'Sports and Play, injuries as secondary effect'

"Looking for complete resolution"

Leo Pruimboom and Tom Fox

Abstract

Exercise, sports and play have been and are part of our society. Sports like footbal, basketbal and athletics attract billons of people in stadiums with an audience up to 100.000. Footbal is the most popular sport in the whole world. Wherever you go, Africa, Asia, Europe, kids could be barefoot, have hardly anything to eat, but they have a bal and play.
In our Western society sports are very important, although more people are engaged in watching it than playing themselves. A tendency worrying the scientifical, economical and political powers, because of health, absence and costs respectvily. Sports is fun, play is even more and people engaging in sports state they need it, it gives them self-esteem, control, while the major secondary effect of exercise seems to be better health. A great number of individuals do their sports in all kind of competitions at local, national and even international level. These people suffer injuries, respiratory inflammation, exhaustion, depression, and their most feared enemy is chronification of their health problems. Chronification of local injury is not rare. Factors such as financial pressure, pain fixation, anxiety, confusion and deficient nutrition seem to play a major role in sportsmen and women suffering prolonged health problems. All these factors lead to the same thing; non complete resolution of inflammation.
Nonresolving inflammation is a major driver of chronic disease and injury. Perpetuation of inflammation is an inherent risk because inflammation can damage tissue and necrosis can provoke inflammation. Nonetheless, multiple mechanisms normally ensure resolution. Cells like macrophages switch phenotypes, secreted molecules like reactive oxygen intermediates switch impact from pro- to anti-inflammatory, and additional mediators of resolution arise, including proteins, lipids, and gasses. Aside from persistence of initiating stimuli, nonresolution may result from deficiencies in these mechanisms when an inflammatory response begins either excessively or subnormally. This greatly complicates the development of anti-inflammatory therapies. Local resolving pathways are influenced by central responses during wound healing and inflammation. Hypothalamical axes, including the HPA, HPG, HPGH and the HPT, react through afferent input of nerves endings, immune-brain interactions and through plasma transport of different danger signals. Further are the sympathetic nervous system and the parasympathetic nervous system involved in the resolving response after tissue damage and microbial infiltration.
Less known is the role of the liver and the spleen in resolution of inflammation. Controlled reaction and interaction between local, systemic and central resolving responses are responsible for the time dependent solution of homeostatic disturbances. Disorders in one, two or all responses could produce secondary tissue damage and perpetuation of the inflammatory response, causing chronic disease, chronic fatigue and prolonged injury. The typical vulnerability to respiratory disorders of people engaging in regular, often

intense, exercise is based on the so called "open window syndrome". A syndrome caused by a state of immune suppression (adapative at start) leading to viral, baterial and microbial susceptibility. Engagement in regular exercise demands higher amounts of fat, protein, several vitamins and minerals, compared with sedentary people. Nevertheless, the nutritional needs of active individuals should be considered normal while sedentary people are ill overall and so is their nutritional intake.
Spontaneous injuries (without physical contact) probably are consequences of deficient nutrition, stress and perhaps overload. The last factor is probably very relative; do you think that homo sapiens is not capable of running a marathon, throwing a javelin or exercise 8 hours a day without injuries, or anyway without chronifying injuries?

Introduction

"When someone declared that life is an evil, Diogenes said: Not life itself, but living ill."

Exercise has been part of human life history since the beginning of hominin evolution. Since hominines like Australopithecus were relative short distanced "sportspeople", the latter Homo erectus was far more a long distance runner. Male (and often female) hunted big game, like elephants, mousses and wild cows named aurochs (figure 1).

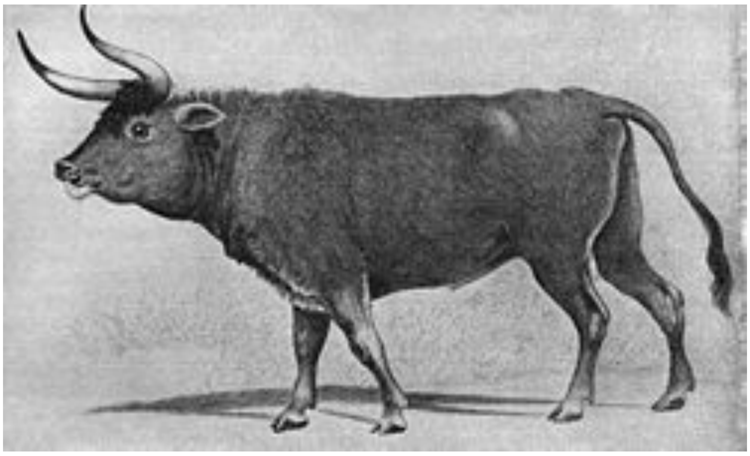


Figure 1 The auroch or wild cow lived in Europe, Asia and the north of Africa till 1627, weighted far more than the actual domestic cow and was oversized (2 metres long)

Chase-hunting males and females were able to walk and run for hours till the hunted animal was so exhausted that it almost fell down spontaneously. For this, hunters had to be able to regulate a row of metabolic challenges including thermoregulation, des-intoxication of metabolic debris, energy source allocation, maintenance of blood and tissue minerals and right decision making. Challenges which have been so demanding that they are considered part of human evolution, like bipedestial behaviour, loss and shortening of hair, development of eccrine sweat glands (4 million) and dopaminergic neuroanatomy. These adaptations made it possible that homo developed a bigger brain, a smaller gut, a restrained amount of muscle mass (see below) and an increase of the amount of fat tissue. Obesity is rare in other animals than human. The majority of animals will not overeat because of a certain "inhibition-system" base on satiety (the sensoric satiety centre). A centre which is overridden by sweet taste. Domestic dogs will develop gluttony like their human owners if dogs eat sweet things like sugar, fruits and refined carbohydrates.

The remote environment (the western actual society) offers abundant nutritional sources which could produce obesity through a so called push system. Push-systems are characterized by "a pushing provider" and an overfilled production-unit. An expensive way of producing and not valid in critical circumstances such as a economical crisis. Cheaper and much healthier would be the use of a "pull-system". The market-demand determines the amount of crude material which is necessary for producing the exact number of products. People engaged in sports still base their diet on high carbohydrate nutrients, low fat and average protein intake. Exercise is the "first choice" treatment for pull-system repair and that´s why active people should be more healthy than sedentary people. Nevertheless, their diet is highly deficient, their brain is push-susceptible and injuries are a logical consequence of bad functioning energy allocation systems and systemic inflammation. Irregular exercise and doping will stress this system, producing possibly a so called "exercise induced" anorexia athletica. A lack of exercise will disturb pull system mechanisms even more, by far outweighing the abundance of nutritional resources in our remote environmental. The majority of human being overeats but not everybody develops overweight and obesity.

In the last 30-40 years, *Homo obesus,* like Diogenes (c. 403-323 B.C.), increasingly says "I am a citizen of the world", thus pointing to the global nature of sports, inactivity and obesity. Homo obesus can be considered as a metabotrophin deficient species at high risk for multiple health problems and needs full medical management. This paper will discuss the evolutionary background of exercise and modern sports, the beneficious effects of exercise and the possible immune challenges for elite sportsman/women. Exercise is *always* better than doing nothing; chronic strenuous, irregular exercise can be deleterious.

Introduction

During the last decade the human being is exposed to a pandemic increase of modern chronic inflammatory diseases. All these chronic systemic diseases reveal systemic inflammation (Hamer, 2009, Kolb, 2009, Miller, 2009, von Kanel, 2008), caused by the innate immune system (IIS) unable to respond properly to solve endogenous inflammation in the body.
Inflammation is as old as life exists. Our genes have evolved to solve inflammation; a process essential for the Homo sapiens to survive. These genes are still almost similar to the genes of our hunting and food gathering ancestors 100.000 years ago and the core regulation and recovery processes are preserved (Macaulay, 1999, Smith, 2004). The control of the inflammation is regulated by the 'self-limited inflammation' process, Resoleomics (Serhan, 2004,

2007, 2008). In the current Western environment, this evolutionary response to inflammation starts often subnormal or excessive causing ronresolution (Nathan 2010).
Today our genes that solve inflammation operate in a completely different environment than for which they were designed. The human being is exposed to an enormous change in environment since the industrial revolution. Especially the last decades a tremendous acceleration of innovations changed our lives completely, such as: the way we move, the kind of labor we do, the environmental pollution, the 'new food', the speed of life, non-self sufficiency, the enormous amount of information we are exposed to and the high expectations of life we have set. The question is whether our IIS and its natural inflammatory response, Resoleomics, still functions properly in the current, fast changing environment and whether there is a relationship between the current disease patterns and the stress-inducing changes in our environment.

Nonresolving inflammation can take distinct histologic forms (figure 1, Nathan 2010). These can succeed each other or coexist in different sites in an affected organ.

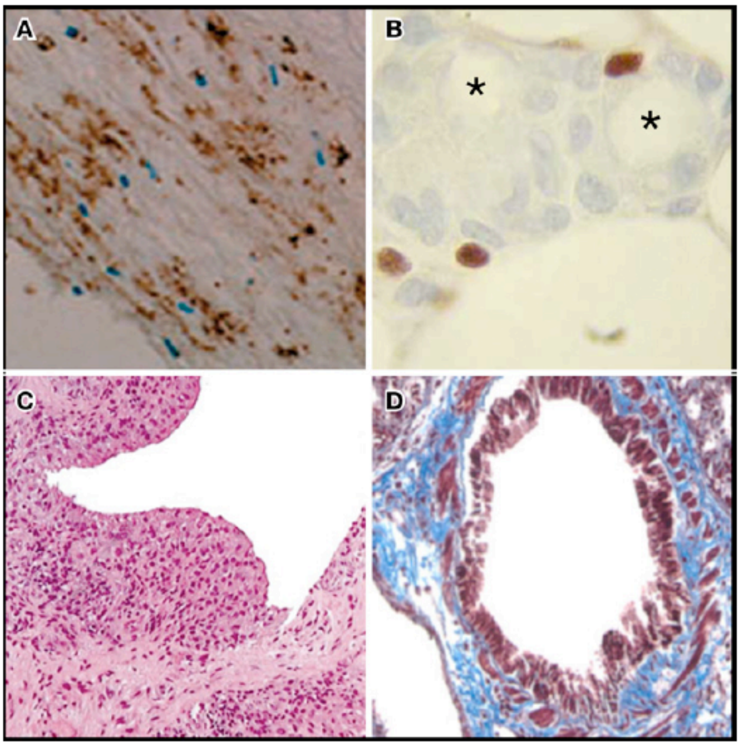


Figure 1 Different histological examples of nonresolution situations of human tissues. (A) Atherosclerosis. Plaque from a human carotid artery containing macrophages stained with anti-CD68.
(B) Obesity. Abdominal adipose tissue from an obese mouse with necrotic-adipocytes (asterisks) surrounded by macrophages. Nuclei of some T cells are stained with anti-Foxp3.
(C) Rheumatoid arthritis. Synovium from a human knee infiltrated by lymphocytes, monocytes, and activated fibroblasts. Cells in the joint space (top), mostly neutrophils, are lost in sample

preparation.
(D) Pulmonary fibrosis after conditional overexpression of TGF-b. Collagen is stained blue; smooth muscle cells are stained brown.

Unresolved inflammation is normally due to tissue damage combined with microbial infiltration, pre-injury stress syndromes, nutritional deficiencies, lack of energy (ATP), and other factors functioning as a so called second hit (Van de Sande 2011, Horton 2007). Multiple etiological possibilities of nonresolving have been described so far and include lack of omega 3 fatty acids, disturbances in the omega 6/omega 3 index, vitamin C deficiency, Zinc deficiency, vitamin D deficiency, psychosocial stress, deficiency of arachidonic acid, insufficient protein intake, high carbohydrate diet and even genetic factors (Das 2011, Das 2010, Zhoua 2010, Peterson 2008). Whatever the reason, chronic inflammation and secondary tissue damage leading to nonresolving is ***always*** related with failure of wound healing, possibly leading to perpetuation of injuries. Resolving interventions for people suffering from disease in general and specifically those suffering from sports-injuries should therefore target local, systemic and central resoleomics pathways including tissue specific responses, hepatic resolving mechanisms and central neuro-endocrinological processes (Klank 2010, Anderson 2010, Tracey 2010).

Complete resolution of wound healing; healing the injury

Wound healing should be considered as a complete coordinated proces involving all humans systems including the immune system, the endocrinological system, the nervous system and even psychology. Factors disturbing normal wound healing are (figure 2):

- Mikrobias (Bakteries, Virus, etc.)
- Oxigen deficiency
- Chronic use of medicines (NSAID, cortisol)
- Doping
- Lack of macrophage migration
- Repetition of injury
- Lack of DHA, EPA, L-arginine and other proteins
- Intoxication
- Spleen “silencing”
- Chronic Stress
- Lack of thyroid hormone

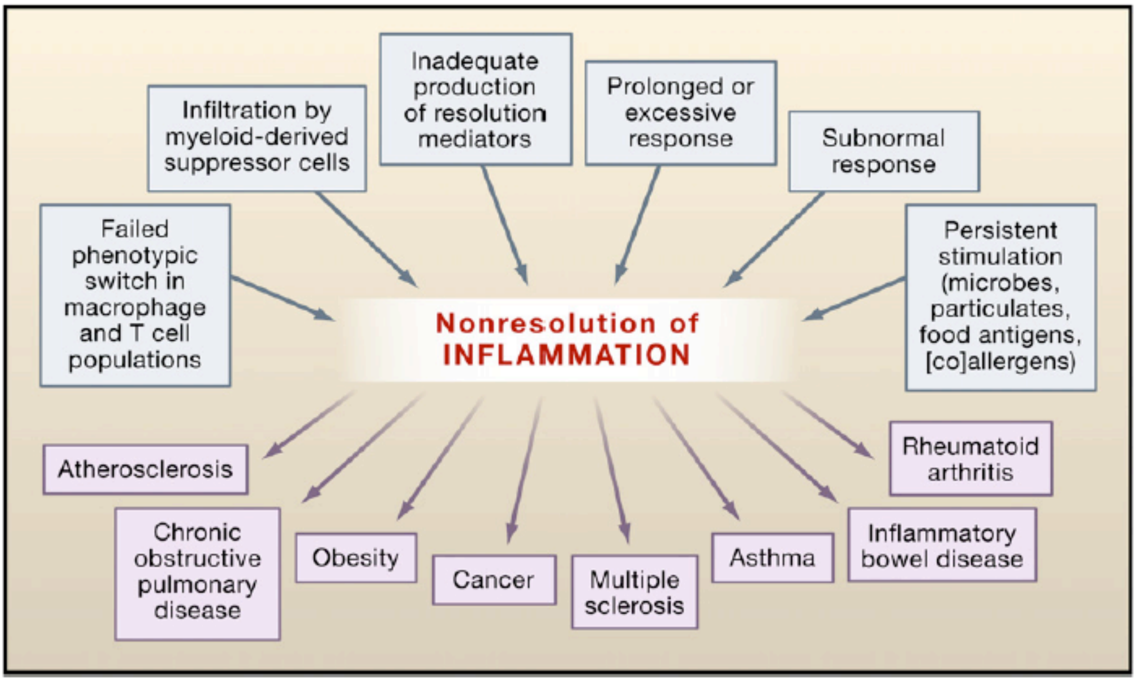


Figure 2 Causes of nonresolution of inflammation and its´consequences (Nathan 2010)

The immune system is made for short, intensive reactions with a beginning, a platform phase and finishing in a maximum period of 4 days. Next to that, the immune system „knows" about external danger with possible infiltration of microbies and therefore reacts ***always*** as if these were present. Internal wounds, such as ankle sprains and other connective tissue injuries are responded as if microbies would be present. The immune reaction to internal wounds could therefore be excessive, producing a reaction like a roller coaster in the centre of a big city, producing possible secondary damage. Secondary damage, or absence of a normal immune response after injury can cause serious complications. These complications can be produced by several factors (Broughton 2006):

1. Over/under-production of pro-inflammatory cytokines
2. Dramatic increase in energy and protein turnover (up to 150%)
3. Muscle waisting
4. Deficiency of L-methionin (connective tissue) and L-arginine (macrophage migration - NO)
5. Deficiency of L-glutamine and BCAA´s (wound healing)
6. Deficiency of Manganese (Mn), Magnesium (Mg), Copper (Cu), Potassium (Ca), Iron (Fe) (co-enzymes during connective tissue repair), Zink (Zn) (Re-epitilisation), Vitamin A, B, C, E and Zn (Immunfunction and inhibition of neutrophils) and deficiency of DHA/EPA as resolving compounds if inflammation
7. Failure of necessary energy allocation capacity; from vital organs to the immune system and connective tissue repair

8. Hyperproduktion of High-Mobile group box 1 and uric acid producing a hyper-activity of the innate immune system (figure 3, Tracey 2010)

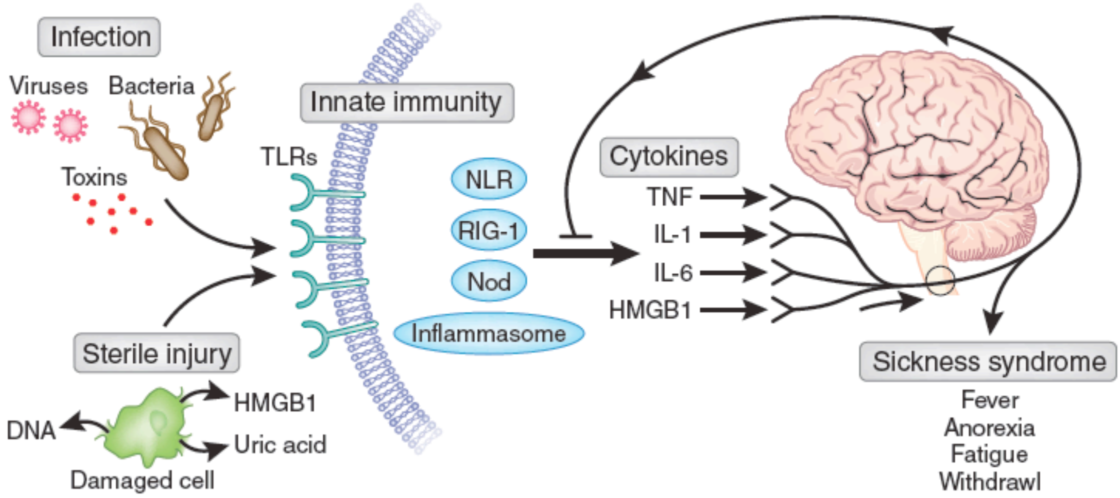


Figure 3 The normal reaction following an immunological challenge such as wound healing or infection. High-Mobile group box 1 and uric acid are strong enough to produce a septic and non-septic shock syndrome (Tracey 2010)

The most important „secondary effects“ of sports

Engaging in regular exercise improves the individual´s general health, including cognitive functions, emotional stability, immune function and life expectancy when compared with sedentary people (Pruimboom 2011). Looking at Western active people and comparing them with individuals form tribes such as the San (Bushmen) in the Kalahari dessert, Haile Gebreselassi of Ethiopie and the Kiwi, than Western active people are more injured, suffer respiratory disorders and hardly can win a marathon anymore. So observing three groups of people, the sedentary individual, the active Western individual (exercising 4 – 5 hours a week) and the people engaging in real activity (every day 3 – 8 hours), only the latter should be considered „normal“ although they are not the norm. Hunter-gatherers show higher bone density, thicker bones and significant more muscle mass than even the best trained western individual (Webb 2006, Webb 2007)

The secondary effects of sports and play in Western society include:

- *improvement of general health*
- (perpetual) injuries (muscle, skeletal and connective tissue)
- respiratory disorders (chronic bronchitis, astma)
- gut disorders
- exhaustion

The first „secondary" effect of regular exercise is obviously very positive. The other ones are deleterious, but are preventable. People still living as hunter-gatherers are much less susceptible for these secondary effects; Why? Because of food intake? Genes? Environment?

The major difference is that healthy active people start exercising very soon when the motor-system (including bones, muscles, heart, connective tissue) are developing (McAllister 2010). Stronger muscle insertion, larger and more muscle cells, chronicity of use of motor units (opposite to late start of moderate and severe activity – rhytmic contraction) and location of the immune system at the outside of the body are just a few benefits of early life (often strenous) exercise.

Local resolution of injury; a role for L-arginine, L-glutamin, BCAA and overall amino acids/protein intake

Every wound healing reaction shows the same chronological sequence (figure 4). The first 48 hours energy is allocated to the innate immune system which, once activated, uses upto 450 – 700 kcal/24 hours (Staub 2010). The major energy source for the activated innate immune system is glucose (fat and glutamin are secondary energy source in activated immune cells) and uptake is insulin dependent.

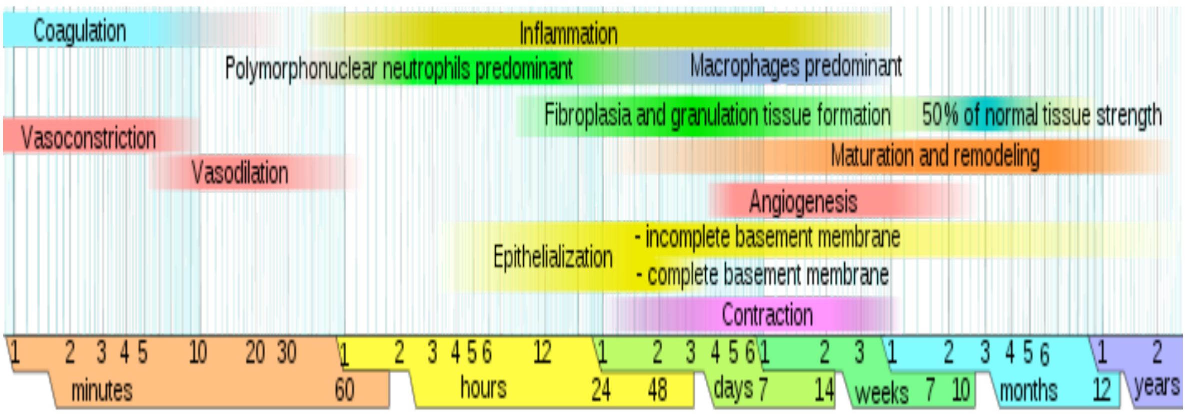


Figure 4 The chronology of wound healing. Activated neutrophils infiltrate the damaged tissue to whipe out all possible microbes. Macrophage migration into the wound eliminates wound debris and phagocytes the neutrophils. After eliminating debris the macrophages produce growth factors and wound healing starts. Energy is first used for the immune system and second for wound healing

The local inflammatory reaction can be fueled by local energy sources such as fat in adipose tissue, the breakdown of local connective tissue (table 1) and circulating glucose (Staub 2010). The chronology of the inflammatory response is a kind of default plan (figure 5, Bosma 2011). First neutrophils are activated through NfkB activation and subsequent macrophage migration inhibiting factor, impeding the migration of macrophages at start. After „sensing" and eventually killing of possible microbes, neutrophils will uptake DHA, AA and EPA out of the exsudate (edema) and convert them in so called resolving substances; lipoxins, resolvins, protectins and maresins. At the same time, local produced cortisol (by keratinocytes, melanocytes) induces the production of the counterplayer of MIF, called miacrophage migration factor, being nitric-monoxide (NO, Das 2010). Long term activation of the innate immune system could give rise to (severe) atrophy of neighbouring tissues such as muscle, skin and tendons (table 1). NO production, a derivate from L-arginine, is induced by lipoxins, resolvins and cortisol, inducing migration of macrophages, finishing the inflammatory reaction and starting wound healing (figure 4 and 5).

Extracellular matrix components	Direct product	Indirect product	Route of ATP provision
Collagen → proline, hydroxyproline	Glutamate	α-Ketoglutarate	Citric acid cycle
Collagen → glycine	Serine	Pyruvate	Citric acid cycle
[a]Glycosaminoglycans → glucuronic acid	UDP-P-glucose	Pyruvate	Glycolysis
[a]Glycosaminoglycans → N-acetylglucosamine	Fructose-6P	Pyruvate	Glycolysis

Table 1 Collagen/connective tissue breakdown to fuel the activated immune system during activation at the start of wound healing

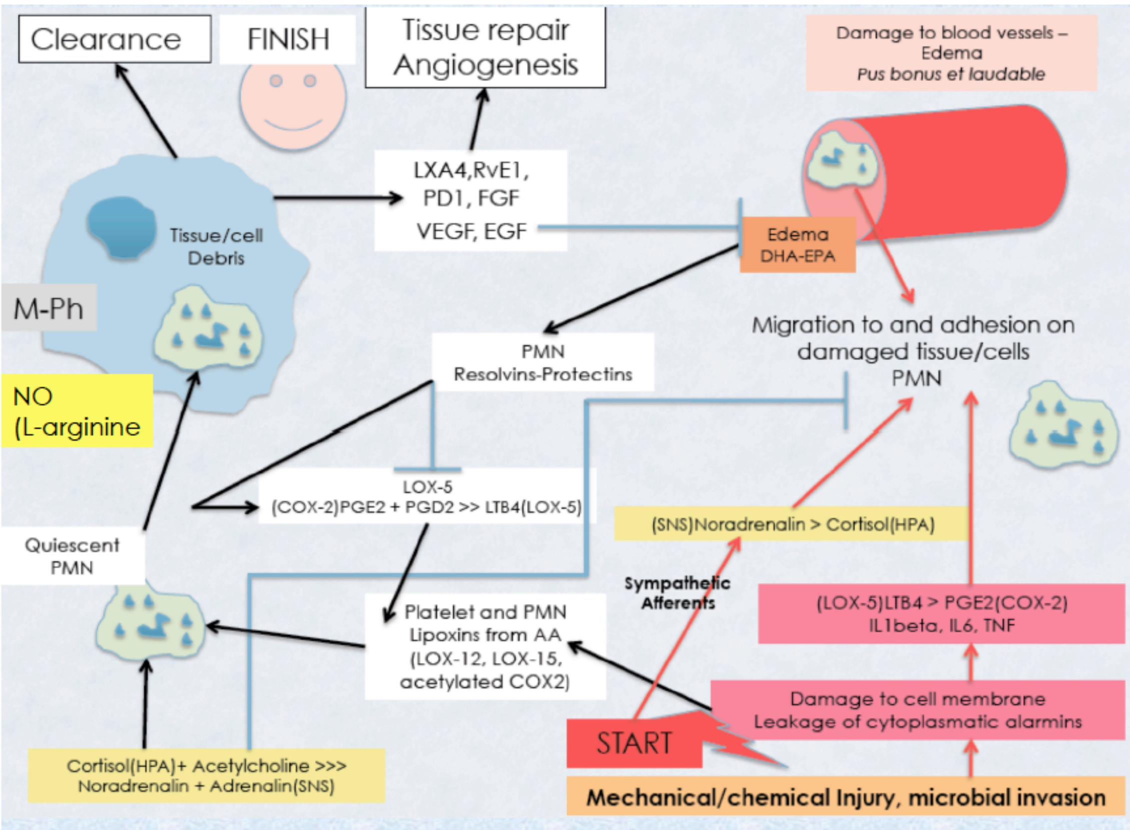


Figure 5 The chronology of events during wound healing – inflammatory reaction. The exsudate provides DHA, AA and EPA to induce the

production of resolving compounds. Cortisol and resolving compounds induce the production of NO, necessary for the migration of macrophages (M-Ph), phagocyting debris and quiescent neutrophils. The production of NO is dependent of L-arginine (Bosma, Wetten, Pruimboom 2011)

NO is produced out of L-arginine (figure 6, Lauer 2002) through activity of NO synthases. The resulting NO is responsible for vasodilatation, Macrophage migration, immune-inhibition and induction of production of connective tissue.

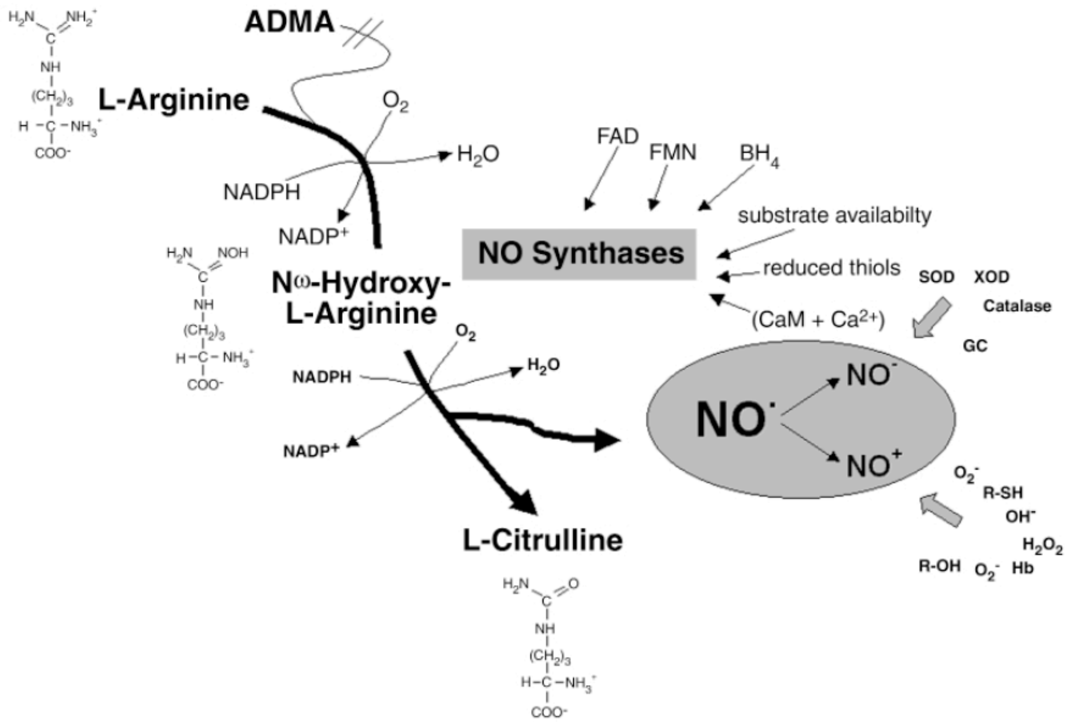


Figure 6 The production of NO out of L-Arginine.

Desneves found that normal wound healing demands up to 9 gramms of L-arginine every 24 hours (Desneves 2005). Nutrients high in L-arginine content are almonds (2.47/100 gr.), cashew nuts (2.17/100 gr), shrimps and salmon (1.79/100 gr.). Using L-arginine as wound healing formula has been proven to be highly effective even in healing of the most difficult wounds like decubitis (Schols 2009). A so called wound healing formula should include vitamin C, L-arginine, zinc, omega 3 fatty acids and vitamin E, as concluded by Schols and Theila in a meta-analysis about wound healing and decubitis (Schols 2009, Theilla 2007).

Figure 7 shows an intervention with L-arginine, omega 3 fatty acids, vitamin C, Zinc and vitamin E in an person with prolonged decubitis. After 9 weeks of treatment the wound (which had been open for more than 6 months) was almost completely healed.

Figure 7

Wound healing with the wound healing formula containing omega 3 fatty acids, L-arginine, vitamin C, vitamin E and Zinc.
Foto a is baseline, b after 3 weeks of treatment and c after 9 weeks of treatment

Willow bark plays a special role in curing injuries and finishing the inflammatory response after tissue damage. Willow bark belongs to the most effective pro-solution natural substances with the working mechanism having been discovered very recently (Bonaterra 2010). Willow bark seems to influence almost all pathways related with inflammation, including inhibition of TNF (figure 8), induction of immunological cell apoptosis (which NSAID´s don´t do), decrease of COX-2 expression (which facilitates a switch or flip-flop reaction of pro-inflammatory in anti-inflammatory function) and inhibition of translocation of NfkB to the nucleus (Bonaterra 2010). Interesting is the fact that the activity of willow bark seems to be mediated by the total willow bark extract including active substances such as naringenine, salicin, salidroside and salicortin (figure 9). This makes it plausible that the use of other naringenine, salicin, salidroside and salicortin containing substances/nutrients could have a significant synergistic effect of the use of willow bark as a natural medicine for inflammatory disorders, impaired wound healing and probably even chronic pain syndromes. Important naringenin sources are citrus fruits (Otaki 2009), whereas salicin and other salicilic compounds are mostly found in organic carrots, garlic, onions, and koriander is such an amount that these nutrients could (and perhaps) should be considered nutritional medicines (Baxter 2001).

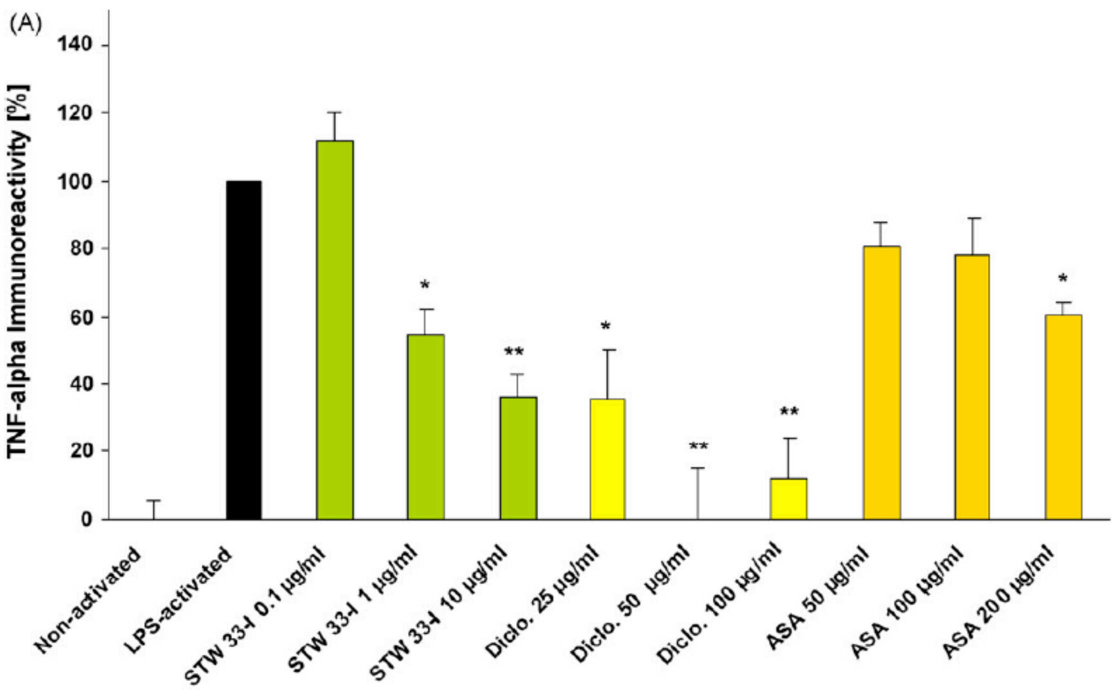


Figure 8 Willow Bark extract (STW) and derivates inhibit the production of TNF-alfa more effective than aspirin and similar to diclofenac (Bonaterra 2010)

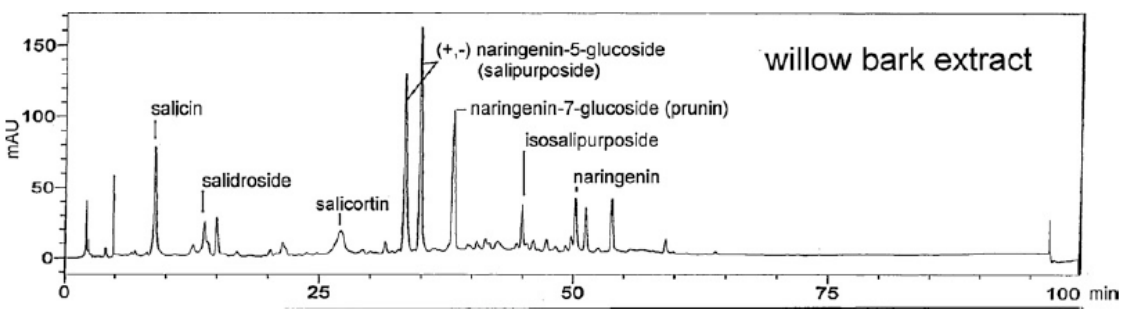


Figure 9 The composition of total willow bark extract; all active substances seem to be of essential for the anti-inflammatory effect of this natural medicine (Bonaterra 2010)

Immune suppression and respiratory disorders; the open window syndrome

Physical activity causes homeostatic changes in the human body. These changes can also be found in the immune system. The higher the intensity or the amount of activity the more impact can be found due to these alterations. This is of course more evident in topsporters. Some examples: Sprinters exercise regularly from 20 to 24 times per week – each workout taking more than 2 hours. This results in a weekly exercise amount of about 50 hours. Triathlon-Long-distance (3,8 km swimming; 180 km cycling and a whole marathon) requires the following weekly exercise-amounts: 15 - 18 km swimming, 600 - 900 km cycling and 140 - 160 km running. In other topsporters daily amounts of exercise of more than 6 to 8 hours are not rare. From these examples can be seen that total exercise amounts are much higher than in a usual working week. Total amount of energy expenditure is he same. On usual racing days cycle racers spend about 600 to 10.000 kcal per day. In 6-day races it's even up to 12.000 kcal / day. Apart from the amount of metabolic pressure there is a problem of caloric-intake. And also the liquid supply is difficult: in the Tour de France, the daily amount of liquid intake can be more than 20 l. Here sophisticated changes between load and rest are very important. Generally the workload-period is a kind of homeostatic disturbance. Performance capability falls within this period. Figure 10 shows this development.

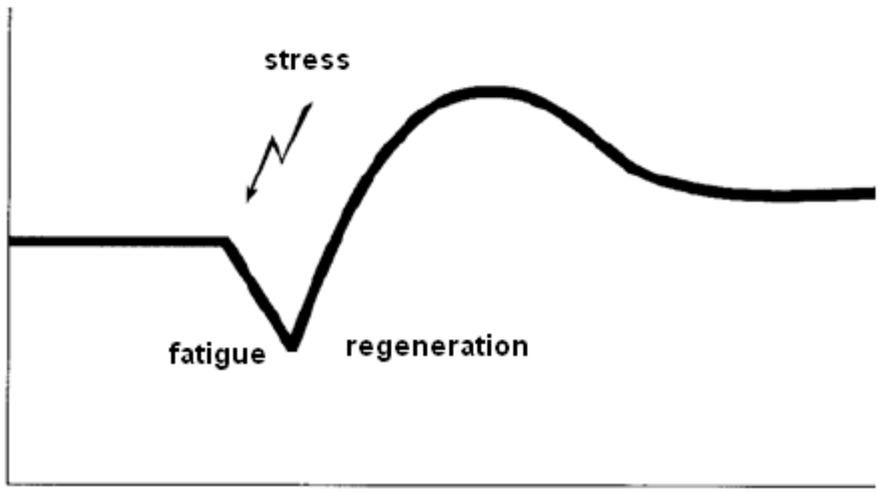


Figure 10 Workload in exercise

One of the basic rules to prevent overtraining is work out at the moment the body shows the highest regeneration ratio.– the next workload will occur on a higher level and repeating this will cause an increase of physical capability.
During exercise, especially in high intensity exercise, the organism is exposed to various potentially threatening situations: heat, hypoxia and acidosis. This may

have deleterious effects on parts of the immune system. On the other hand advantagous effects of regular physical exercise have been reported in several publications (Matthews 2002, Waschbisch 2009, Jeurissen 2003, Pedersen 2006, Hollmann 2000). Taken together the opinion of the last 20 years has been that high intensity exercise is able to suppress functions of the immune system (e.g. IgA levels in the upper respiratory tract, lowered lymphocytes in response to exercise, the so-called "open-window-hypothesis", figure 11).

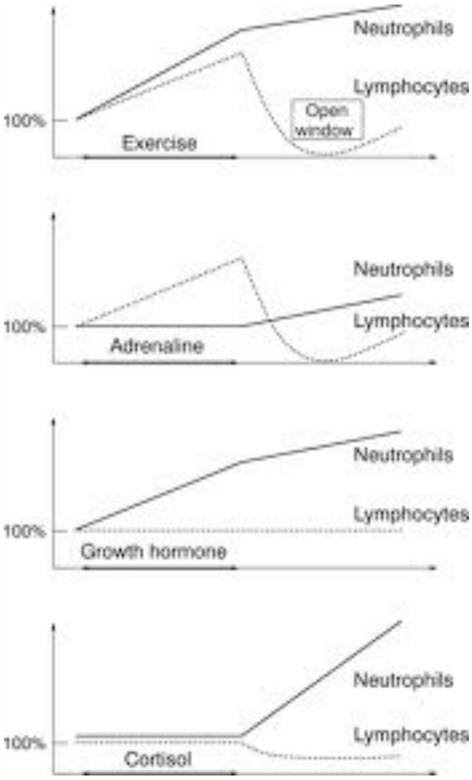


Figure 11 The open window hypothesis. Intense exercise produces a pro-inflammatory state (neutrophils upregulated) while other immune cells are down-regulated. Growth hormone and cortisol (like substances) could counter this effect (Klarlund Pedersen 2000)

In contract to these findings athletes show a better immune function analogue to their amount of aerobic activity (Hollmann 2000). Lowered immune function in athletes is more frequent with a) higher number of workout units and b) higher intensities. Usually this happens when these athletes are overtrained. This may also be a reason for the improved immune function that can be reported among people who are regularly physical active in aerobics. Research has shown that receptors responsible for the identification of pathogens (toll-like-receptors, TLR) are downregulated by regular physical activity. These TLR's are seen as a link between the innate and the adaptive immune-system. As physical exercise activates the innate immune-system, a downregulation of the TLR's can be seen an adaptive effect or something called "immune tolerance" (Cooper 2007). In the end the usage of physical activity is again a matter of dosage. But there is more about the preventive effects of physical exercise concerning immunological functions. The work of researchers like BK Pedersen

shows that muscles are able to produce several cytokines during work which are usually responsible for inflammation. In the state of chronic low grade inflammation the cytokines TNF-alpha, IL-6 and c-reactive protein (CRP) belong to the most important players within this circuit. TNF-alpha is produced by adipose tissue and stimulates the production of IL-6. This enhances the production of C-reactive protein in the liver and promotes insulin resistance (Figure 12 and 13). Produced the muscles the cytokines do not act inflammatory but anti-inflammatory (Figure 14). The most important cytokine in this case is IL-6. Normally it is found in response to pathogens or stress – acting as a mediator or signal transducer for neutrophils invading tissue. Muscular IL-6 inhibits one of the main inflammatory cytokines TNF-alpha. Concerning to this, muscle derived IL-6 acts anti-inflammatory (Pedersen 2005). Beyond that, additional muscle derived substances have influence on immune function. Recent data show that glutamine, an amino acid responsible for the function of immune cells is produced by skeletal muscle. This semi-essential amino acid is an important energetic source for leukocytes. It regulates gene expression and protein activity in leukocytes, mesangial cells, and hepatocytes and influences signal transduction in leukocytes, neurons, and hepatocytes (Lagranha 2007). The amounts of muscle derived production increase after short term exercise while long term exercise decrease plasma glutamine (Costa Rosa 2004). This is interesting as glutamine is also produced by intestinal bacteria and also kown as one of the main energy-providing substance for epithelial cells. Glutamine is known as one of the three amino acids that build glutathion. Glutathion works as the possibly most important anti-oxidative substance in the intracellular space (human muscle cells contain more glutathion than glycogen). The activity of the enzymes catalyzing the activity and amount of this molecule is influenced predominantly by regular aerobic exercise (Gomez-Cabrera 2007). In top sport athletes there is broad recommendation for supplementing glutamine before or after intensive physical activity - e.g. workout or competition (Cordain 2005, Favano 2008, Lagranha 2008).
L-Glutamine supplementation is safe and effective in a wide range of problems in people engaged in physical exercise, including respiratory disorders, gut problems, immune suppresion, viral susceptibility and even burn out. The use of 20-30 gramms a day has no-side effects and could have beneficial effects on immune function, tissue strength, muscular performance, respiratory disorders and energy, although more research has to be done (Wang 2012, Gleeson 2008).

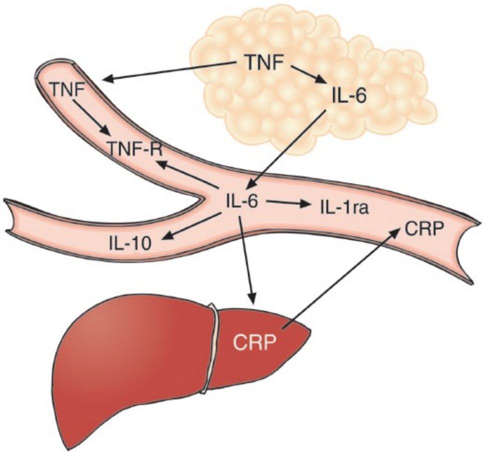


Figure 12 Cytokines in chronic low grade

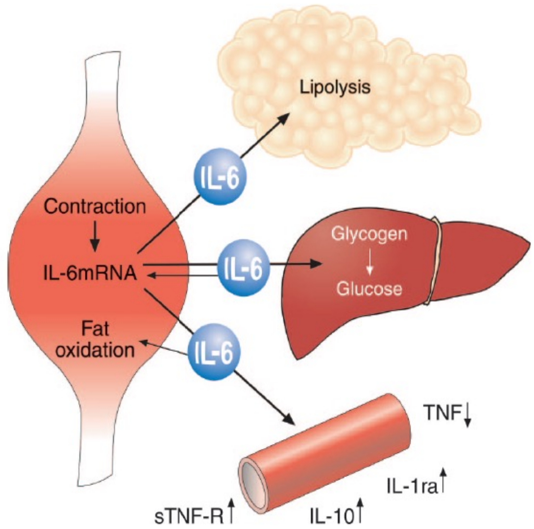
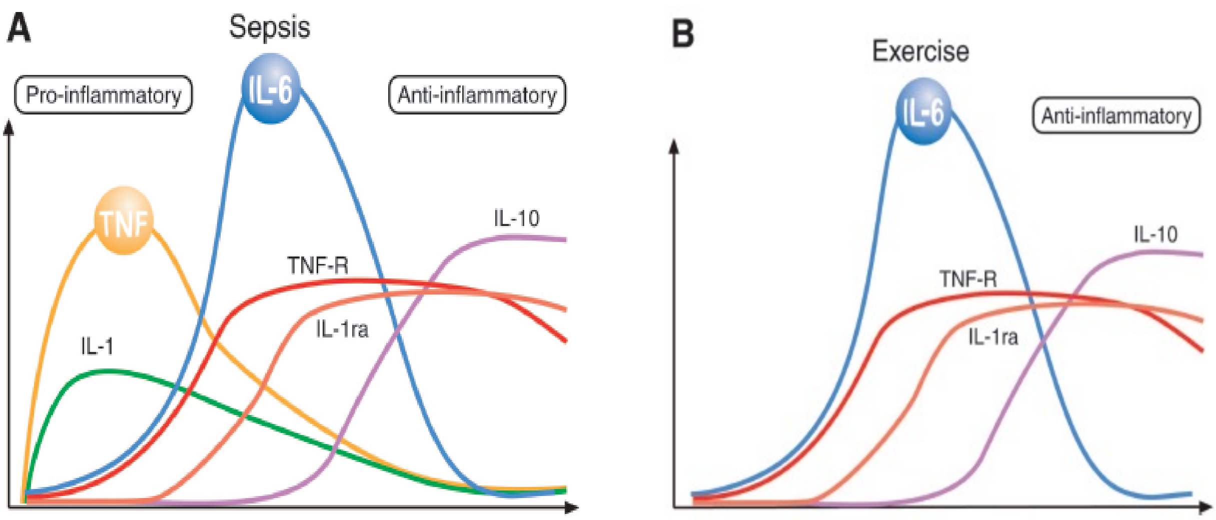


Figure 13 Physical activity and neurodegeneration



Exercise and the gut; a need for probiotics in topsports

Nutritional practices that promote good health and optimal athletic performance are of interest to athletes, coaches, exercise scientists and dietitians. Probiotic supplements modulate the intestinal microbial flora and offer promise as a practical means of enhancing gut and immune function. The intestinal microbial flora consists of diverse bacterial species that inhabit the gastrointestinal tract. These bacteria are integral to the ontogeny and regulation of the immune system, protection of the body from infection, and maintenance of intestinal homeostasis. The interaction of the gut microbial flora with intestinal epithelial cells and immune cells exerts beneficial effects on the upper respiratory tract, skin and uro-genital tract. The capacity for probiotics to modulate perturbations in immune function after exercise highlight their potential for use in individuals exposed to high degrees of physical and environment stress. Probiotics show a wide range of effects on different functions of the immune system in people engaged in exercise (Cox 2010). Not only gut function seems to be normalized but also susceptibility for respiratory disorders is significantly reduced by the use of probiotics.
Figure 15 shows the pathways in which the use of oral probiotics are involved (West 2011).

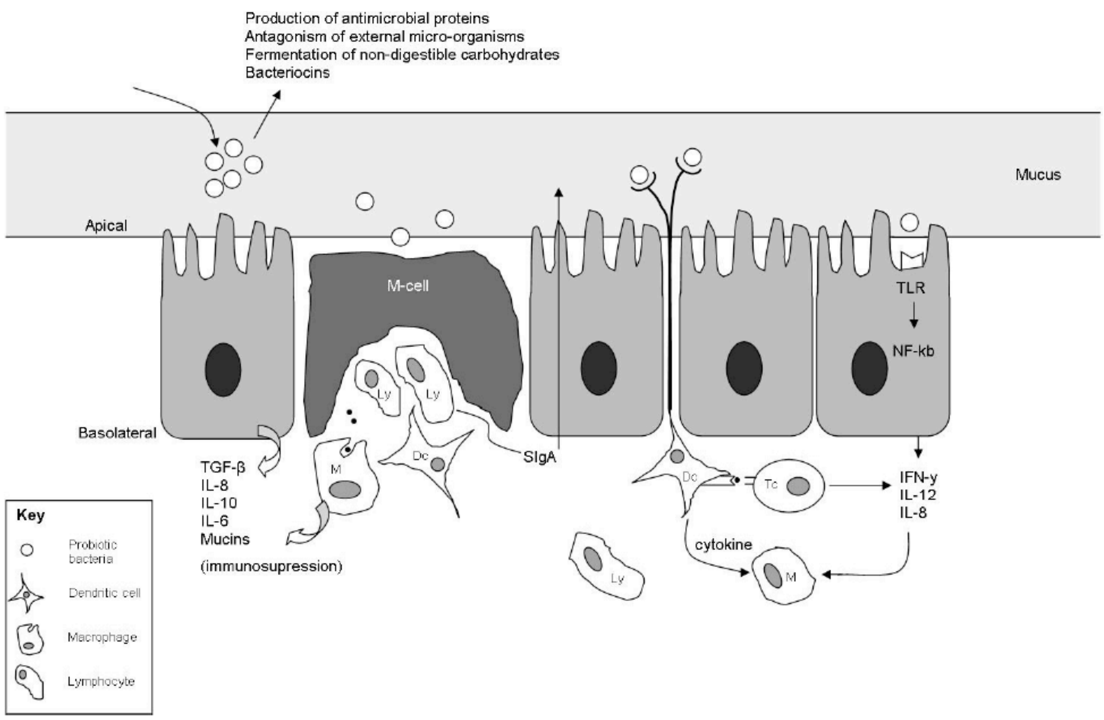


Figure 15 The use of oral probiotics and immune system functions. Regulation is through multiple pathways

Recent research shows that daily intake of probiotics is essential for maintaining gut health, immune function and resistance against respiratiry disorders in people engaged in regular exercise (citation of Gleeson 2011):

"The purpose of this study was to examine the effects of a probiotic supplement during 4 mo of winter training in men and women engaged in endurance-based physical activities on incidence of upper respiratory-tract infections (URTIs) and immune markers. Eighty-four highly active individuals were randomized to probiotic (n = 42) or placebo (n = 42) groups and, under double-blind procedures, received probiotic (PRO: Lactobacillus casei Shirota [LcS]) or placebo (PLA) daily for 16 wk. Resting blood and saliva samples were collected at baseline and after 8 and 16 wk. Weekly training and illness logs were kept. Fifty-eight subjects completed the study (n = 32 PRO, n = 26 PLA). The proportion of subjects on PLA who experienced 1 or more weeks with URTI symptoms was 36% higher than those on PRO (PLA 0.90, PRO 0.66; p = .021). The number of URTI episodes was significantly higher (p < .01) in the PLA group (2.1 ± 1.2) than in the PRO group (1.2 ± 1.0). Severity and duration of symptoms were not significantly different between treatments. Saliva IgA concentration was higher on PRO than PLA, significant treatment effect F(1, 54) = 5.1, p = .03; this difference was not evident at baseline but was significant after 8 and 16 wk of supplementation. Regular ingestion of LcS appears to be beneficial in reducing the frequency of URTI in an athletic cohort, which may be related to better maintenance of saliva IgA levels during a winter period of training and competition."

Total protein intake, carbohydrates and fatigue; the myth defeated

One of the longest existing paradigms in sports has been the supposed need of high carbohydrate in people engaged in regular exercise. Recent research challenges this "dogma" and gives evidence that high carbohydate intake can even be deleterious for health and performance in sport.
Enhanced inflammation, reduction of beta oxidation and loss of endurance/sprint performance have been shown to be direct consequences of high carbohydrate intake (CHO) in (top) sporters (Deppner 2010, Guerra 2010, van Proeyen 2010). CHO intake increases pro-inflammatory cytokine production during recovery, inducing inflammatory disorders (figure 16, Deppner 2010).

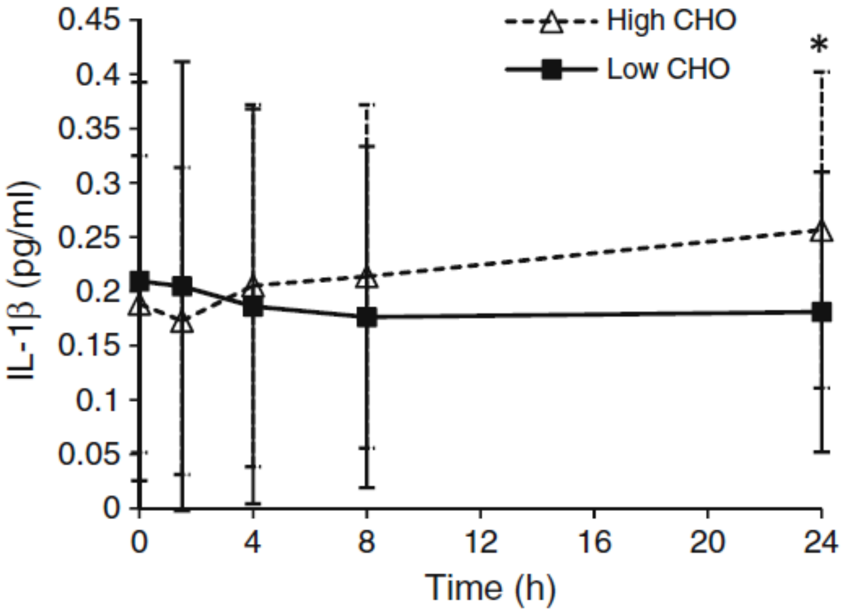


Figure 16 Increased inflammatory profile in athletes with high CHO

Protein turnover is increased in active people (table 2) and therefore higher protein intake is needed.

Group	Protein intake (g/kg/day)
Sedentary men and women	0.80–1.0 or ~10% of dietary energy
Elite male endurance athletes	1.5–1.7
Moderate-intensity endurance athletes[a]	1.1–1.4
Recreational endurance athletes[b]	0.80–1.0 or ~10% of dietary intake
Football, power sports	1.5–1.8
Resistance athletes (early training)	1.5–1.7

Table 2 Protein turnover in active people.

Research shows that high protein intake (35 en%) and training in a fasting state are the most effective interventions to induce metabolic flexibility; the capability to use fat as energy source when it´s available (van Proeyen 2010), while high glucose intake reduces this vital function (Citivarese 2005). Metabolic flexibility, as said the capability to use fat as major energy source when fat is available, should be considered "the secret" of long distance runners such as Bekele and Gebresellasi. Training in a fating state, the use of protein and fat as most important macronutrients and, if necesarry supplementation of protein powder, are interventions to make Western people competitive againin comparance with African athletes.

Non-injured people should therefore use 1.5 – 2.0 gramms of total protein/kilo body weight/day to cover their basic needs for maintenance of performance, tissue viability and immune functions. A person with a body weight of 70 kilo also needs:

1.5 – 2.0 x 70 = 105 – 140 gramms protein/day

100 gramm chicken breast	22 gramms of protein
100 gramm salmon	20 gramm of protein
100 gramm mushrooms	19 gramm of protein

Supplemental protein powder should contain all amino acids in an optimal relationship.

Conclusion

Sport and play are necessary and normal traits of modern human behavior. The most important secondary effect of exercise is a better global health. Injuries, fatigue and other typical disorders (such as respiratory inflammation) belong to the most feared limitation factors of people engaged in sports. Nutrition, famine/feast, rest/exercise and the use of certain supplements can improve wound healing, prevent new injuries, increase performance and optimize immune function. The use of the nutritional, exercise and supplemental pyramids developed by the pioneers in clinical PNI, could provide a western active phenotype capable of competing with people who are engaged in activity since early life (supplemental material)

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