who did not develop any symptoms with respect to age, gender, height and weight. Furthermore, the Symptomatic group was not at greater risk for the development of URTS on the basis of being weakened due to other disease processes. The hypothesis suggesting atopy in the cause of the development of URTS is based on the premise that endurance athletes have a higher incidence of URT allergies (allergic rhinitis, sinusitis and rhinoconjunctivitis) [45], and that as there is a significant overlap in symptoms with URT infections [79], that the URTS seen after an endurance event may be, in fact, due to this allergic process. However, the present study showed that allergy was not a significant cause for the development of URTS

in the Symptomatic group. This, however, needs to be interpreted with caution due to the small sample size in this study. Increased training is associated with a higher risk of the development of URTS [32;40;41], but the findings in the present study also excluded this as a cause for the development of URTS. Therefore when looking at predisposing factors for the development of URTS after an ultra-endurance event, the only significant risk factor shown in this study was the prevalence of URTS in the triathletes for the period 6 weeks and 1 week prior to the race. This significant finding may be regarded as a risk factor in the development of post-race URTS in ultra-endurance triathletes.

A further significant finding was that there was a higher pre-race salivary α-amylase concentration measured in the Symptomatic group as compared to the Control group, although there was no significant time effect. Furthermore, the pre-race salivary α-amylase concentrations in the Symptomatic group returned to values within the Control group after the race and during the follow-up consultation. Salivary α-amylase concentrations normally increase in response to an exercise bout, probably as a result of sympathetic stimulation [136] and subsequent increased circulating catecholamine concentrations [119;136;137]. However, the α-amylase concentrations in the Symptomatic group showed the opposite, in that they were initially high and decreased post-race. This finding would suggest that there was a priming of the adrenergic system before the race in this group, as the α-amylase concentration in the saliva in response to exercise has been regarded as an indicator of adrenergic response to the stress of the bout of exercise [119], followed by a very poor response by the adrenergic system to the stress of the

Ironman event as evidenced by the decrease in salivary α-amylase concentration.

There was, however, evidence of a normal adrenergic response to the stress of the Ironman Triathlon when the salivary cortisol response is considered. Salivary cortisol concentrations are also regarded as a good indicator of the body's adrenergic response to the stress of exercise. Although salivary cortisol concentrations measured pre-, post- and at consultation showed no significant changes between the Symptomatic group and Matched control sub-group, there were changes with respect to time, thereby indicating a normal adrenergic response to ultra-endurance exercise. Thus it may be concluded that the development of URTS in the post-race period is associated with a high pre-race salivary α-amylase concentration. Although the importance of this finding is at present unknown, this appears to be a novel finding. As we are not aware of any other studies which corroborate this finding, it is clear that this relationship needs further study and clarification.

The cytokines IL-2 and IL-12 concentrations were measured before the race, after the race, and at follow-up consultation for those who developed URTS and for those who formed the Matched Control sub-group. These cytokines are markers of TH1 response and the proposed changes in their concentrations would lend insight into the changes in the TH1 response to an endurance event, as well as provide insight into a probable mechanism for the development of URTS. The results in the present study showed no changes in IL-2 concentrations over time between the 2 groups. IL-12 showed a tendency

to be lower in the symptomatic than the Matched Control sub-group at the follow up consultation, yet there was no difference seen over time. TH1 lymphocytes favour the phagocytic dependent CMI, the lack of activation thereof could render the body susceptible to infection. Smith described the cytokine response to a marathon, and reported that the overall post-marathon cytokine pattern was suggestive of a blunted TH1 response with a lack of elevation of IL-12 [53]. Although there was only a tendency for the Symptomatic group IL-12 to be lower than that of the Matched Control sub-group at follow-up, this finding is in keeping with the findings of Smith [53].

The expected change in TH2 response was however not demonstrated by the absolute concentrations of TH2 cytokines (IL-4, IL-6, Il-10).There was however a significant time effect from pre-race to post-race and from post-race to consultation of IL-6 and IL-10 concentrations. As reported in the same study mentioned previously [53], a significant increase in the markers of the TH2 response, especially IL-10 were noted. Although none of the cytokine markers for TH2 response (IL-4, IL-6, IL-10) showed any significant difference between the 2 groups when measuring absolute concentrations, the time effect analysis demonstrated evidence of up-regulation of TH2 (increased IL-4,IL-6 IL-10), with this response proposed as a mechanism for the development of URTS.

The results of the salivary IgA analysis showed a tendency for the post-race concentrations to be higher in the Symptomatic group than the asymptomatic or control groups. Although this is only a trend, this finding is not supported by

the available literature, where it has been shown that exercise results in a decrease in salivary IgA concentrations for up to 60 minutes after the cessation of the exercise bout, after which the concentrations will return to normal [118;119]. As salivary IgA is important in mucosal protection, this decrease in salivary IgA concentrations has been linked to the development of URTI in athletes [27;29;118;120]. The relatively small numbers of the sample size in the present study may have a role in explaining this discrepancy.

Analysis of the performance history provided by the triathletes in the self-reported questionnaire, showed that the Control group tended to be a better calibre of triathlete than those who developed URTS. The personal best times for an Ironman Triathlon in the previous year, and the best time for a 10km run over the 15 weeks before the event, showed a tendency in the Control group to be faster than the Symptomatic group that developed URTS. The Matched Control sub-group was significantly faster over that same 10km than the Symptomatic group. In each of the sprint triathlons, and in the personal best times for a 10km run, 21.1km run, and sprint triathlon over the last 12 months, the Matched Control sub-group tended to have faster times than the Symptomatic group. The Symptomatic group predicted a faster swim than the control group, although the Matched Control sub-group performed better relative to predicted times in the swim than those who developed URTS. Furthermore, overall the controls performed better in being closer to their predicted times than the Symptomatic group who were slower relative to their predictions.

These findings can be interpreted that the Control group of triathletes tended to of a better calibre than the group who developed symptoms. Simply put, as a group they were faster than the group who developed URTS. Peters and Bateman (1983) [14] found that whilst URTS was twice as high in ultra-distance athletes in the first 10-14 days following an endurance race, when compared with suitable sedentary controls followed up in the same time period, the incidence of URTS was higher among the faster runners [50]. Based on this finding, one would have expected the Symptomatic group to have been the faster group. However, the findings of prevalence of URTS in the triathletes for the period 6-weeks and 1-week prior to the race and the development of post-race symptoms (as discussed earlier), may explain why the Symptomatic group, while expected to perform better according to previous research [50], actually performed relatively worse than the Control group relative to predicted times.

In conclusion, the main findings of this study are:

1. The triathletes who did not develop URT symptoms in the 2-weeks post-race period tended to be a better calibre of triathlete than those that developed symptoms
2. The triathletes who were symptomatic had a significantly higher incidence of pre-race URTS in both the 6- and 1-week periods before the race, with no other predisposing factors
3. The Symptomatic group had a larger change in salivary α-amylase concentration between pre-race levels, and both the post-race and consultation levels, yet there was no significant time effect demonstrated

4. Salivary cortisol concentrations showed a significant change over time, thereby demonstrating a normal adrenergic response to the Ironman event

Chapter 4

Summary and conclusion

A prospective cohort study was undertaken at the 2006 South African Ironman Triathlon held in Port Elizabeth, South Africa to: (1) determine the incidence of post-race URTS in triathletes competing in an Ironman triathlon; (2) identify the clinical and immunological factors that are associated with the development of post-race URTS in these triathletes. Of the 1136 registered entrants, 99 were recruited as subjects for the study, 14 of these either not finishing or lost to post-race follow-up. The remaining 85 were followed over the 14-day period immediately after the race and monitored for the development of URTS. Of this cohort, 12 developed URTS, and they were compared to a closely matched subgroup of controls.

The results of this comparison showed that there was a strong association between pre-race URTS in the 1-and 6-week periods before the event, and the development of URTS in the 14-day post-race period. Furthermore, there was a strong association between pre-race URTS and a high pre-race salivary α-amylase concentration, with those athletes who developed URTS, showing a greater change in salivary α-amylase concentration from pre- to post-race and consultation, suggesting that there was a priming of the adrenergic system before the race in this group, followed by a very poor response by the adrenergic system to the stress of the Ironman event. However, the salivary

cortisol concentrations, also a marker of adrenergic response to stress, showed that there was, in fact, an appropriate response to the stress of the Ironman Triathlon

A further interesting finding in the present study was that the symptomatic group tended to be a lower calibre triathlete and their performance in the race relative to their predicted time for the event was slower than that of the Control group. This phenomenon may be related to the attenuation of sympathetic response in the Symptomatic group.

In summary, the clinical implication of this study is that the sports physician should be aware that triathletes who develop URTS up to 6 weeks prior to an event such as the Ironman Triathlon, run a significantly higher risk of developing further URTS in the 14-day post-race period. Furthermore, these triathletes will probably perform worse than their predicted times.

Finally, it is clear that there needs to be further research conducted in this area of Sports Medicine as there remains a lack of a definitive causative factor in the development of URTS.

References

1. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ.* 2006;**174**:801-9.
2. Karacabey K. Effect of regular exercise on health and disease. *Neuro.Endocrinol.Lett.* 2005;**26**:617-23.
3. Kohl HW, III. Physical activity and cardiovascular disease: evidence for a dose response. *Med Sci Sports Exerc.* 2001;**33**:S472-S483.
4. Pescatello LS. Exercise and hypertension: recent advances in exercise prescription. *Curr.Hypertens.Rep.* 2005;**7**:281-6.
5. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc* 2004;**36**:533-53.
6. Donnelly JE, Smith B, Jacobsen DJ, Kirk E, Dubose K, Hyder M *et al.* The role of exercise for weight loss and maintenance. *Best.Pract.Res.Clin Gastroenterol.* 2004;**18**:1009-29.
7. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl.Physiol* 2005;**99**:1205-13.
8. Lichaba, M. Upper Respiratory Tract Symptoms and Allergies in Ironman Triathletes. 2006. Unpublished University of Cape Town MPhil (Sports Medicine) Dissertation.
9. Dallam GM, Jonas S, Miller TK. Medical considerations in triathlon competition: recommendations for triathlon organisers, competitors and coaches. *Sports Med.* 2005;**35**:143-61.

10. Hiller WD, O'Toole ML, Fortess EE, Laird RH, Imbert PC, Sisk TD. Medical and physiological considerations in triathlons. *Am.J.Sports Med.* 1987;**15**:164-7.

11. Laird RH. Medical care at ultraendurance triathlons. *Med Sci Sports Exerc* 1989;**21**:S222-S225.

12. Mayers L,.Noakes TD. A guide to treating Ironman triathletes at the finishing line. *Phys Sports Med* 2000;**28**:35-50.

13. O'Toole ML, Massimino FA, Douglas W, Hiller WD, Laird RH. Medical Considerations in Triathletes:The 1984 Hawaiian Ironman Triathlon. *Annals of Sports Medicine* 1987;**3**:121-3.

14. Peters EM,.Bateman ED. Ultramarathon running and upper respiratory tract infections. An epidemiological survey. *S.Afr.Med J.* 1983;**64**:582-4.

15. Sulzer NU, Schwellnus MP, Noakes TD. Serum electrolytes in Ironman triathletes with exercise-associated muscle cramping. *Med Sci Sports Exerc* 2005;**37**:1081-5.

16. Laird RH. Medical Complications During the Ironman Triahlon World Championship 1981-1984. *Annals of Sports Medicine* 1987;**3**:113-6.

17. Sharwood KA, Collins M, Goedecke JH, Wilson G, Noakes TD. Weight changes, medical complications, and performance during an Ironman triathlon. *Br.J Sports Med* 2004;**38**:718-24.

18. Friman G,.Wesslen L. Special feature for the Olympics: effects of exercise on the immune system: infections and exercise in high-performance athletes. *Immunol.Cell Biol.* 2000;**78**:510-22.

19. Peters EM, Goetzsche JM, Grobbelaar B, Noakes TD. Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners. *Am.J.Clin.Nutr.* 1993;**57**:170-4.

20. Nieman DC, Nehlsen-Cannarella SL, Markoff PA, Balk-Lamberton AJ, Yang H, Chritton DB *et al.* The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. *Int.J.Sports Med.* 1990;**11**:467-73.

21. Schumacher YO, Pottgiesser T, Koenig D. The risk of upper respiratory tract infections (URTI) in athletes. *International Sportmed Journal* 2003;**4**:1-12.

22. Rohde T, MacLean DA, Hartkopp A, Pedersen BK. The immune system and serum glutamine during a triathlon. *Eur.J Appl.Physiol Occup.Physiol* 1996;**74**:428-34.

23. Shinkai S, Kurokawa Y, Hino S, Hirose M, Torii J, Watanabe S *et al.* Triathlon competition induced a transient immunosuppressive change in the peripheral blood of athletes. *J.Sports Med.Phys.Fitness* 1993;**33**:70-8.

24. Steerenberg PA, van Asperen IA, van Nieuw AA, Biewenga A, Mol D, Medema GJ. Salivary levels of immunoglobulin A in triathletes. *Eur.J.Oral Sci.* 1997;**105**:305-9.

25. Shephard RJ. Special feature for the Olympics: effects of exercise on the immune system: overview of the epidemiology of exercise immunology. *Immunol.Cell Biol.* 2000;**78**:485-95.

26. Mackinnon LT. Immunity in athletes. *Int.J.Sports Med* 1997;**18 Suppl 1**:S62-S68.

27. Libicz S, Mercier B, Bigou N, Le Gallais D, Castex F. Salivary IgA response of triathletes participating in the French Iron Tour. *Int.J.Sports Med* 2006;**27**:389-94.

28. Spence L, Brown WJ, Pyne DB, Nissen MD, Sloots TP, McCormack JG *et al.* Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. *Med Sci.Sports Exerc.* 2007;**39**:577-86.

29. Mackinnon LT,.Jenkins DG. Decreased salivary immunoglobulins after intense interval exercise before and after training. *Med Sci.Sports Exerc.* 1993;**25**:678-83.

30. Schwellnus M P, Kiessig M, Derman W, Noakes T D. Fusafungine reduces symptoms of Upper Respiratory Tract Infections (URTI) in runners after a 56km race. *Med Sci Sports Exerc* 1997;**29**:S296.

31. Hosey RG,.Rodenberg RE. Training room management of medical conditions: infectious diseases. *Clin.Sports Med.* 2005;**24**:477-506, vii.

32. Heath GW, Ford ES, Craven TE, Macera CA, Jackson KL, Pate RR. Exercise and the incidence of upper respiratory tract infections. *Med.Sci.Sports Exerc.* 1991;**23**:152-7.

33. Peters EM, Anderson R, Nieman DC, Fickl H, Jogessar V. Vitamin C supplementation attenuates the increases in circulating cortisol, adrenaline and anti-inflammatory polypeptides following ultramarathon running. *Int.J Sports Med.* 2001;**22**:537-43.

34. Peters EM, Anderson R, Theron AJ. Attenuation of increase in circulating cortisol and enhancement of the acute phase protein

response in vitamin C-supplemented ultramarathoners. *Int.J Sports Med.* 2001;**22**:120-6.

35. Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Henson DA, Shannon M, Hjertman JM *et al.* Immune function in female elite rowers and non-athletes. *Br.J.Sports Med.* 2000;**34**:181-7.
36. Gleeson M, McDonald WA, Pyne DB, Clancy RL, Cripps AW, Francis JL *et al.* Immune status and respiratory illness for elite swimmers during a 12- week training cycle. *Int.J.Sports Med.* 2000;**21**:302-7.
37. Gleeson M, Pyne DB, Austin JP, Lynn FJ, Clancy RL, McDonald WA *et al.* Epstein-Barr virus reactivation and upper-respiratory illness in elite swimmers. *Med Sci Sports Exerc* 2002;**34**:411-7.
38. Berglund B,.Hemmingsson P. Infectious disease in the elite cross-country skiers: a one-year incidence study. *Clinical Sports Medicine* 1990;**2**:19-23.
39. Nieman DC, Johanssen L M, Lee J W. Infectious episodes in runners before and after a roadrace. *J Sports Med Phys.Fitness* 1989;**29**:289-96.
40. Linde F. Running and upper respiratory tract infections. *Scan J Sports Sci* 1987;**9**:21-3.
41. Konig D, Grathwohl D, Weinstock C, Northoff H, Berg A. Upper respiratory tract infection in athletes: influence of lifestyle, type of sport, training effort, and immunostimulant intake. *Exerc.Immunol.Rev.* 2000;**6**:102-20.
42. Nieman DC. Exercise immunology: nutritional countermeasures. *Can.J Appl Physiol* 2001;**26 Suppl**:S45-S55.

43. Calabrese LH,.Nieman DC. Exercise, immunity, and infection. *J.Am.Osteopath.Assoc.* 1996;**96**:166-76.

44. Klentrou P, Cieslak T, MacNeil M, Vintinner A, Plyley M. Effect of moderate exercise on salivary immunoglobulin A and infection risk in humans. *Eur.J Appl Physiol* 2002;**87**:153-8.

45. Maiolo C, Fuso L, Todaro A, Anatra F, Boniello V, Basso S *et al.* Prevalence of asthma and atopy in Italian Olympic athletes. *Int.J Sports Med* 2004;**25**:139-44.

46. Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi M. Wheezing requiring hospitalization in early childhood: predictive factors for asthma in a six-year follow-up. *Pediatr.Allergy Immunol.* 2002;**13**:418-25.

47. Matthews CE, Ockene IS, Freedson PS, Rosal MC, Merriam PA, Hebert JR. Moderate to vigorous physical activity and risk of upper-respiratory tract infection. *Med Sci Sports Exerc* 2002;**34**:1242-8.

48. Jedrychowski W, Maugeri U, Flak E, Mroz E, Bianchi I. Cohort study on low physical activity level and recurrent acute respiratory infections in schoolchildren. *Cent.Eur.J Public Health* 2001;**9**:126-9.

49. Nieman DC. Upper respiratory tract infections and exercise. *Thorax* 1995;**50**:1229-31.

50. Hemila H. The effect of nutrition on exercise-induced immunodepression. *Nutr.Rev.* 2006;**64**:476-7.

51. Schouten WJ, Verschuur R, Kemper HC. Physical activity and upper respiratory tract infections in a normal population of young men and

women: the Amsterdam Growth and Health Study. *Int.J.Sports Med.* 1988;**9**:451-5.

52. Gleeson M. Immune system adaptation in elite athletes. *Curr.Opin.Clin.Nutr.Metab Care* 2006;**9**:659-65.
53. Lakier SL. Overtraining, excessive exercise, and altered immunity: is this a T helper-1 versus T helper-2 lymphocyte response? *Sports Med* 2003;**33**:347-64.
54. Malm C. Susceptibility to infections in elite athletes: the S-curve. *Scand.J.Med Sci.Sports* 2006;**16**:4-6.
55. Nieman DC. Marathon training and immune function. *Sports Med* 2007;**37**:412-5.
56. Nieman DC. Special feature for the Olympics: effects of exercise on the immune system: exercise effects on systemic immunity. *Immunol.Cell Biol.* 2000;**78**:496-501.
57. Friman G. Effect of acute infectious disease on human isometric muscle endurance. *Ups.J Med Sci* 1978;**83**:105-8.
58. Nieman DC,.Pedersen BK. Exercise and immune function. Recent developments. *Sports Med.* 1999;**27**:73-80.
59. Nieman DC, Peters EM, Henson DA, Nevines EI, Thompson MM. Influence of vitamin C supplementation on cytokine changes following an ultramarathon. *J Interferon Cytokine Res.* 2000;**20**:1029-35.
60. Peters-Futre EM. Vitamin C, neutrophil function, and upper respiratory tract infection risk in distance runners: the missing link. *Exerc.Immunol.Rev.* 1997;**3**:32-52.

61. Krause R, Patruta S, Daxbock F, Fladerer P, Biegelmayer C, Wenisch C. Effect of vitamin C on neutrophil function after high-intensity exercise. *Eur.J Clin.Invest* 2001;**31**:258-63.

62. Malm C. Exercise immunology: the current state of man and mouse. *Sports Med* 2004;**34**:555-66.

63. Mackinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. *Immunol.Cell Biol.* 2000;**78**:502-9.

64. Mackinnon LT. Chronic exercise training effects on immune function. *Med.Sci.Sports Exerc.* 2000;**32**:S369-S376.

65. Gleeson M, Pyne DB, Callister R. The missing links in exercise effects on mucosal immunity. *Exerc Immunol.Rev* 2004;**10**:107-28.

66. Jeurissen A, Bossuyt X, Ceuppens JL, Hespel P. [The effects of physical exercise on the immune system]. *Ned.Tijdschr.Geneeskd.* 2003;**147**:1347-51.

67. Gleeson M. Mucosal immune responses and risk of respiratory illness in elite athletes. *Exerc Immunol.Rev* 2000;**6**:5-42.

68. Gleeson M. Special feature for the Olympics: effects of exercise on the immune system. Overview: exercise immunology. *Immunol.Cell Biol.* 2000;**78**:483-4.

69. Novas AM, Rowbottom DG, Jenkins DG. Tennis, incidence of URTI and salivary IgA. *Int J Sports Med* 2003;**24**:223-9.

70. Tiollier E, Gomez-Merino D, Burnat P, Jouanin JC, Bourrilhon C, Filaire E *et al.* Intense training: mucosal immunity and incidence of respiratory infections. *Eur.J Appl Physiol* 2005;**93**:421-8.

71. Ciloglu F. The effect of exercise on salivary IgA levels and the incidence of upper respiratory tract infections in postmenopausal women. *Kulak.Burun.Bogaz.Ihtis.Derg.* 2005;**15**:112-6.

72. Pedersen BK. Special feature for the Olympics: effects of exercise on the immune system: exercise and cytokines. *Immunol.Cell Biol.* 2000;**78**:532-5.

73. Dressendorfer RH, Petersen SR, Moss Lovshin SE, Hannon JL, Lee SF, Bell GJ. Performance enhancement with maintenance of resting immune status after intensified cycle training. *Clin J Sport Med* 2002;**12**:301-7.

74. Krieger JW, Crowe M, Blank SE. Chronic glutamine supplementation increases nasal but not salivary IgA during 9 days of interval training. *J Appl Physiol* 2004;**97**:585-91.

75. Peters EM. Nutritional aspects in ultra-endurance exercise. *Curr.Opin.Clin.Nutr.Metab Care* 2003;**6**:427-34.

76. Venkatraman JT,.Pendergast DR. Effect of dietary intake on immune function in athletes. *Sports Med* 2002;**32**:323-37.

77. Nieman DC,.Bishop NC. Nutritional strategies to counter stress to the immune system in athletes, with special reference to football. *J Sports Sci* 2006;**24**:763-72.

78. Komarow HD,.Postolache TT. Seasonal allergy and seasonal decrements in athletic performance. *Clin.Sports Med.* 2005;**24**:e35-50, xiii.

79. MacKnight JM,.Mistry DJ. Allergic disorders in the athlete. *Clin.Sports Med.* 2005;**24**:507-viii.

80. Helenius IJ, Tikkanen HO, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol.* 1998;**101**:646-52.

81. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br.J Sports Med* 1998;**32**:125-9.

82. Katelaris CH, Carrozzi FM, Burke TV. Allergic rhinoconjunctivitis in elite athletes: optimal management for quality of life and performance. *Sports Med* 2003;**33**:401-6.

83. Alaranta A, Alaranta H, Heliovaara M, Alha P, Palmu P, Helenius I. Allergic rhinitis and pharmacological management in elite athletes. *Med Sci Sports Exerc* 2005;**37**:707-11.

84. Katelaris CH. Atmospheric emissions and the allergic athlete. *International Sportmed Journal* 2000;**1**:1-7.

85. Bonsignore MR, Morici G, Vignola AM, Riccobono L, Bonanno A, Profita M *et al.* Increased airway inflammatory cells in endurance athletes: what do they mean? *Clin Exp.Allergy* 2003;**33**:14-21.

86. Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjermer L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir.Crit Care Med* 2000;**161**:2086-91.

87. Viljoen, D. The effect of Upper Respiratory Tract Illness on exercise performance. 1999. Unpublished University of Cape Town MPhil (Sports Medicine Dissertation.

88. Leonard EG. Viral myocarditis. *Pediatr.Infect.Dis.J* 2004;**23**:665-6.

89. Shephard RJ,.Shek PN. Infectious diseases in athletes: new interest for an old problem. *J Sports Med Phys Fitness* 1994;**34**:11-22.

90. Roberts JA. Viral illnesses and sports performance. *Sports Med.* 1986;**3**:298-303.

91. Katelaris CH, Carrozzi FM, Burke TV, Byth K. A springtime olympics demands special consideration for allergic athletes. *J Allergy Clin Immunol.* 2000;**106**:260-6.

92. Katelaris CH. Allergic rhinoconjunctivitis--an overview. *Acta Ophthalmol.Scand Suppl* 2000;66-8.

93. Guyton A, Hall JE. *Textbook of medical physiology.* 10th ed. Philadelphia: Saunders, 2001, pp.402-412.

94. Elenkov IJ,.Chrousos GP. Stress Hormones, Th1/Th2 patterns, Pro/Anti-inflammatory Cytokines and Susceptibility to Disease. *Trends Endocrinol.Metab* 1999;**10**:359-68.

95. Oberholzer A, Oberholzer C, Moldawer LL. Cytokine signaling--regulation of the immune response in normal and critically ill states. *Crit Care Med.* 2000;**28**:N3-12.

96. Ploegh HL. Viral strategies of immune evasion. *Science* 1998;**280**:248-53.

97. Schaffer M,.Barbul A. Lymphocyte function in wound healing and following injury. *Br.J.Surg.* 1998;**85**:444-60.

98. Moldoveanu AI, Shephard RJ, Shek PN. The cytokine response to physical activity and training. *Sports Med* 2001;**31**:115-44.

99. Shephard RJ, Rhind S, Shek PN. The impact of exercise on the immune system: NK cells, interleukins 1 and 2, and related responses. *Exerc.Sport Sci.Rev.* 1995;**23**:215-41.

100. Morel PA,.Oriss TB. Crossregulation between Th1 and Th2 cells. *Crit Rev.Immunol.* 1998;**18**:275-303.

101. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J.Immunol.* 1986;**136**:2348-57.

102. Elenkov IJ, Chrousos GP, Wilder RL. Neuroendocrine regulation of IL-12 and TNF-alpha/IL-10 balance. Clinical implications. *Ann.N.Y.Acad.Sci.* 2000;**917**:94-105.

103. Faist E, Schinkel C, Zimmer S. Update on the mechanisms of immune suppression of injury and immune modulation. *World J.Surg.* 1996;**20**:454-9.

104. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. *Pharmacol.Rev.* 2000;**52**:595-638.

105. Romagnani S. T-cell subsets (Th1 versus Th2). *Ann.Allergy Asthma Immunol.* 2000;**85**:9-18.

106. Shephard RJ, Rhind S, Shek PN. Exercise and training: influences on cytotoxicity, interleukin-1, interleukin-2 and receptor structures. *Int.J.Sports Med* 1994;**15 Suppl 3**:S154-S166.

107. Chicharro JL, Lucia A, Perez M, Vaquero AF, Urena R. Saliva composition and exercise. *Sports Med* 1998;**26**:17-27.

108. Baum BJ. Neurotransmitter control of secretion. *J.Dent.Res.* 1987;**66 Spec No**:628-32.

109. Anderson LC, Garrett JR, Johnson DA, Kauffman DL, Keller PJ, Thulin A. Influence of circulating catecholamines on protein secretion into rat parotid saliva during parasympathetic stimulation. *J.Physiol* 1984;**352**:163-71.

110. Asking B,.Emmelin N. Amylase in parotid saliva of rats after sympathetic nervous decentralization. *Arch.Oral Biol.* 1985;**30**:337-9.

111. Pilardeau P, Richalet JP, Bouissou P, Vaysse J, Larmignat P, Boom A. Saliva flow and composition in humans exposed to acute altitude hypoxia. *Eur.J.Appl.Physiol Occup.Physiol* 1990;**59**:450-3.

112. Speirs RL, Herring J, Cooper WD, Hardy CC, Hind CR. The influence of sympathetic activity and isoprenaline on the secretion of amylase from the human parotid gland. *Arch.Oral Biol.* 1974;**19**:747-52.

113. Mackinnon LT, Chick TW, van As A, Tomasi TB. The effect of exercise on secretory and natural immunity. *Adv.Exp.Med.Biol.* 1987;**216A**:869-76.

114. Tomasi TB, Trudeau FB, Czerwinski D, Erredge S. Immune parameters in athletes before and after strenuous exercise. *J.Clin.Immunol.* 1982;**2**:173-8.

115. Brandtzaeg P, Jahnsen FL, Farstad IN. Immune functions and immunopathology of the mucosa of the upper respiratory pathways. *Acta Otolaryngol.* 1996;**116**:149-59.

116. Brandtzaeg P, Baekkevold ES, Farstad IN, Jahnsen FL, Johansen FE, Nilsen EM *et al.* Regional specialization in the mucosal immune

system: what happens in the microcompartments? *Immunol.Today* 1999;**20**:141-51.

117. Kaetzel CS, Robinson JK, Chintalacharuvu KR, Vaerman JP, Lamm ME. The polymeric immunoglobulin receptor (secretory component) mediates transport of immune complexes across epithelial cells: a local defense function for IgA. *Proc.Natl.Acad.Sci.U.S.A* 1991;**88**:8796-800.

118. Gleeson M,.Pyne DB. Special feature for the Olympics: effects of exercise on the immune system: exercise effects on mucosal immunity. *Immunol.Cell Biol.* 2000;**78**:536-44.

119. Calvo F, Chicharro JL, Bandres F, Lucia A, Perez M, Alvarez J *et al.* Anaerobic threshold determination with analysis of salivary amylase. *Can.J.Appl.Physiol* 1997;**22**:553-61.

120. Mackinnon LT, Ginn E, Seymour GJ. Decreased salivary immunoglobulin A secretion rate after intense interval exercise in elite kayakers. *Eur.J.Appl.Physiol Occup.Physiol* 1993;**67**:180-4.

121. Mackinnon LT,.Hooper S. Mucosal (secretory) immune system responses to exercise of varying intensity and during overtraining. *Int.J.Sports Med.* 1994;**15 Suppl 3**:S179-S183.

122. McDowell SL, Chaloa K, Housh TJ, Tharp GD, Johnson GO. The effect of exercise intensity and duration on salivary immunoglobulin A. *Eur.J.Appl.Physiol Occup.Physiol* 1991;**63**:108-11.

123. Sari-Sarraf V, Reilly T, Doran DA. Salivary IgA response to intermittent and continuous exercise. *Int.J.Sports Med* 2006;**27**:849-55.

124. Koch AJ, Wherry AD, Petersen MC, Johnson JC, Stuart MK, Sexton WL. Salivary immunoglobulin A response to a collegiate rugby game. *J.Strength.Cond.Res.* 2007;**21**:86-90.

125. Nieman DC, Henson DA, Fagoaga OR, Utter AC, Vinci DM, Davis JM *et al.* Change in salivary IgA following a competitive marathon race. *Int.J.Sports Med* 2002;**23**:69-75.

126. Takai N, Yamaguchi M, Aragaki T, Eto K, Uchihashi K, Nishikawa Y. Effect of psychological stress on the salivary cortisol and amylase levels in healthy young adults. *Arch.Oral Biol.* 2004;**49**:963-8.

127. Kirschbaum C,.Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. *Psychoneuroendocrinology* 1994;**19**:313-33.

128. Stupnicki R,.Obminski Z. Glucocorticoid response to exercise as measured by serum and salivary cortisol. *Eur.J.Appl.Physiol Occup.Physiol* 1992;**65**:546-9.

129. Vining RF, McGinley RA, Maksvytis JJ, Ho KY. Salivary cortisol: a better measure of adrenal cortical function than serum cortisol. *Ann.Clin.Biochem.* 1983;**20 (Pt 6)**:329-35.

130. Hiramatsu R. Direct assay of cortisol in human saliva by solid phase radioimmunoassay and its clinical applications. *Clin.Chim.Acta* 1981;**117**:239-49.

131. Cook NJ, Ng A, Read GF, Harris B, Riad-Fahmy D. Salivary cortisol for monitoring adrenal activity during marathon runs. *Horm.Res.* 1987;**25**:18-23.

132. Vining RF, McGinley RA, Symons RG. Hormones in saliva: mode of entry and consequent implications for clinical interpretation. *Clin.Chem.* 1983;**29**:1752-6.

133. del Corral P, Mahon AD, Duncan GE, Howe CA, Craig BW. The effect of exercise on serum and salivary cortisol in male children. *Med.Sci.Sports Exerc.* 1994;**26**:1297-301.

134. Farrell PA, Garthwaite TL, Gustafson AB. Plasma adrenocorticotropin and cortisol responses to submaximal and exhaustive exercise. *J.Appl.Physiol* 1983;**55**:1441-4.

135. Few JD, Cashmore GC, Turton G. Adrenocortical response to one-leg and two-leg exercise on a bicycle ergometer. *Eur.J.Appl.Physiol Occup.Physiol* 1980;**44**:167-74.

136. Dawes C. The effects of exercise on protein and electrolyte secretion in parotid saliva. *J.Physiol* 1981;**320**:139-48.

137. Gilman S, Thornton R, Miller D, Biersner R. Effects of exercise stress on parotid gland secretion. *Horm.Metab Res.* 1979;**11**:454.

138. Walsh NP, Blannin AK, Clark AM, Cook L, Robson PJ, Gleeson M. The effects of high-intensity intermittent exercise on saliva IgA, total protein and alpha-amylase. *J.Sports Sci.* 1999;**17**:129-34.

139. Nater UM, La Marca R, Florin L, Moses A, Langhans W, Koller MM *et al.* Stress-induced changes in human salivary alpha-amylase activity -- associations with adrenergic activity. *Psychoneuroendocrinology* 2006;**31**:49-58.

140. Yamaguchi M, Deguchi M, Miyazaki Y. The effects of exercise in forest and urban environments on sympathetic nervous activity of normal young adults. *J.Int.Med Res.* 2006;**34**:152-9.

141. Sharwood K, Collins M, Goedecke J, Wilson G, Noakes T. Weight changes, sodium levels, and performance in the South African Ironman Triathlon. *Clin J Sport Med* 2002;**12**:391-9.

Appendix 1: Website Information

Welcome to the Spec-Savers Ironman South Africa Research program - 2006

Dear Tri-athlete

We have the privilege to inform you that scientific and medical research at the Port Elizabeth Spec-Savers Ironman South Africa triathlon has been planned in collaboration with the UCT/MRC Research Unit for Exercise Science and Sports Medicine based at the Sports Science Institute of South Africa, and Tswane University in Pretoria. This will provide a unique opportunity for a research programme to address important medical and physiological problems that are associated with participation in the Spec-Savers Ironman South Africa triathlon.

The research study will concentrate on the following 6 main components that will ultimately assist you to **improve your performance** and **improve the standard of your medical treatment** at future triathlons and other endurance events:

- Management of the collapsed tri-athlete
- Causes and treatment of Exercise Associated Muscle Cramping
- Preventing post-exercise decreases in immune function and upper respiratory tract (URT) symptoms
- Genetic basis for performance and physiological responses during an Ironman Triathlon
- Identifying causes of chronic Achilles tendon injuries in tri-athletes
- Identifying the relationship between training history, perception of effort (RPE) during the race and the subsequent recovery after the race.

How can I volunteer to participate in the research study?

As a participant in the Port Elizabeth Spec-Savers Ironman South Africa triathlon, you will be given the unique opportunity to participate in this research effort. Please understand that your participation is entirely voluntary. Please read through the details of the following six components of the study. You will be given the opportunity to participate in any number, or all the components of the study. The details of each component are summarized below and a detailed explanation of each component can be downloaded as a PDF file. If you wish to participate in the study, please **download** the information related to each component of the study (PDF file), and read through it carefully. Please bring the INFORMED CONSENT FORM of the study with you to Port Elizabeth, and then visit our RESEARCH area at the registration venue. Here we will discuss any questions you may have, and then sign the INFORMED CONSENT FORM with you. In addition please download and complete the QUESTIONNAIRES. We will let you know once the questionnaires are available. Printed copies of all the documentation will also be available at the REGISTRATION research area.

Will my participation in the research affect my preparation, race participation, or recovery after the race?

All the components of this study have been carefully designed NOT to 1) interfere with your preparation or participation in the Ironman, 2) affect your performance on race day, and 3) your recovery after the event. All the tests are not painful and non-invasive (apart from a small blood sample taken at registration and after the race).

Will I have access to the results of the study?

Once the study results are known, you will be able to access a summary of the findings of the study on the website and you can also request, this be sent to you by email. You will also be given the opportunity to attend a feedback meeting where the results of the study will be discussed. The results will only be that of the whole group, and no individual results will be made public.

Who can I contact for more information?

In the next few weeks, please feel free to contact members of the research team should you have any questions related to the study (or any component of the study). Contact details of the research team are as follows: ironman@sports.uct.ac.za or (021) 650 4572.

The following documents can be downloaded:-

1. Subject information sheets (PDF File)
2. Consent form (PDF File)
3. Questionnaires (MS Word document)
4. Summary of the study (This web page) (PDF File)
5. Adobe Acrobat Reader

Summary of each component of the research study:-

1. Management of the collapsed triathlete

The precise causes and best treatment of collapsed endurance athletes is still widely debated. We would like to see if collapsed athletes have a greater incidence of serum sodium and plasma volume abnormalities than athletes who do not collapse at the end of the race. Accordingly, if these abnormalities do exist in collapsed athletes, are intravenous fluids superior to oral fluids in the treatment and restoration of sodium and plasma volume levels? Close monitoring of sodium levels, heart rate and blood pressure and time to discharge will help our team answer these questions.

2. Exercise associated muscle cramping

The precise causes of Exercise Associated Muscle Cramping (EAMC) are still widely debated. Contrary to popular belief, heat, dehydration and electrolyte (salt) abnormalities may NOT be the cause of EAMC. In this component of the study we would like to measure these changes in tri-athletes who cramp, and then follow what happens once we treat these athletes. We also want to measure the muscle "twitchiness" during the recovery period, once again trying to see oif these

related to changes in serum electrolyte concentrations (salt). Tri-athletes who are prone to EAMC may well be interested in this component of the study.

3. **Post-exercise upper respiratory tract (URT) symptoms**

It is well documented that intense training, as well as participation in a prolonged strenuous endurance evenst (such as the Ironman) can cause changes in the immune system, and may increase the risk of infections (mainly of the upper respiratory tract). In this component of the study we want to examine the immune changes, as well as find out what causes the upper respiratory tract symptoms in endurance athletes after participation in the Ironman. Triathletes that are prone to developing symptoms such as sore throaot, runny or blocked nose or cough after a race may well be specifically interested in participating in this component of the study.

4. **Genetic basis for performance and physiological responses during an Ironman Triathlon**

Athletic ability is partly determined by an intervals genetic make-up. Various gene (DNA material) have been shown to be associated with endurance performance, including the South African Ironman Triathlons. In addition it has also been suggested that the inter-individual physiological responses, such as blood salt and water imbalance, as well as the development of tendon overuse injuries, during endurance activities is partially determined by ones genes. The aim of this component of the study is to identify genes associated with performance and susceptibility to salt and water imbalances and indicators of underlying tendon pathology during the Ironman Triathlon. Volunteers for this component of the study will be asked to complete a questionnaire. At registration they will be asked to donate a small blood sample from which your genetic material (DNA) will be extracted and your blood salt levels measured. You will also be weighed before the swim and again immediately after the race. A second blood sample will also be taken after the measure to measure your blood salt levels. Some volunteers will also have there Achilles tendons scanned at registration.

5. **Chronic Achilles tendon injuries in tri-athletes**

Chronic Achilles tendon injuries are common in athletes participating in weight-bearing sports. It is well established that repetitive forces that are applied to the Achilles tendon (such as during running) may cause microscopic damage to the tendon. In the initial phases this may not cause any symptoms (pain or swelling). However, these changes can be observed using a technique known as soft tissue diagnostic ultrasound (non painful scan of the tendon). In this component of the study we wish to assess the changes in the Achilles tendon before and then after (immediately and 6 weeks later) the Ironman. In particular we wish to find out what damage (if any) takes place in the tendon as a result of the race, and how does this recover after 6 weeks. The findings of this study will also be linked to the genetic basis component (described in 4 above). Here we will be able to determine if your genetic make up determines how your tendons responds to a race such as the Ironman.

6. **The relationship between training history, perception of effort during the race and the subsequent recovery after the race.**

The relationship between training history, perception of effort during the race and the subsequent recovery after the race is poorly understood. Knowing more about this relationship is important as it will have practical implications for the preparation for the race and minimise any health risks associated with too much physical stress which may occur after the race. Volunteers for this study will be asked to complete a short questionnaire on their training habits in preparation for the Ironman. During the race subjects will be asked to shout out a "perception of effort" score at they go past one of the 8 stations along the route. A researcher at the station will record the race number and the score. Volunteers will be sent emails on a daily basis for a week after the race with a short questionnaire on their recovery. Thereafter, they will be sent an email on a weekly basis for 12 weeks. Volunteers living near a big centre will be asked to donate a small blood sample at 1, 3, 5, 7 and 9 days after the race for the measurement of creatine kinase, a marker of muscle damage (however, blood donations are not essential for entry into the study)

If I decide to participate in the research study, what will be required of me?

The following table summarises the details of your participation in the study:-

	Details of Your Participation in the Study
Before Race	1. Download information sheets, questionnaires and consent forms from web page 2. Complete questionnaires using Microsoft Word 3. E-mail completed questionnaires to researchers at ironman@sports.uct.ac.za
At Registration	1. Hand in and sign the informed consent forms 2. Donate a sample of blood Ultrasound scan of both Achilles tendons in some athletes (Achilles Tendon component - No 5) Donate a saliva sample and have a throat swab (URT component - No 3)
Before Swim (Race Day)	1. Have yourself weighed near the start of the swim before donning your wetsuit in your costume
During Race	1. Shout out a "perception of effort" score at they go past one of the 8 stations along the route (RPE component - No 6)

Immediately After Race (Medical Tent)	1. Have yourself weighed in your running gear, without shoes, at the medical tent 2. Donate a sample of blood Ultrasound scan of both Achilles tendons in those athletes who had a scan during registration (Achilles Tendon component - No 5) Donate saliva samples and have throat swabs (URT component - No 3) Treatment of athletes with cramps and testing of unaffected volunteers (cramps component- No 2) Treatment of the collapsed athletes (collapsed athlete component - No 1)
Continuing Follow-up	**At 6 Weeks:** Ultrasound scan of both Achilles tendons (Achilles Tendon component - No 5) **Daily for 2 Weeks:** Complete symptoms questionnaire, available for telephonic surveillance calls every second day, **and only if required,** visit a designated centre for a clinical examination, donation of saliva and blood samples and have a throat swab taken (URT component - No 3) **For 12 weeks after the race:** Complete a short electronic questionnaire on your recovery daily for a week after the race, thereafter, on a weekly basis for 12 weeks. Volunteers living near a big centre will be asked to donate a blood sample at 1, 3, 5, 7 and 9 days after the race (however, blood donations are not essential for entry into this component of the study) (RPE component - No 6)

We look forward to meeting you at the Spec-Savers Ironman South Africa Registration area, and wish you well in your race preparation and participation.

Prof Martin Schwellnus, Dr Malcolm Collins, Prof Tim Noakes, and the rest of the Ironman Research Team

Appendix 2: Subject Information Sheet

SUBJECT INFORMATION SHEET

Dear Tri-athlete

We have the privilege to inform you that scientific research at the Port Elizabeth IRONMAN triathlon has been planned in collaboration with the MRC/UCT Bioenergetics of Exercise Research Unit based at the Sports Science Institute of South Africa. This will provide a unique opportunity for a research programme to address important medical and physiological problems associated with the IRONMAN triathlon. Each participant will be able to access a summary of the findings of the study by email, and the website, once it has been completed. You will also be given the opportunity to attend a feedback meeting where the results of the study will be discussed. The results will only be that of the whole group, and no individual results will be made public.

The research study will concentrate on the following 6 main components that will ultimately improve your performance and improve the standard of your medical treatment at future triathlons and other endurance events:

- Management of the collapsed tri-athlete
- Exercise associated muscle cramping
- Post-exercise upper respiratory tract symptoms
- Genetic basis for performance and physiological responses during an Ironman Triathlon
- Chronic Achilles tendon injuries in tri-athletes
- The relationship between training history, perception of effort during the race and the subsequent recovery after the race.

As a participant in the Port Elizabeth IRONMAN triathlon, you will be given the choice to participate in this research effort. Your participation is entirely voluntary. Please read through the details of the following six components of the study. You will be given the opportunity to participate in one or more components of the study. The details of each component are explained in this document, and if you wish to participate in one or more components of the study, please read through and sign the INFORMED CONSENT FORMS that relate to each component of the study. Please feel free to contact members of the research team should you have any questions related to the study (or any component of the study). Contact details of the research team are as follows: ironman@sports.uct.ac.za or (021) 650 4572.

SUBJECT INFORMATION SHEET:

COMPONENTS OF THE RESEARCH STUDY TO BE CONDUCTED AT THE 2006 IRONMAN TRI-ATHLON IN PART ELIZABETH

The research study at the 2006 Ironman triathlon, comprise of six components. The detailed information on each of these components of the study is as follows:

Component 1: A study on the management of the collapsed tri-athlete

General information:

The aim of this study is to evaluate the optimum treatment strategies for which to treat collapsed tri-athletes, after an Ironman race. Although intravenous (IV) fluid replacement is a common practice in the treatment of collapsed tri-athletes, medical personnel need to be advised of a treatment method that will prevent possible fluid overload (hyponatraemia) which can be a very severe condition. Your participation in this trial will aid in the understanding and management of how best to correct any fluid imbalance following this race.

If you collapse during or after the Ironman Triathlon and are brought into the medical tent, you will be evaluated and treated according to the current best standard of care principles. Your legs will be elevated and your heart rate, blood pressure, mental status and serum sodium concentration will be measured. If you are confused and your sodium level is normal, other laboratory tests will be performed such as an evaluation of your body temperature and blood sugar levels. If your body temperature is normal and do not have evidence for another treatable medical condition, an IV line will be placed in your arm and the appropriate fluid will be administered - IV or oral fluid (ad libitum – you choose how much you wish to drink) - until you recover and can leave the medical tent without assistance. Your discharge will be at the discretion of the supervising medical officer. If your condition deteriorates at any time, you will be immediately removed from the trial, treated appropriately and transported to the nearest hospital.

The risk of adverse affects of placement of an intravenous line include: infection, delayed healing, bruising, physical pain, mental discomfort and possible injury to a nerve or vessel.

The risk of these adverse effects are rare and every attempt to minimize these risks will be undertaken by the use of sterile technique and use of disposable, single use, material. Your blood will be used for evaluation of serum sodium or blood glucose concentration only. No other tests will be performed on your blood and your blood samples will be appropriately discarded after these tests are performed.

We will obey the strict practices of confidentiality and anonymity. Each subject's identity will be known only to the researchers and numbers will be assigned to each sample in lieu of names. No results will be publicly available and the scientific publication of results will never disclose subject identity.

Potential risks of this component of the study

- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.
- The potential risks to subjects of blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing, haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 15ml prior to the race.
- Body weight will be measured using a standard electronic scale, and there is no risk associated with this procedure.
- The risks associated with participation in this component of the study do not exceed the risks associated with competing in the Ironman competition. The administration of IV fluids will involve an invasive placement of an intravenous line. The risks associated with the placement of an intravenous line include: infection, delayed healing, hematoma, physical pain, mental discomfort and injury to a nerve or vessel. These risks will be minimized by the use of trained phlebotomists, sterile technique and disposable, single use materials. If at any time the condition of a collapsed tri-athlete deteriorates, the most appropriate treatment will be initiated, the trial terminated and the patient will be transported to the local hospital if necessary. The support form the local hospital is part of the normal standard medical care associated with this event.

Potential benefits of this component of the study

- The data collected in this component of the study will aid in the development of optimal treatment strategies for collapsed tri-athletes. Although intravenous fluid replacement is a common practice in the treatment of collapsed tri-athletes, medical personnel need to be advised of a more judicious approach to treatment as to avoid the deleterious effects of fluid overload (hyponatraemia). This information will aid in the understanding and management of serum sodium disorders in collapsed tri-athletes by scientifically 1) evaluating the efficacy of intravenous versus oral rehydration and 2) assessing if the normalization of serum sodium levels are important in the recovery of collapsed tri-athletes.

Component 2: A study to determine the cause of Exercise Associated Muscle Cramping (EAMC)

General information

The purpose of this component of the study is to determine the possible cause of exercise associated muscle cramping (EAMC) in endurance athletes. At registration, tri-athletes will be given the opportunity to volunteer to participate in this component of the study.

Details of the study are as follows:

- Prior to or at registration, a questionnaire detailing personal particulars, medical information, training information, and history of muscle cramping will be completed.
- At registration, a blood sample (5ml – 1 teaspoon) will be collected from the vein in the arm using standard procedures.
- Body weight will be determined at the time of registration, and on the morning before the race starts by stepping onto an electronic scale
- Should you develop muscle cramping during or immediately after the race, and if you agree to participate, you will be admitted to a designated area of the medical facility at the finish of the race.
- At the finish your core body temperature will be measured using a rectal thermometer. This procedure will take place in privacy, and entails placing a thermometer in the rectum (backside) for about 3 minutes. This procedure may associated with mild discomfort but no pain. Normal precautions will be taken to ensure that the thermometer is clean and properly lubricated. Trained medical staff will perform this procedure.
- Disposable surface patches (electrodes) will be attached to your cramping muscle/s and also to your arm (back of the arm on the triceps muscle) to record the electrical activity of the muscles. This procedure is not associated with any pain or discomfort.
- During the time of your admission to the medial facility you will be treated for cramping using standard accepted medical procedures.

- You will be asked to stand and walk periodically (every 15min), unless you are still actively cramping. Once you are able to stand and walk with no cramping, you will be discharged from the medical facility.
- Should you develop any medical complications or if your condition deteriorates, you will be treated according to normal accepted medical practices, and this can include admission to hospital if required.

Potential risks of this component of the study

- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.
- The potential risks to subjects of blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing, haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 15ml prior to the race.
- Body weight will be measured using a standard electronic scale, and there is no risk associated with this procedure.
- All medical conditions, including EAMC, will be treated appropriately, based on the current standard of care or evidenced based paradigms. If at any time the condition of a tri-athlete with EAMC deteriorates, the most appropriate treatment will be initiated, the trial terminated and the patient will be transported to the local hospital if necessary. The support form the local hospital is part of the normal standard medical care associated with this event. Surface electrode placement and measurement of EMG activity is not associated with any known risk to the subject.

Potential benefits of this component of the study

- The anticipated benefits of this component of the study are that the results will further our understanding of the possible cause/s of EAMC in endurance athletes. In particular, once the aetiology of EAMC is better understood, this will improve our ability to prevent this condition, and to treat it effectively if it does occur.

Component 3. A study to determine the cause of post-exercise upper respiratory tract symptoms

General information

Upper respiratory tract (URT) symptoms such as a sore throat, runny or blocked nose, and throat irritation are particularly common in ultra distance athletes including tri-athletes. These symptoms occur mostly in the 2 weeks after a race. It has been shown to occur in 30-50% of all athletes after endurance events. It is important to understanding the relationship between exercise and URT symptoms as it is known that infections have potential negative effects for the athlete. Having an infection or not may mean the difference between being able to compete safely, performing at a sub-optimum level at risk, or missing the event altogether because of illness. In recent years we have become aware that the symptoms of URT infections that endurance athlete suffer from after a race may NOT be caused by an infection. Instead this may reflect an irritation of the inner cell lining of the nose and throat due to allergy or perhaps pollution. However, we still need more evidence to prove this.

The aim of this component of our research is to determine if the symptoms experienced by athletes after an Ironman race are due to an infective cause (microbial agent such as a virus or a bacteria) or due to a non-infective inflammatory process in the upper respiratory tract.

The study will involve recruiting in excess of 120 tri-athletes who participate in the Port Elizabeth IRONMAN endurance race. You will be requested to report to a specific area at the registration desks in the 3 days prior to the event. At this time you will be asked to complete a questionnaire, and have a blood sample taken from your vein in the forearm. In addition nasal and throat swabs will be taken and you will be required give a specimen of your saliva (spit).

Immediately after you finished the race, you will be asked to report to a specific section of the medial tent at the finish, where a further blood sample and saliva sample will be taken.

You will then be asked to be available for a follow up in the 14 days after the race. Follow-up will take place in four cities (Cape Town, Port Elizabeth, Durban and Gauteng).You will be required to complete a short symptom chart every day, and you will be contact regularly (every 2 days) by a member of the research team to obtain this information. Should you develop any symptoms of upper respiratory tract irritation (such as blocked nose, runny nose, sore throat, cough) you will be asked to report to a research centre in the city (as mentioned above). There will be no financial compensation to attend this centre, but the medical consultation will be free of charge. During that visit you will be seen by a doctor, who will take a medical history, and conduct a medical examination of your upper respiratory tract (ears, nose throat and chest). In addition a blood and saliva samples will be taken. You will receive treatment and advice for the management of these symptoms.

Potential risks of this component of the study

- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.
- The potential risks to you during blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing, haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 15ml prior to the race.
- The potential risks associated with the collection of saliva and throat swabs are minimal. Local minimal and transient discomfort in the upper respiratory tract is the only anticipated risk. The collection procedure will be conducted by trained staff.

Potential benefits of this component of the study

- The anticipated benefits to subjects participating in this component of the study are firstly that the knowledge of the cause of the symptoms of the URT after an endurance event will be known, secondly that the treatment of these symptoms will be based on sound scientific and clinical evidence and finally, that tri-athletes can be given accurate and safe advice on training during the recovery period.

Component 4: A study to determine the genetic basis for performance and physiological responses during an Ironman Triathlon

General information

A study to determine the genetic basis for performance and physiological responses during an Ironman Triathlon will be conducted by the UCT/MRC Research Unit for Exercise Science and Sports Medicine at the University of Cape Town in Cape Town, South Africa, in conjunction with the Molecular Genetics Department B and Laboratory of Forensic Genetics of the Cyprus Institute of Neurology and Genetics in Nicosia, Cyprus.

The study involves donate ten millilitres (2 teaspoon) of venous blood and this will be done at race registration and after the race (five millilitres - 1 teaspoon). Five millilitres of the sample

will be used for the extraction and analysis of genetic material (DNA), while the remainder of the sample will be used to measure serum electrolyte (salt) levels. In addition, body weight will be measured prior to the start of the race and again in the medical tent on completion of the race.

The DNA will only be used for scientific research purposes relating to the genetic basis of (1) athletic ability, (2) tendon and ligament overuse injuries and (3) dysnatraemia during ultra-endurance events. Personal particulars and sporting and medical questionnaires will have to be completed and this information will be treated with the strictest confidentiality and will only be used for scientific research purposes. All data will be analysed anonymously and DNA samples will be destroyed on completion of the study.

Part of the DNA extracted form the donated blood sample will be sent to the Cyprus Institute of Neurology and Genetics in Cyprus for analysis. DNA samples will be shipped to and analysed in Cyprus anonymously. DNA will be genotyped (analysed) for variations (polymorphisms) within genes relating to the genetic basis of athletic ability, tendon and ligament overuse injuries as well as water and salt imbalance during ultra-endurance events only.

Potential risks of this component of the study

- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.
- The potential risks to you during blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing, haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 15ml prior to the race.

Potential benefits of this component of the study

The anticipated benefits of this component of the research study are to identify genetic factors that may predispose to 1) improved performance or 2) increased risk of medical consequences (such as abnormal electrolyte imbalances). This information will eventually assist tri-athletes in predicting and improving their performance, and decrease their risk of medical complications during participation in triathlon.

Component 5. A study to determine the genetic risk/s associated with chronic Achilles tendon injuries in tri-athletes

General information

The purpose of this component of the research study is to determine if there are specific genetic factors (refer to the details for component 4) that are associated with the development of chronic tendon injuries. In addition, we want to determine what the effect of an endurance event (such as the Ironman) is on the structure of the Achilles tendon.

At registration you will be required to complete a questionnaire with personal details, training details, past injury details, and details about family history. In addition, a 5ml (1 teaspoon) blood sample will be taken from a vein in your arm. Finally, a qualified radiologist will examine both you Achilles tendons using a soft tissue diagnostic ultrasound machine. This procedure entails putting a clear jelly on your skin, and then using a probe to examine the tendon by passing it over the skin. This is not associated with any discomfort.

After you complete the race, you will be asked to undergo the same procedure (blood collection and ultrasound examination) in the medical facility at the finish. If possible, you will be asked to report to a medical centre close to your home for a final ultrasound examination approximately 6 weeks after the race. The cost of this will be free, but you will not receive any financial compensation to attend this centre.

Potential risks of this component of the study

- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.
- The potential risks to you during blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing,

haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 15ml prior to the race.

- Soft tissue diagnostic ultrasound is a well described and common clinical diagnostic procedure that is associated with no known risk. This procedure will be undertaken by a trained radiologist.

Potential benefits of this component of the study

- The anticipated benefits of this component of the study are that the results will clarify why certain tri-athletes may be more or less prone to chronic tendon injuries, based on their genetic make-up. In future, this work may lead to the screening and early identification of an increased risk for tendon injuries, so that preventative measures can be undertaken.

Component 6: A study to determine the relationship between training history, perception of effort during the race and the subsequent recovery after the race

General information

The purpose of this component of the study is to investigate whether the strain experienced in the recovery period after an Ironman is directly proportional to the perception of effort and racing intensity in a group of similarly trained tri-athletes. The answer to this question has a practical application for training and also contributes to a better understanding of the physiological responses of ultra-endurance events.

The research project will involve the following:

- About 1 week before the race you will be asked to complete a questionnaire on your training habits for swimming, cycling and running in preparation for the Ironman and your personal best times for the 3 disciplines. This will take about 30 minutes.
- You will be familiarised with the subjective scores for "perception of effort rating" and "pain assessment" before the race.
- During the race researchers will be allocated to about 12 stages throughout the race. As you swim, run or cycle past these researchers they will hold up two boards with the scores for "perception of effort rating" and "pain assessment". You will be asked to shout out your respective scores as you go past them and they will record these scores against your race number.
- You will be sent an email on a daily basis for a week after the race with a short questionnaire on your subjective perception of recovery. This questionnaire will take

about 2 minutes to complete. Thereafter, you will be sent an email on a weekly basis for 12 weeks with the same short questionnaire.

- Blood samples after the race will be obtained 1, 3, 5, 7 and 9 days later for the measurement of creatine kinase.

Potential risks of this component of the study

- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.
- The potential risks to you during blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing, haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 15ml prior to the race.
- Data for this component of the study will involve contact with subjects during the race. There is a potential risk that in the process of data collection, the performance of subjects in the race will interfered with. This risk will be minimal, as the nature of the data collection is such that subjects will only be asked to shout out two number as they pass members of the research team at designated points in the race. However, should tri-athletes feel that this affects their performance during the race, they will be free to withdraw from this component of the study. There will be no interference with other race participants during this data collection process.

Potential benefits of this component of the study

- The anticipated benefits of this component of the study are firstly that subjects will receive a full summary of their individual results, as well as the overall findings from this component of the study. Secondly, and more specifically, the individual results will include information about their training and development of fatigue during the race which will be of interest. Finally, these results may assist tri-athletes in modifying their training to improve their performance.

Appendix 3: Informed Consent Form

THE PORT ELIZABETH IRONMAN TRIATHLON 2006: MEDICAL CONSEQUENCES FOLLOWING ENDURANCE SPORTS RESEARCH PROJECT

I, _____, agree voluntarily to participate in the UCT/MRC Research Unit for Exercise Science and Sports Medicine's research project with the following components titled:-

- "A study on the management of the collapsed tri-athlete",
- "A study to determine the cause of Exercise Associated Muscle Cramping (EAMC)",
- "A study to determine the cause of post-exercise upper respiratory tract symptoms",
- "A study to determine the genetic basis for performance and physiological responses during an Ironman Triathlon",
- "A study to determine the genetic risk/s associated with chronic Achilles tendon injuries in tri-athletes",
- "A study to determine the relationship between training history, perception of effort (RPE) during the race and the subsequent recovery after the race",

performed by the University of Cape Town and the Sports Science Institute of South Africa. I have read the subject information sheets and the following procedures and concepts have been explained to me in full:

1. Completion of a questionnaire: The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the research team without the consent of the individual subjects.

2. Blood sample collection at registration, immediately after the race, and if required in the 14 days after the race: The potential risks to subjects of blood collection are minimal and are related to 1) blood sample collection technique, and 2) the volume of blood collected prior to racing and the potential risk of a decreased performance in the race. The potential risks associated with blood collection technique from the ante-cubital veins are: infection, delayed healing, haematoma, physical pain, mental discomfort and injury to a nerve or a vessel. These risks are small and will be minimized by the use of trained phlebotomists, use of sterile techniques and the use of disposable, single use materials. The risk of decreased performance as a result of blood collection will be reduced by not subjecting any participant to the collection of a blood volume exceeding 25ml prior to the race.

3. Measurement of body weight before and after the race: Body weight will be measured using a standard electronic scale, and there is no risk associated with this procedure.

4. Treatment if I collapse after the race: **(only for the collapsed athlete component)** If I collapse during or after the race I might receive either IV (drip into arm vein) or oral fluids ad libitum (as much fluid as I want). I will be attended to in a separate section of the medical tent under the supervision of a qualified doctor. I will be assessed regularly (every 15 minutes) and I understand that

optimum care will be provided to me according to the current standard of care. Treatment will cease when I am alert, oriented, able to walk and when my laboratory tests are normal. I will be transported to the local hospital if my condition requires more urgent medical attention.

5. Treatment if I develop muscle cramps during or after the race: **(only for the cramps component)** If I develop muscle cramps during after the race I will receive treatment in a designated area of the medical facility. Optimum care will be provided to me according to the current standard of care. I will be required to have a rectal temperature measurement taken, blood samples will be collected, body weight will be measured, and I will have surface electrodes attached to my muscle to measure electrical activity. Treatment will cease when my cramps have stopped and I am able to stand up and walk. I will be transported to the local hospital if my condition requires more urgent medical attention.

6. Saliva sample collection at registration, immediately after the race, and if required in the 14 days after the race: **(only for the URT component)** The potential risks associated with saliva sample collection are very small. I may experience transient discomfort as the inner lining of my throat is swabbed with a soft swab. I understand that all the normal precautions will be taken during this procedure, and that it will be undertaken by trained staff.

7. Assessment and treatment of symptoms of the upper respiratory tract in the two weeks after the race: **(only for the URT component)** I understand that should I develop any symptoms of the upper respiratory tract in the 14 days after the race, I will be required to report to a research centre in my home town, to be examined by a doctor, give a blood sample and have a throat swab as well a saliva sample taken. I understand that I will then be treated for my symptoms according to standard medical practice. I understand that I will not receive any financial compensation to attend the centre.

8. Soft tissue diagnostic ultrasound examination: **(only for the Achilles tendon component)** I understand that I will be subjected to a soft tissue diagnostic ultrasound examination of my Achilles tendons during the registration period, on completion of the race, and if possible 6 weeks after the race at a medical facility close to my home. I understand that I will not receive any direct financial compensation to attend this centre for the ultrasound, but that the investigation will be free of charge. I understand that these investigations are not associated with any risk, and will be performed by a trained radiologist.

9. The genetic basis for performance and physiological responses during an Ironman Triathlon as well as to determine the genetic risk/s associated with chronic Achilles tendon injuries in tri-athletes: **(only for the genetics components)** These components of the study are been performed in conjunction with the Molecular Genetics Department B and Laboratory of Forensic Genetics of the Cyprus Institute of Neurology and Genetics in Nicosia, Cyprus. At race registration, I have agreed to donate ten ml (2 teaspoon) of venous blood. Half the sample will be used for the extraction and analysis of genetic material (DNA), while the remainder of the sample will be used to measure serum electrolyte (salt) levels. I also agree to donate an additional five ml (1 teaspoon) of venous blood after the race in the medical tent which will be used to measure post-race serum electrolyte (salt) levels.

The DNA will only be used for scientific research purposes relating to the genetic basis of (1) athletic ability, (2) tendon and ligament overuse injuries and (3) dysnatraemia during ultra-endurance events. I also understand that all data will

be analysed anonymously and my DNA sample will be destroyed on completion of the study. I understand that some of the DNA extracted form the donated blood sample will be sent to the Cyprus Institute of Neurology and Genetics in Cyprus for analysis. I understand that the DNA samples will be shipped to and analysed in Cyprus anonymously. I understand that the DNA will be genotyped (analysed) for variations (polymorphisms) within genes relating to the genetic basis of athletic ability, tendon and ligament overuse injuries and dysnatraemia during ultra-endurance events only.

I understand that whilst there is no direct benefit to myself, if a genetic predisposition for (1) athletic ability, (2) tendon and ligament overuse injuries and (3) dysnatraemia during ultra-endurance events can be established, then future generations will be able to establish their risk for this condition. This may allow better prevention and treatment options in the future. I understand that I will receive the overall results of the study.

I have read (or, where appropriate, have had read to me) and understood the information about this study, and any questions I have asked have been answered to my satisfaction. I agree to participate in the study, realising that I have the right to request that my DNA sample be destroyed at anytime. I agree that research data provided by me or with my permission during the project may be included in a thesis, presented at conferences and published in journals on the condition that neither my name nor any other identifying information is used.

10. Providing information on my rating of effort and fatigue status during the race: **(only for the RPE component)** I understand that I will be required to study and familiarize myself with two scales of perceived effort and fatigue before the race starts. I understand that during the race, at designated stages, I will be required to report (by shouting) my perception of effort and fatigue to members of the research team.

I have read the preceding subject information sheet and understand the testing procedures outlined therein. I understand any accompanying risks and discomforts. Knowing these risks and discomforts and having had the opportunity to pose questions answered to my satisfaction, I hereby consent to participate in this study. I understand that I may withdraw from this study at any time without further question. I have been informed that the individual data derived from my participation in these protocols will remain confidential. I understand that the medical staff and the research team have professional medical insurance.

Name of the tri-athlete: _____
Signature of tri-athlete _____

Date: _____
Name of investigator: ___Prof Martin Schwellnus_____
Signature of Investigator: _____
Date: _____ _____

Appendix 4: 2006 Ironman Medical and Training Questionnaire

Department of Human Biology

UCT/MRC RESEARCH UNIT FOR EXERCISE SCIENCE & SPORTS MEDICINE

Faculty of Health Sciences, University of Cape Town
Private Bag, Rondebosch 7700, South Africa
Tel: + 27 21 650 4561
Fax: + 27 21 686 7530

2006 IRONMAN – MEDICAL AND TRAINING QUESTIONNAIRES

These questionnaires have been constructed by the Medical Research team, in conjunction with the Medical Director of the Ironman 2006. The information obtained from these questionnaires is essential for the planning of medical care during events such as the Ironman 2006. We acknowledge that the questionnaires are long, but we are asking about 20 minutes of your valuable time to complete them. The completion of the questionnaires is voluntary, all the information will be kept confidential and will only be used for research and medical care planning purposes. We suggest that you consider completing this before the event, or at the time of registration.

Prof Martin Schwellnus (Chairman, Research Team)
Dr Peter Schwartz (Medical Director, Ironman 2006)

Instructions

You can either complete the questionnaires electronically using Microsoft word or print the questionnaires and complete them manually. Please answer each question by filling in the details in the allocated space or checking one or more of the option boxes.

If you complete the questionnaire electronically using Microsoft word, please e-mail the completed forms to ironman@sports.uct.ac.za and bring the signed consent form to the research table at race registration.

If you complete the questionnaire manually, please bring the completed forms together with the signed consent form to the research table at race registration.

Please complete sections A, B, C, D and E

Please complete only the relevant questions in the following section

Section A: Personal details			
2006 Ironman Race Number			
Surname			
First Name			
Postal Address		Postal/ Zip Code	
E-mail address		Phone (day time)	code number
Date of birth	y y y y - m m - d d	Cell	
Height	cm	Gender	Male ☐ Female ☐
Weight	kg	Age	
Ethnic group (Only Required and Used for Research Purposes)	Black/African ☐ White ☐ Indian ☐ Mixed Ancestry (Coloured) ☐ Asian ☐ Other ☐		
Ancestry: Tribal or national background (eg Xhosa, Dutch, Zulu, German, Italian)	Father: Unknown ☐		
	Mother: Unknown ☐		
Country of Birth			
Dominant Hand	Left ☐ Right ☐ Both ☐	Dominant Leg	Left ☐ Right ☐ Both ☐
Occupation			
What **percentage** of your **working** day is spent in the following activities?	Sitting: ____ % Standing: ____ % Walking (Lower body activity) ____ % Manual Labour (upper and body activity) ____ %		

Section B. Racing and training history				
Type of triathlon	**Sprint**	**Standard (1.6, 40, 10)**	**½ Ironman**	**Ironman**
Which triathlons have you **ever** participated in?	Yes ☐ No☐	Yes ☐ No☐	Yes ☐ No☐	Yes ☐ No☐
Year of first event				
How many events have you **ever** participated in?				
How many Olympic (or above) triathlon races have you completed over the **past 2 years**?				
Personal best time **ever**	_____ hrs:min	_____ hrs:min	_____ hrs:min	_____ hrs:min
What was your time for your last triathlon race during the **past 12 months**?	_____ hrs:min	_____ hrs:min	_____ hrs:min	_____ hrs:min
Type of running event	**5 km**	**10 km**	**21.1 km**	**42.2 km**
Which races have you **ever** participated in?	Yes ☐ No☐	Yes ☐ No☐	Yes ☐ No☐	Yes ☐ No☐
Year of first event				
How many events have you **ever** participated in?				
Personal best time **ever**	_____ hrs:min	_____ hrs:min	_____ hrs:min	_____ hrs:min
What is your best time, in a running race, in the **last 15 weeks**?	_____ hrs:min	_____ hrs:min	_____ hrs:min	_____ hrs:min

Type of event	**Two Oceans Marathon**	**Comrades Marathon**
Which races have you **ever** participated in?	Yes ☐ No☐	Yes ☐ No☐
Year of first event		
How many events have you **ever** participated in?		
Personal best time	_____ hrs:min	_____ hrs:min

What is your best average cycling speed (km/h) in a race over 80 km in the **last 15 weeks**?	Average speed: _____ Distance: _____	km/h; km
What is your best swimming performance in the **last 15 weeks**?	Time: _____ Distance: _____	min m
What is your predicted time for the entire 2006 Ironman event and each of the three splits?	Entire event: _____ Swim: _____ Cycle: _____ Run: _____	min min min min

Please answer the following questions, with your answers reflecting your average in the **most recent 15 weeks i.e. beginning December 2005 to 18th March, 2006.**

How many days a week did you train during the **last 15 weeks**?	days/week

What distances did you train in an average week during the **last 15 weeks**?	Swim: _____ km/week Cycle: _____ km/week Run: _____ km/week
How many hours a week did you train in an average week during the **last 15 weeks**?	Swim: _____ hrs/week Cycle: _____ hrs/week Run: _____ hrs/week
What **distances** did you train in the week before the race?	Swim: _____ km Cycle: _____ km Run: _____ km
How many **hours** did you train in the **week before** the race?	Swim: _____ hours Cycle: _____ hours Run: _____ hours

Flexibility training history	
Do you perform flexibility training (stretching exercises)?	Yes ☐ No ☐
If YES, please complete the rest of the flexibility training history section below:- If NO, continue completing the questionnaire from the top of page 5 (Equipment use history).	
On average, how many days a week do you perform a stretching session?	days/week
On average, how times a day do you perform a stretching session?	times/day
Please tick which muscle groups do you include in your stretching session?	☐ Hamstrings ☐ Quadriceps ☐ Calf (gastrocnemius) ☐ Calf (soleus) ☐ Groin (inner thigh) ☐ Upper body limbs ☐ Other: _____
Please tick when you stretch? (before, during and/or after exercising. You can tick more than one box)	☐ Before Exercise ☐ During Exercise ☐ After Exercise
When you stretch an individual muscle group, on average, **how long do you hold the stretch** for?	seconds
When you stretch an individual muscle group, on average, **how many times do you stretch the muscle for**?	☐ Once ☐ Twice ☐ 3 times ☐ 4 times ☐ 5 times ☐ 6 or more times

Equipment use history	
Please indicate which type of **bicycle** you use?	☐ Kuota ☐ Kestrel ☐ Trek ☐ Aegis ☐ Litespeed ☐ Softride ☐ Felt ☐ Quintana Roo ☐ Javelin ☐ Cervelo ☐ Argon 18 ☐ Scott ☐ Elite ☐ Specialized ☐ Guru ☐ Giant ☐ Other: _____
Please indicate which type of **handle bars** you use?	☐ Bontrager ☐ HED ☐ Zipp ☐ Profile Design ☐ Vision Tech ☐ Oval Concepts ☐ Deda ☐ Easton ☐ Syntace ☐ Pedalsoft ☐ Kestrel ☐ Other: _____
Please indicate which type of **saddle** (Brand - model) you use?	☐ Selle San Marco- Azoto TriathGel ☐ Profile Design- Tri Stryke (with a groove) ☐ Selle San Marco- Rever Profil ☐ Fizik- Arione Tri ☐ Terry ☐ Koobi ☐ Other: _____
Please indicate which brand of **helmet** you use?	☐ Trek ☐ Bell ☐ Giro ☐ MET ☐ Other: _____
Please indicate which type of **cycling shorts** you use?	☐ Thin lycra (no padding) ☐ Padded cycling shorts ☐ Triathlon shorts with some padding ☐ Swimming costume ☐ Other: _____
Do you normally wear **underwear** together with cycling shorts?	☐ Yes ☐ No
Please indicate which type of **cycling shoes** you use?	☐ Olympic ☐ Nike ☐ Diadora ☐ Shimano ☐ Carnac ☐ Sidi ☐ Other: _____
Please indicate which type of **kit** you use?	☐ Anatomic ☐ Nike ☐ Velo ☐ Howzit ☐ Adidas ☐ Orca ☐ De Soto ☐ Louis Garneau ☐ Quintana Roo ☐ Zoot ☐ Other: _____
Please indicate which **brand of running shoe** you use?	☐ Adidas ☐ Asics ☐ Brooks ☐ New Balance ☐ Nike ☐ Mizuno ☐ Puma ☐ Reebok ☐ Saucony ☐ Other: _____
Please indicate which **type of running shoe** you use?	☐ Soft neutral shoe ☐ Mild anti-pronation shoe ☐ Motion control shoe ☐ Light racing shoe ☐ Unknown or not sure ☐ Other: _____

Section C. History of medication and supplement use			
What medication, if any, are you currently using? (please list)	Name of medication		Years taken
Do you use protective skin sunscreen during training session or when competing?	Yes ☐ No ☐	☐ Every session ☐ Most sessions	
		☐ Some sessions ☐ Very occasionally	
Are you currently taking dietary supplements/vitamins?			Yes ☐ No ☐
If **yes** to the above question, please list names of dietary, sports or vitamin supplements.	Name of supplement		Years taken
	☐ Multi-vitamins		_____
	☐ Anti-oxidants		_____
	☐ Immune boosters		_____
	☐ Protein powders/supplements, Protein bars. BCAAs		_____
	☐ Creatine		_____
	☐ Caffeine		_____
	☐ Fat cutters		_____
	☐ Carbohydrate drinks/powders/gels		_____
	☐ Other: _____		_____
Have you ever used oral corticosteroids (cortisone tablets)? (If **yes**, how long ago?)	Yes ☐ No ☐	☐ 3 months ☐ 6 months	
		☐ 12 months ☐ 24 or more months	
Have you ever been given an injection with corticosteroids? (If **yes**, how long ago?)	Yes ☐ No ☐	☐ 3 months ☐ 6 months	
		☐ 12 months ☐ 24 or more months	
Have you ever been given an injection of corticosteroids in or around the **Achilles** tendon? (If **yes**, how many times?)	Yes ☐ No ☐	☐ Once ☐ Twice	
		☐ 3 times ☐ >3 times	
Have you ever used fluoroquinoline antibiotics? (refer to the following list)	Yes ☐ No ☐	☐ 3 months ☐ 6 months	
		☐ 12 months ☐ 24 or more months	

List of some fluoroquinoline antibiotics:		
ADCO-CIPRIN	CIPROBAY	SANDOZ CIPROFLOXACIN
AVELON	CIPROGEN	TAFLOC
BACTIDRON	CPL ALLIANCE CIPROFLOXACIN	TARIVID
CIFLOC	DYNAFLOC	TAVANIC
CIFRAN	FACTIVE	TEQUIN
CIPLA-CIPROFLOXACIN	FLOXIN	UNIQUIN
CIPLOXX	MAXAQUIN	UTIN-400
CIPRO-HEXAL	NOROXIN	ZANOCIN
	ORPIC	

Lifestyle and habits history			
Please indicate your smoking status	Current smoker ☐	Ex smoker ☐	Never smoked ☐
If you answered yes, (past or current smoker) please complete the section on the right	Number of years of smoking:	If stopped, how many years ago:	
	What is (was) the average number of cigarettes per day:		
On average, how much alcohol do you drink per week (tots, glasses) of spirits, wine or beer?	_____ glasses beer/cider per week _____ glasses wine per week _____ tots of spirits per week		

Fluid Intake		
How do you best describe your fluid intake during an Ironman triathlon race?	(a) I drink to thirst ☐ (b) I drink as much as tolerable ☐ (c) I drink according to a predetermined fluid intake schedule ☐ (d) I drink to prevent any weight loss during exercise ☐ (e) I combine (a) with (c) ☐ (f) I combine (b) with (c) ☐ (g) Other: _____ ☐	
What percentage of your fluid intake will consist of these beverages?	Water: ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ 76-100% Sports drink: ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ 76-100% Coke: ☐ 0-25% ☐ 26-51% ☐ 51-75% ☐ 76-100% Other: ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ 76-100% Specify other: _____	
What will be your estimated **total** fluid intake be **(if at all)** during the **swim**?		ml
What will be your estimated **total** fluid intake be during the **cycle**?		ml
What will be your estimated **total** fluid intake be during the **run**?		ml
Rank the following sources of information on their importance in formulating your drinking strategy. (1 being most influential and the lowest number being least influential)	_____ Fellow triathletes _____ Coach / trainer _____ Magazines / books _____ Website (please specify: _____) _____ Drinking guidelines from sports associations _____ Adverts _____ Self-experimentation _____ Other: _____	

Section D. Family medical history		
Have any of your blood (biological) relatives ever had the following? **Please tick yes or no. If yes, please tick the relationship of that person to you (You may tick more than one of the relationship blocks).**		
Description		**If Yes, please indicate the relationship**
Exercise associated muscle cramps	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Night muscle cramps	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Chronic Achilles tendon injury	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Achilles tendon rupture	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Any ligament injury	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Asthma	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Allergies (in general)	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Heart Disease	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother
Diabetes	Yes ☐ No ☐	☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Child ☐ Grandfather ☐ Grandmother

Section E. Personal general medical history	
In this section, you are asked to read through 14 questions about your personal general medical history. If you answer "yes" to any of questions 1 to 12, please complete the additional questions at the end of the section (section F on page 11).	
1. In the **6 weeks before this race** (from 1st February) did you suffer from any **symptoms of flu** (fever, sore throat, blocked or runny nose, cough, wheeze, muscle aches and pains)?	Yes ☐ No ☐
2. Have you **ever** in triathlon career suffered from **muscle cramping** during or immediately (within 6 hours) after exercise (in training or competition)?	Yes ☐ No ☐
3. Have you **ever** in your triathlon career suffered from **a tendon or ligament injury** (pain, swelling, stiffness) in any tendon (including Achilles tendon, knee tendons, and shoulder tendons) or ligaments (partial or complete tear)?	Yes ☐ No ☐
4. Have you **ever** in your triathlon career **used medicines to treat injuries** in the week **before or during a race** – including anti-inflammatory drugs, cortisone (pills, or injection), or pain killers?	Yes ☐ No ☐
5. Have you **ever** in your triathlon career suffered **gastrointestinal** symptoms **during exercise** including heartburn, nausea, vomiting, abdominal pain, urge to defecate (pass a stool), diarrhoea, or blood in the stools?	Yes ☐ No ☐
6. Have you **ever** in your triathlon career suffered from symptoms of the **nervous system** including exercise induced headaches, nerve tingling or loss of sensation?	Yes ☐ No ☐
7. Have you **ever** in your triathlon or cycling career (in particular with **cycling**) suffered from **injury to the genital area** including genital numbness after cycling, genital pain after cycling, genital swelling or altered sexual function after cycling?	Yes ☐ No ☐
8. Have you **ever** in your triathlon career suffered from **symptoms of allergies** including nose allergies (hay fever), allergic sinusitis, allergic asthma, skin allergies, a past history of allergies to medication, plant material or animal material?	Yes ☐ No ☐
9. Do you **currently suffer from asthma** including exercise induced asthma, or symptoms of asthma such as shortness of breath, wheezing, or chronic coughing?	Yes ☐ No ☐
10. Have you ever **collapsed** (fell down **not because of an accident,** needing medical attention) during, at the finish or after a race or training session?	Yes ☐ No ☐
11. Do you **currently** suffer from any **symptoms of injury** in the muscles, tendons, bones, ligaments or joints?	Yes ☐ No ☐
12. Do you **currently**, or did you **in the last year**, suffer from any symptoms of **exercise related skin disease**?	Sunburn: Yes ☐ No ☐ Skin cancer: Yes ☐ No ☐ Other skin damage resulting sun exposure: Yes ☐ No ☐

13. Please tick in which anatomical area you ever had **surgery** performed.	☐ Head ☐ Neck ☐ Face ☐ Front chest ☐ Back chest ☐ Shoulder ☐ Upper arm ☐ Elbow ☐ Forearm ☐ Wrist ☐ Other (Specify: _____) ☐ Finger ☐ Lower back ☐ Hip ☐ Thigh ☐ Knee ☐ Lower leg ☐ Achilles ☐ Ankle ☐ Foot ☐ Abdomen

14. **Female athletes only:**
Please complete the following questions (14a. to 14g.) related to your menstrual cycle and other gynaecological history

14a. At what age did you start your periods (menstruating)?	(years)
14b. In the last 12 months, how many menstrual cycles did you have?	
14c. Have you ever had irregular menstrual periods in the past? (excluding pregnancy)?	Yes ☐ No ☐
14d. Have you had a hysterectomy/ovarectomy?	Yes ☐ No ☐
14e. How many times have you been pregnant?	(times)
14f. What form of contraception are you currently using?	☐ None ☐ Oral contraceptive pill ☐ Injection ☐ Intra-uterine device ☐ Sterilization (tubes tied) ☐ Other: _____
14g. If yes to question 14f. above, for oral contraceptive pill, for what reason was the pill prescribed?	☐ Not applicable ☐ Dermatological ☐ Contraception ☐ Regulate period ☐ Other: _____

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

If you have answered **YES** to any of the first 11 questions of the Personal General Medical History questionnaollow in section F.

If you have completed the questionnaire manually, please bring the completed forms together with the signed consent form to the research table at race registration.

If you have completed the questionnaire electronically using Microsoft word, please e-mail the completed forms to ironman@sports.uct.ac.za and bring the signed consent form to the research table at race registration.

Section F. Additional detailed medical history

(Please complete all the sections to which you answered "Yes" in the Personal general medical history)

1. Flu symptoms in the last 6 weeks

If you answered **YES** to **question 1** in section E, please complete the following two questions related to flu symptoms in the last 6 weeks.

(1a) Please tick which of these flu symptoms you suffered from **in the last 6 weeks**.	☐ Fever ☐ Cough ☐ Joint pains ☐ Blocked nose ☐ Wheezing ☐ Runny nose ☐ Muscle aches ☐ Any other flu symptoms (Specify: _____)
(1b) Please tick which of these flu symptoms you suffered from **in the last 7 days**.	☐ Fever ☐ Cough ☐ Joint pains ☐ Blocked nose ☐ Wheezing ☐ Runny nose ☐ Muscle aches ☐ Any other flu symptoms (Specify: _____)

2. Muscle cramping

If you answered **YES** to **question 2** in section E, please complete the following questions (2a. to 2m.) related to your cramping.

(2a) For how many years have you suffered from cramping?	(years)
(2b) Did you suffer from cramping during or after exercise in the **last 12 months**?	Yes ☐ No ☐
(2c) With what **type of exercise** is your cramping associated (You can tick more than one form of exercise)?	☐ Swimming ☐ Cycling ☐ Running
(2d) In the **last 10 races or training sessions**, how many times have you experienced cramping?	Races: ____/10 Training sessions: ____/10
(2e) What treatment/s have you had that **successfully relieved** an acute cramp? (can tick more than one)	☐ Stretching ☐ Resting ☐ Drinking fluid ☐ Ice application ☐ Massage ☐ Magnesium ☐ Salt (tablets or solution) ☐ Other (Specify: _____)
(2f) At **what point in the race or training run** do you usually first experience cramping?	☐ First quarter ☐ Second quarter ☐ Third quarter ☐ Fourth quarter ☐ After the race ☐ No pattern
(2g) In which **muscles** do you usually cramp (please list the muscle by the one which cramps most frequently (as 1) and the others after that (2-4)?	☐ Calves ☐ Hamstrings ☐ Quadriceps (thigh) ☐ Foot muscles ☐ Other (Specify: _____)
(2h) Have you **ever** suffered from cramping in your **whole body** (arms and legs)?	Yes ☐ No ☐
(2i) Have you **ever** been **admitted to hospital** following cramping?	Yes ☐ No ☐
(2j) Have you **ever** been **confused or in a coma** during or after a cramping episode?	Yes ☐ No ☐
(2k) Have you ever had **"dark urine"** in the 3 days following a cramping episode?	Yes ☐ No ☐
(2l) If you cramp, **how long** does the cramp usually last for (min)?	(minutes)
(2m) If you cramp, how **severe** is the cramp usually? (please tick).	☐ Mild: < 5 minutes and you are able to continue exercising ☐ Moderate: 5-15 minutes and you are able to continue exercising ☐ Severe: >15 minutes or if you have to STOP exercising

3. Past Tendon and Ligament Injury History

If you answered **YES** to **question 3** in section E, please complete the following questions (3a. to 3d.) related to your past history of tendon/ligament injury/ies.

(3a) Please tick which **tendon/s** you have injured? (next column on the tright)

Also indicate (tick) if your injured tendon was longstanding pain (tendinopathy) or an acute tear/rupture

Tendon		Longstanding Pain (Tendionapthy)	Acute Tear/ Rupture
Foot and ankle:	☐ Achilles tendon	☐	☐
	☐ Tibialis posterior	☐	☐
	☐ Plantar fascia	☐	☐
Knee:	☐ Patellar tendon	☐	☐
Elbow and wrist:	☐ Wrist extensor tendon	☐	☐
Shoulder:	☐ Rotator cuff	☐	☐
Other: _____		☐	☐

(3b) Please tick which **ligament/s** you have injured? (next column on the tright)

Also indicate if your sprained or completely tore the ligamant.

Ligament	Sprain	Complete Tear
☐ Shoulder ligaments	☐	☐
☐ Elbow ligaments	☐	☐
☐ Wrist ligaments	☐	☐
☐ Finger ligaments	☐	☐
☐ Knee (ACL)	☐	☐
☐ Knee (MCL)	☐	☐
☐ Knee (PCL)	☐	☐
☐ Knee (LCL)	☐	☐
☐ Ankle lateral ligaments	☐	☐
☐ Ankle medial ligaments	☐	☐
☐ Spinal ligaments	☐	☐
☐ Other: _____	☐	☐

(3c) Please tick if you have you ever suffered from any of the following **joint capsule** injuries?

☐ Acute shoulder dislocation
☐ Chronic shoulder instability
☐ Other: _____

(3d) Do you suffer from any other **connective tissue or rheumatological diseases** or disorders? (If yes, please specify which one)

Yes ☐ No ☐ (refer to the list on the next page)
(If yes, specify: _____)

List of some Connective Tissue and/or Rheumatic Diseases and Disorders		
Ankylosing Spondylitis	Lipid Storage Diseases	Pseudogout
Aspartylglycosaminuria (AGU)	Marfan Syndrome	Reactive Arthritis
Behcet's Syndrome	Menkes Kinky Hair Syndrome	Reiter's Syndrome
Crohn's Disease	Mucopolysaccharidoses	Relapsing Polychrondritis
Discoid Lupus Erythematosus	Myopathies and Dystrophies	Scleroderma
Ehlers-Danlos syndrome (EDS)	Ochronosis (Homocystinuria)	Sjogren's Syndrome
Eosinophilic Fascitis	Osteogenesis imperfecta (OI)	Systemic Lupus Erythematosus (SLE)
Giant Cell (Temporal) Arthritis	Polyarteritis Nodosa	Systemic Sclerosis
Gout	Polymyalgia Rheumatica	Wegener's Granulomatosis
Hypersentive Vasulatis	Polymyositis & Dermatomyositis	

4. Use of medicines to treat an injury before or during participation

If you answered **YES** to **question 4** in section E, please complete the following two questions related to medicine use for injuries before or during races.

(4a) Which of the following medicines have you used in the past to treat an injury **in the week just before** a race?	☐ Paracetamol (e.g. Panado, Tylenol) ☐ Non-steroidal anti-inflammatories (e.g. Voltaren, Cataflam) ☐ Cortisone (pills) ☐ Cortisone injection ☐ Codeine ☐ Anti-inflammatory gels/creams/patches ☐ Any other pain killers (Specify: _____)
(4b) Which of the following medicines have you used in the past to treat an injury **during a race**?	☐ Paracetamol (e.g. Panado, Tylenol) ☐ Non-steroidal anti-inflammatories (e.g. Voltaren, Cataflam) ☐ Cortisone (pills) ☐ Cortisone injection ☐ Codeine ☐ Anti-inflammatory gels/creams/patches ☐ Any other pain killers (Specify: _____)

5. Gastrointestinal symptoms during exercise

If you answered **YES** to **question 5** in section E, please indicate which gastrointestinal symptoms you have ever suffered from **during exercise** and, how frequently (in the last 12 months and in the last 10 races), and in which type of exercise.

Symptom	Number of times in the last 12 months **(during exercise)**	Number of times in last 10 races **(during races)**	**Tick type of exercise**
Nausea			☐ Swimming, ☐ Cycling, ☐ Running
Vomiting			☐ Swimming, ☐ Cycling, ☐ Running
Heartburn			☐ Swimming, ☐ Cycling, ☐ Running
Abdominal pain			☐ Swimming, ☐ Cycling, ☐ Running
Urge to pass a stool (defecate)			☐ Swimming, ☐ Cycling, ☐ Running
Diarrhoea			☐ Swimming, ☐ Cycling, ☐ Running
Passing blood in the stool			☐ Swimming, ☐ Cycling, ☐ Running

6. Diseases of the nervous system

If you answered **YES** to **question 6** in section E, please indicate which nervous disease symptoms you have ever suffered from **during exercise** and, how frequently (in the last 12 months and in the last 10 races), and in which type of exercise.

Symptom	Number of times in the last 12 months **(during exercise)**	Number of times in last 10 races **(during races)**	**Tick type of exercise**
Headaches			☐ Swimming, ☐ Cycling, ☐ Running
Nerve tingling in the hands			☐ Swimming, ☐ Cycling, ☐ Running
Loss of sensation in the hands			☐ Swimming, ☐ Cycling, ☐ Running

7. Genital tract injury during cycling

If you answered **YES** to **question 7** in section E, please indicate which symptoms of genital tract injury have you suffered from **during or after cycling**, how frequently (in the last 10 sessions), how long symptoms last, and what factors prevent or relieve symptoms?

Symptom	Number of times in the last 10 cycling sessions	Please indicate when the symptoms occur	Please indicate if any of the following reduce or prevent the symptoms (can tick more than one)
Genital numbness		☐ Only during cycling ☐ During and up to 1 hour after cycling ☐ During and 1-24 hours after cycling ☐ During and > 24 hours after cycling	☐ Changing the saddle type ☐ Changing the saddle position ☐ Using padded cycling shorts ☐ Wearing no underwear ☐ Wearing additional underwear ☐ Other (Specify: _____)
Genital pain		☐ Only during cycling ☐ During and up to 1 hour after cycling ☐ During and 1-24 hours after cycling ☐ During and > 24 hours after cycling	☐ Changing the saddle type ☐ Changing the saddle position ☐ Using padded cycling shorts ☐ Wearing no underwear ☐ Wearing additional underwear ☐ Other (Specify: _____)
Genital bruising		☐ Only during cycling ☐ During and up to 1 hour after cycling ☐ During and 1-24 hours after cycling ☐ During and > 24 hours after cycling	☐ Changing the saddle type ☐ Changing the saddle position ☐ Using padded cycling shorts ☐ Wearing no underwear ☐ Wearing additional underwear ☐ Other (Specify: _____)
Altered sexual function following a cycling session		☐ Up to 1 hour after cycling ☐ 1-24 hours after cycling ☐ > 24 hours after cycling	☐ Changing the saddle type ☐ Changing the saddle position ☐ Using padded cycling shorts ☐ Wearing no underwear ☐ Wearing additional underwear ☐ Other (Specify: _____)

8. Allergy history

If you answered **YES** to **question 8** in section E, please complete the following questions (8a. to 8e.) related to your current and past history of allergies.

(8a) Please indicate how long (years) have you been suffering from allergies?					years
(8b) Please tick which <u>type of allergy</u> do you currently suffer from					
Nose (hay fever)	Yes ☐ No ☐	Sinusitis	Yes ☐ No ☐	Asthma (allergic)	Yes ☐ No ☐
Skin allergies	Yes ☐ No ☐	Eye allergies	Yes ☐ No ☐	Allergy to plant material	Yes ☐ No ☐
Allergy to foods	Yes ☐ No ☐	Allergy to animals	Yes ☐ No ☐	Other	
(8c) Please tick which <u>type of allergy</u> do you <u>currently take medication</u> for					
Nose (hay fever)	Yes ☐ No ☐	Sinusitis	Yes ☐ No ☐	Asthma (allergic)	Yes ☐ No ☐
Skin allergies	Yes ☐ No ☐	Eye allergies	Yes ☐ No ☐	Allergy to plant material	Yes ☐ No ☐
Allergy to foods	Yes ☐ No ☐	Allergy to animals	Yes ☐ No ☐	Other	
(8d) Please tick which <u>type of medication</u> do you <u>currently take</u>					
Cortisone nose spray	Yes ☐ No ☐	Cortisone nose inhaler	Yes ☐ No ☐	Anti-histamine tablets	Yes ☐ No ☐
Cortisone cream	Yes ☐ No ☐	Anti-histamine cream	Yes ☐ No ☐	Other inhaler / tablets or cream	Yes ☐ No ☐
(8e) Please tick which <u>symptoms of allergy</u> do you <u>currently suffer</u> from					
Sneezing	Yes ☐ No ☐	Itchy runny nose	Yes ☐ No ☐	Headache	Yes ☐ No ☐
Itchy palate	Yes ☐ No ☐	Streaming eyes	Yes ☐ No ☐	Fatigue	Yes ☐ No ☐
Itchy eyes	Yes ☐ No ☐	Blocked nose	Yes ☐ No ☐	Poor sleep	Yes ☐ No ☐
Post nasal drip	Yes ☐ No ☐	Coughing	Yes ☐ No ☐	Wheezing	Yes ☐ No ☐
In which months of the year do you <u>currently</u> have symptoms of allergies? (You tick more than one)	☐ Jan ☐ Feb ☐ March ☐ April ☐ May ☐ June ☐ July ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec				
(8f) Please tick which <u>type of allergy</u> did you suffer from in the past (NOT currently)					
Nose (hay fever)	Yes ☐ No ☐	Sinusitis	Yes ☐ No ☐	Asthma (allergic)	Yes ☐ No ☐
Skin allergies	Yes ☐ No ☐	Eye allergies	Yes ☐ No ☐	Allergy to plant material	Yes ☐ No ☐
Allergy to foods	Yes ☐ No ☐	Allergy to animals	Yes ☐ No ☐	Other	

9. Asthma history

If you answered **YES** to **question 9** in section E, please complete the following questions (9a. to 9k.) related to your current history of asthma

(9a) Do you currently suffer from asthma?	Yes ☐ No ☐
(9b) How many years have you suffered from asthma?	(years)
(9c) How was your asthma diagnosed?	☐ A doctor taking a history and performing an examination ☐ Lung function test (blow test) but no exercise ☐ Lung function test (blow test) before and after exercise ☐ Metacholine challenge test ☐ Eucapnic hyperventilation test (rebreathing test) ☐ Other test (Specify: _____)
(9d) Which **type of asthma** do you currently suffer from?	☐ Asthma that occurs at any time but not during exercise ☐ Asthma that occurs at any time including during exercise ☐ Asthma that only occurs during exercise
(9e) Please indicate **how frequently do you currently experience the symptoms** of asthma (shortness of breath, wheezing, coughing or coughing after exercise)?	**Daytime symptoms (per week)** ☐ < 2 / week ☐ 2-4 / week ☐ >4 / week ☐ All the time **Night time symptoms (per month)** ☐ < 1 / month ☐ 2-3 / month ☐ ≥4 / month ☐ All the time **Exercise related symptoms (per 10 exercise sessions)** ☐ <1 per 10 sessions ☐ 2-3 per 10 sessions ☐ ≥4 per 10 sessions
(9f) Please indicate if you had symptoms of asthma that were severe enough to necessitate **hospital admission in the last 12 months**	☐ No hospital admission for asthma in the last 12 months ☐ 1-2 hospital admissions for asthma in the last 12 months ☐ 3-4 hospital admissions for asthma in the last 12 months ☐ >4 hospital admissions for asthma in the last 12 months
(9g) Which **symptoms of asthma** do you currently suffer from?	☐ Wheezing ☐ Dry cough ☐ Shortness of breath ☐ Tight chest ☐ Chest pain ☐ Other (Specify: _____)

(9h) What **medication do you currently use** for your asthma? (you may tick more than one option)	☐ Cortisone inhaler (e.g. Beclate, Becloforte, Becodisks, Becotide, Budeflam, Flixotide, Inflammide, Pulmicort, Qvar, etc) ☐ Salbutamol (bronchodilator) inhaler (e.g. Ventolin, Venteze, Vomax, Airomir, Asthavent etc.) ☐ Salmeterol (bronchodilator) inhaler (Serevent) ☐ Fenoterol (bronchodilator) inhaler (Berotec) ☐ Terbutaline (bronchodilator) inhaler (Bricanyl) ☐ Formoterol (bronchodilator) inhaler (e.g. Foradil, Foratec, Oxis) ☐ Ipratropium (bronchodilator) inhaler (Atrovent) ☐ Tiotropium (bronchodilator) inhaler (Spiriva) ☐ Combined cortisone and bronchodilator inhaler (e.g. Atrovent, Berodual, Combivent, Duolin, Duovent, Seretide, Symbicord) ☐ Cortisone tablets ☐ Bronchodilator tablets ☐ Leukotriene receptor antagonist tablets (e.g. Acccolate, Singulair) ☐ Other inhaler ☐ Other medication (Specify: _____)
(9i) **When do you use your medication** for your asthma?	☐ Daily (irrespective of exercise) ☐ Only before exercise ☐ Other (Specify: _____)
(9j) **How long before an exercise session** do you use your medication for asthma?	min
(9k) Have you obtained **TUE (therapeutic use exemption forms)** for your asthma medication?	Yes ☐ No ☐

10. History of previous collapse If you answered **YES** to **question 10** in section E, please complete the following questions (10a. to 10d.) related to your current history of asthma	
(10a) Have you collapsed during training or racing?	☐ Training ☐ Racing ☐ Training and racing
(10b) How many times have you collapsed in training session or races during the last **five years**?	_____ training session _____ races
(10c) When you collapse, does it mostly occur before of after the finish line / completion of the training session?	☐ Before the finish ☐ After the finish
(10d) What is the cause of you collapse?	☐ Dehydration ☐ Heat illness ☐ Hyponatremia ☐ Low blood pressure ☐ Low blood sugar ☐ Other condition (Specify: _____)

11. History of any current injury that you suffer from

If you answered **YES** to **question 11** in section E, please complete the following questions (11a. to 11g.) related to each of your current injury/ies (Space is provided for two injuries)

Injury 1	
(11a) What was the approximate date when you first became aware of the injury?	Month Year
(11b) Please indicate which side of your body is injured (if applicable)	☐ Right ☐ Left
(11c) Please indicate which anatomical area is currently injured	☐ Head ☐ Neck ☐ Face ☐ Front chest ☐ Back chest ☐ Shoulder ☐ Upper arm ☐ Elbow ☐ Forearm ☐ Wrist ☐ Finger ☐ Lower back ☐ Hip ☐ Thigh ☐ Hamstring ☐ Quadriceps ☐ Knee ☐ Shin ☐ Achilles ☐ Ankle ☐ Foot Other (Specify: _____)
(11d) Please indicate the type of structure that was injured	☐ Muscle ☐ Tendon ☐ Bone ☐ Ligament ☐ Joint Other (Specify: _____)
(11e) Please indicate in which sport (discipline) the injury occurred	☐ Running ☐ Cycling ☐ Swimming Other (Specify: _____)
(11f) Please indicate the severity of the injury (tick one box please)	☐ I only experience symptoms after exercise - Grade 1 ☐ I experience symptoms during exercise, but it does not interfere with exercise - Grade 2 ☐ I experience symptoms during exercise that may interfere with my training/ competition - Grade 3 ☐ I am so painful that I may not be able to train or compete - Grade 4
(11g) Please indicate how your injury was treated to date (you can tick more than one)?	☐ Rest ☐ Stretches ☐ Physiotherapy ☐ Surgery ☐ Strengthening exercises ☐ Equipment change ☐ Tablets ☐ Cortisone injection ☐ Other injection ☐ Orthotics Other (Specify: _____)

Injury 2			
(11a) What was the approximate date when you first became aware of the injury?	Month	Year	
(11b) Please indicate which side of your body is injured (if applicable)	☐ Right	☐ Left	
(11c) Please indicate which anatomical area is currently injured	☐ Head ☐ Neck ☐ Face ☐ Front chest ☐ Back chest ☐ Shoulder ☐ Upper arm	☐ Elbow ☐ Forearm ☐ Wrist ☐ Finger ☐ Lower back ☐ Hip ☐ Thigh	☐ Hamstring ☐ Quadriceps ☐ Knee ☐ Shin ☐ Achilles ☐ Ankle ☐ Foot
	Other (Specify: _____)		
(11d) Please indicate the type of structure that was injured	☐ Muscle ☐ Tendon ☐ Bone	☐ Ligament ☐ Joint	
	Other (Specify: _____)		
(11e) Please indicate in which sport (discipline) the injury occurred	☐ Running ☐ Swimming	☐ Cycling	
	Other (Specify: _____)		
(11f) Please indicate the severity of the injury (tick one box please)	☐ I only experience symptoms after exercise - Grade 1 ☐ I experience symptoms during exercise, but it does not interfere with exercise - Grade 2 ☐ I experience symptoms during exercise that may interfere with my training/ competition - Grade 3 ☐ I am so painful that I may not be able to train or compete - Grade 4		
(11g) Please indicate how your injury was treated to date (you can tick more than one)?	☐ Rest ☐ Stretches ☐ Physiotherapy ☐ Surgery ☐ Strengthening exercises ☐ Equipment change	☐ Tablets ☐ Cortisone injection ☐ Other injection ☐ Orthotics	
	Other (Specify: _____)		

Appendix 5: Research Ethics letter of approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: preaward@curie.uct.ac.za

13 January 2006

REC REF: 425/2005

Assoc Prof MP Schwellnus
Department of Human Biology
UCT/MRC Research Unit for Exercise Science and Sports Medicine
Medical School

Dear Prof Schwellnus

THE PORT ELIZABETH IRONMAN TRIATHLON 2006: MEDICAL CONSEQUENCES FOLLOWING ENDURANCE SPORTS.

Thank you for your letter to the Research Ethics Committee dated 14 December 2005, addressing the issues raised by the committee. It is a pleasure to inform you that the Ethics Committee has formally approved the above mentioned study.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROF. T ZABOW
CHAIRPERSON

Appendix 6: DAILY SELF ASSESSMENT FORM

NAME : ..... **RACE NO:** .....

RACE TIME: .....

Please tick the appropriate block indicating the day of onset and days of duration of any symptoms experienced.

SYMPTOMS	Post Race Day 1 20/03	Post Race Day 2 21/03	Post Race Day 3 22/03	Post Race Day 4 23/03	Post Race Day 5 24/03	Post Race Day 6 25/03	Post Race Day 7 26/03	Post Race Day 8 27/03	Post Race Day 9 28/03	Post Race Day 10 29/03	Post Race Day 11 30/03	Post Race Day 12 31/03	Post Race Day 13 01/04	Post Race Day 14 02/03
Fever														
Chills														
Malaise (tiredness /fatigue)														
Watery or itching eyes														
Sneezing														
Nasal discharge														
Blocked nose														
Earache														
Sore throat														
Laryngitis (hoarseness)														
Headache														
Cough														
Joint ache														
Muscle ache														

PLEASE COMPLETE ON A DAILY BASIS

Appendix 7: FOLLOW UP MEDICAL EXAMINATION - MEDICAL PRACTITIONER

NAME : **RACE NO. :**

RACE TIME :

	YES	NO	
1. Athlete self-assessment form received	☐	☐	
2. Does athlete have symptoms of URTI?	☐	☐	If no, athlete is a **control**, proceed to 4.

If yes, specify

.....

.....

.....

.....

3. **Examination :** Pulse : ..... BP : .....

Temp : ..... RR : .....

Are any of the following present :

			DETAILS
• Lymph nodes in neck	☐	☐	.....
• Inflamed tympanic membrane	☐	☐	.....
• Fluid in middle ear	☐	☐	.....
• Mucopurulent nasal discharge	☐	☐	.....
• Nasal crease	☐	☐	.....
• Inflamed nasal mucosa	☐	☐	.....
• Inflamed pharynx	☐	☐	.....
• Post nasal discharge	☐	☐	.....
• Tender sinuses	☐	☐	.....
• (L) lung abnormal findings	☐	☐	.....
• (R) lung abnormal findings	☐	☐	.....
• Heart murmurs (pathological)	☐	☐	.....

4. **Specimen collection :** Blood sample
Saliva sample
Swabs (please see accompanying instructions for sample collection)

5. **Treatment :** .....
.....
.....
.....

Signed : ..... **Date :** .....