Sports and Immunity

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Introduction
Sports: Does it enhance or impair immunity?

Ivan Roitt writes in his textbook „Essential Immunology“:

• «Exercise, particularly severe exercise, induces stress and raises plasma levels of cortisol, catecholamines, interferon-, interleukin-1, (...).

• It can lead to reduced Immunoglobulin A levels, immune deficiency and increased susceptibility to infection.

• Maniacal joggers and other such like masochists — you have been warned!»

In contrast, popular belief says:

• Sports is healthy and strengthens immunity!

Who is right?
Observations / anecdotic reports are contradictive

- Anecdotic reports of coaches: Athletes are more susceptible to infectious diseases during and following important competitions (cold, diarrhoea).

- 170 marathon runners (ø running time 3h25, ø 12 years experience): 90% report „rarely ill“ (Nieman 1993).

- Athletes who trained a lot had 2-times as often a cold 2 months prior to a marathon as compared to a group who ran only little. Athletes who participated to a marathon reported a 6-times higher susceptibility to colds as compared to those who planned to participate but were not able to (business matters, injuries etc.) (Nieman et al. 1990).

- Moderate exercise prior to exposure to an infectious agent protected against infection. Severe exercise, however, led to increased susceptibility (Davis et al. 1997, Gross et al. 1998).
Frequency of colds with ultra marathon runners and inactive controls in 2 weeks window following run

Following both runs the runners reported more colds as compared to an inactive control group

(Nieman et al. 1990)
Number of colds in relation to physical activity

Nieman et al. 1998a+b
126 women
45 min walking for 5 days per week
*URTI: Upper respiratory tract infections*

Nieman et al. 1993
Number of people who took a cold (during a period of 12 weeks)
Very active and fit  8 %
Moderately active and fit  21 %
Inactive, less fit  50 %
Introduction into Immunology
The range of infectious agents which challenge the immune system

- **Worms**
  - Tapeworm
  - Guinea worm

- **Protozoa**
  - Amoeba
  - Leishmania
  - Trypanosome
  - Malaria

- **Fungi**
  - Aspergillus
  - Candida

- **Bacteria**
  - Mycobacterium
  - Staphylococcus
  - Rickettsia
  - Chlamydia
  - Mycoplasma

- **Viruses**
  - Pox
  - Influenza
  - Polio
Definition of immunology, Immune System, and Immunity

• The science of immunology deals with the biological and biochemical basis of the defence mechanisms protecting the human body when exposed to infectious agents and toxins.

• These defence mechanisms represent our immune system which may provide immunity, even long-lived protection.
The immune system not only deals with infectious agents

The immune system has the following tasks:

1) Detection and inactivation of infectious agents gaining access to the body (viruses, bacteria, fungi, protozoa and worms) or their toxins.

2) Detection and killing of virus infected body cells.

3) Detection and killing of cancer cells.
The proper function of the immune system depends on many factors such as

- Sleep
- Age
- Psychological stress
- Social distress
- Immunity
- Malnutrition
- Environmental factors
- Inherited factors
- Physical stress
The immune system is made up of many „subsystems“

<table>
<thead>
<tr>
<th></th>
<th>Unspecific immune system</th>
<th>Specific, adaptive immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Susceptibility does not change with repeated infection</td>
<td>Susceptibility decreases with repeated infection</td>
</tr>
<tr>
<td>Soluble (humoral) defence</td>
<td>Complement, lysozyme, interferon</td>
<td>Antibodies (Immunoglobulins, secreted by B-lymphocytes)</td>
</tr>
<tr>
<td>Cellular defence</td>
<td>Phagocytes, natural killers</td>
<td>T-lymphocytes helper cells, cytotoxic cells</td>
</tr>
<tr>
<td>mechanisms</td>
<td></td>
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</tbody>
</table>
Challenge by an infectious agent –
do I get ill or not?

If an infectious agent gains
access to the body, it may be
stopped by:

- body surface
- unspecific immune system

If these barriers are broken,
you usually get ill. Next the
adaptive immune response
takes over. Once the infection
is terminated this way, you
recover and longterm immunity
may protect you against further
infection with the same agent
(typical examples: measles,
German measles, mumps). The
success of vaccinations is
based on the same
mechanisms.
Basic immune response mechanisms

Infectious agent (=antigen) gains access
Skin, mucus membrane

Phagocytosis

Macrophage

Processing

Antigen-presentation in association with MHC II

Release of lymphokines and chemotactic factors such as interferon-α, interleukin-1 & 6, TNF, etc.; neopterin

Receptor recognition of antigen in association with MHC II

T- and B-lymphocytes

Release of lymphokines such as interferon-γ and interleukin-2

Helper

Lymphocyte activation

Lymphocyte proliferation

T-cell mediated immunity

Production and secretion of antibodies (immunglobulines M, G, A and E)
The first lines of defence: External body surfaces

- Cilia
- Mucus in saliva
- Mucus
- Lysozyme
- Acid
- Normal bacterial skin flora
- Normal gut flora
- Fatty acids
- Washing action of urine
- Washing action of saliva
- Lysozyme

Diagram showing the first lines of defence, including cilia, mucus, lysozyme, and fatty acids as natural immune responses.
More unspecific defence lines:

- Phagocytosis of bacteria and fungi by macrophages

- Inflammation: Acute inflammatory response, release of **acute phase proteins** (following bacterial infection or tissue damage (viruses, sore muscles (!))).

- Release of interferon by macrophages, T-cells, and virus-infected tissue cells, Interferon leads to inhibition of proteins synthesis (mRNA translation) and degradation of viral and host mRNA in infected and healthy tissue cells.
Inflammation: Acute phase proteins

• Acute phase proteins (e.g. c-reactive protein (CRP), a protease, as an example are blood plasma proteins which show a dramatic increase in concentration in response to infection or tissue damage (up to 1000-fold). These proteins are part of the second line of defence: Humoral defence mechanisms.

• CRP can bind to a number of bacteria and fungi and activates complement.

• After the deposition of complement factor C3b the microbe becomes opsonised. Opsonisation enhances adherence of macrophages.

• Since the dramatic increase of new proteins changes the viscosity of blood serum, one of the earliest tests to detect inflammation processes in the body was to measure blood sedimentation. Today the concentration of acute phase proteins is determined by direct methods.

(Gabriel et. al. 2000)
Biological functions of complement

- The name complement is given to a complex series of some 20 proteins, which, along with blood clotting, fibrinolysis and kinin formation, forms one of the triggered enzyme systems found in plasma. Complement produces a rapid, highly amplified response to a trigger stimulus.

- 1) Components of complement can kill bacteria.
- 2) Complement can direct phagocytes to the site of inflammation.
- 3) Complement can opsonize bacteria and fungi.
- Complement is part of the innate, unspecific immune defence. However, it can also be activated by specific, adaptive immune mechanisms.
1) Bacterial killing by complement fragments

How complement may kill bacteria:

- C5b binds to a bacterium
- C6 and C7 bind to C5b
- C8 binds to C5b and penetrates the cell wall
- C5b678 catalyzes the polymerisation of C9
- C9 forms an annular cylinder across the bacterial cell wall
- Pore formation initiates cell lysis (loss of solutes). Breakdown of the chemoosmotic gradient which is essential to drive ATP-synthesis taking place in the bacterial cell membrane.
2) Chemotaxis

A leukocyte is attracted by a chemical signal (chemotaxis) and by squeezing between endothelial cells gets to the site of infection.
2) Chemotaxis: Come to help!

- Bacteria and traumas damage tissue cells. Lysed cells trigger a number of reactions which are known as inflammation (in medical terms: rubor, calor, dolor and tumor).
- Fragments of the complement system, in particular C5a, attract phagocytes along a concentration gradient. This process is called chemotaxis.
- Substances which act chemotactically diffuse from the site of infection/tissue damage into surrounding tissue and blood capillaries nearby.
- Pavementing: Phagocytes adhere to blood vessel endothelium.
- Diapedesis: Phagocytes lyse and cross the basal membrane.

[Diagram showing chemotaxis process]
3) Opsonization: Flavouring of intruders

<table>
<thead>
<tr>
<th>phagocyte</th>
<th>opsonin</th>
<th>binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>2</td>
<td>complement C3b</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>antibody</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>antibody and complement C3b</td>
<td>++++</td>
</tr>
</tbody>
</table>

- Phagocytes have an innate capability to bind to microbes such as bacteria (1). Binding is enhanced by complement fragments (C3b). Thus, C3b-coated bacteria favor binding (2).
- Some microbes do not trigger the complement cascade. In this case antibodies (immunoglobulins) take over. Antibodies also act as opsonins and enhance binding of phagocytes to microbes (3).
- Interestingly, the combination of C3b and immunoglobulins results in maximum binding (4).
Plasma levels of acute phase proteins prior to, during and following a 3 hours run to exhaustion

- The graph shows plasma concentration of 3 typical acute phase proteins prior to, during and following an exhaustive 3 hours run. It takes up to 2 days until normal levels are restored.
- Why are acute phase proteins released by strenuous exercise?
Mind the reasons why plasma concentration of a substance can increase:

- Dehydration (Perspiration, breathing)
- Changes of concentration in different body compartments
- Changes in production and/or release (glands)
- Changes in rate of decomposition (e.g. liver)
- Changes in rate of elimination (e.g. urine, sweat)
Mind the reasons why plasma concentration of a substance can increase:

- Dehydration (Perspiration, breathing)
- Changes of concentration in different body compartments
- Changes in production and/or release (glands)
- Changes in rate of decomposition (e.g. liver)
- Changes in rate of elimination (e.g. urine, sweat)

- Measuring hematocrite (blood centrifugation, percentage of particles) allows compensation for loss of water.
Raster electron microscopy shows blood cells of a patient with leukaemia. This is why there are so many leukocytes on this picture. White blood cells are globular in shape, red blood cells are disc-like. Scale (5µm) is indicated at the bottom to the right.
White blood cells: Most important players

- White stem cell
  - Precursor
    - Neutrophilic granulocytes
    - Killer cells
      - Monocytes
        - Macrophages
    - Eosinophils
  - Precursor
    - T-lymphocyte
    - B-lymphocyte
    - Helper cells
    - Cytotoxic cells
Differentiation of white blood cells

- **Flow Cytometry / Cell Sorting**

  - Labelling cells with dyes/fluorescent dyes

  - Flow-cytometry using laser light. Option: cell sorting

  - Final analysis (Cluster of Differentiation = CD)
Cellular immunity:

(a) Traditional view

(b) Revised view

(Smith, 2003)
Monocytes, macrophages and phagocytes

Phagocytes are found in the bloodstream but also in the reticuloendothelial system (RES), i.e. in many organs:

(s. figure to the left)
- Lungs: Alveolar macrophages
- Spleen: Macrophages
- Blood: Monocytes
- Lymph nodes: Resident and recirculating macrophages
- Precursor cells in bone marrow

(s. figure to the right)
- Brain: Microglial cells
- Liver: Kupffer cells
- Kidney: Mesengial phagocytes
- Joints: Synovial A cells

The human body produces every day 100 g of granulocytes! This amount corresponds to about $10^{11}$ cells.
Effect of short strenuous exercise on the number of leucocytes

The figure to the left shows changes in leukocyte numbers in the bloodstream following short strenuous exercise (less than about 30 minutes). The graph comprises the results of several studies (number N). The range and the average of changes is given. 0% means the value at rest (range: 4 - 10 \(10^9\) cells l\(^{-1}\)).

In most cases, the number of leucocytes in the bloodstream increases by about 50% and recovers following 2 hours of rest.

Changes are usually statistically significant (but most probably meaningless to immunity, the reason for the increase is a shift from cell pools sitting at rest on walls of blood vessels into the bloodstream).

(D. Escher, 1992)
Effect of prolonged exercise (3 h) on the number of leucocytes

The graph shows the average of increase in leukocyte numbers as a percentage of the resting value following a 3 hours run. The increase is more enhanced, continues to rise even following the run, and it takes much more time to recover as compared to short bouts of exercise.

Changes are usually statistically significant (but most probably meaningless to immunity, the reason for the increase is a shift from cell pools sitting at rest on walls of blood vessels into the bloodstream).

(D. Escher, 1992)
Lymphocytes

- Lymphocytes belong to white blood cells
  - White blood cells: $4 - 10 \times 10^9$ per litre (=Giga)
  - Lymphocytes: $1.5 - 4 \times 10^9$ per litre
- Lymphocytes represent about 2% of the body weight, i.e. about 1.5 kg or $10^{12}$ cells
- Only 1 - 2% of the lymphocytes swim in the bloodstream - the rest is found in the spleen, in lymph nodes and patrolling in body tissue
- About $10^9$ lymphocytes are produced daily
- About $80 \times 10^6$ phagocytes are formed per minute, corresponding to 100 g per day
- B-lymphocytes produce antibodies (immunoglobulins)
- T-cells represent the cellular defence (cell-mediated immunity) and are made up of so called „sub populations“ such as:
  - Helpers
  - Suppressors
  - Cytotoxic cells etc.
Lymphocyte trafficking

After differentiation in the bone marrow, Lymphocytes get to the thymus, which they leave after maturation. They follow the pathways shown in the graph and patrol through tissue compartments. Most of the lymphocytes (98%) is found in tissue and not in the bloodstream. Lymphocytes can park in lymph nodes and the spleen for several weeks and months.
T-cell school: learning self-tolerance and reaction to foreign antigens

- T-cells are formed from stem cells in the red bone marrow. They learn self-tolerance in the thymus gland behind the sternum. T-lymphocytes actively learn self tolerance; otherwise they would attack own body tissue and cells.
- In T-cells that do not have the ability to tolerate self, a suicide mechanism is triggered (apoptosis).
- Matured lymphocytes leaving the thymus reach various tissue pools via the blood stream: Spleen, MALT (Mucosal-associated lymphoid tissue), lymph nodes, peripheral tissue.
- Patrolling lymphocytes recirculate via lymph vessels, lymph nodes back to the blood stream.
- 2% of the lymphocyte pool is found in the bloodstream, the rest is in the spleen, MALT and tissue.
- B-cells need no „teaching“ as T-cells do, for activation B-cells depend on T-cells (helper cells).
Effect of short strenuous exercise on the number of lymphocytes

Change in % of value at rest

The figure to the left shows changes in lymphocyte numbers in the bloodstream following short strenuous exercise (less than about 30 minutes). The graph comprises the results of several studies (number N). The range and the average of changes is given. 0% means the value at rest.

In most cases, the number of lymphocytes in the bloodstream increases by about 100% and recovers quickly.

Changes are usually statistically significant (but most probably meaningless to immunity, the reason for the increase is a shift from cells sitting at rest on walls of blood vessels into the bloodstream).

(D. Escher, 1992)
Possible mechanisms of lymphocyte recruitment

The following mechanisms of changes blood concentrations of lymphocytes are presently discussed:

• Changes in cell adherence (adhesion proteins, selectins)
• Changes in circulation patterns between different compartments (trafficking)

Possible mechanisms at molecular level:

• Blocking of adhesion proteins in cell membranes by a ligand
• Detachment of soluble adhesion proteins
• Regulation of adhesion proteins by cytokins and catecholamines
• Mechanical deformation of leukocytes by mechanical forces (shear forces)

(Nielsen und Lyberg 2004)
Effect of prolonged exercise on number of lymphocytes

21 km run (workout intensity)

- Line in red: 75% percentile
- Line in blue: median
- Line in black: 25% percentile.
- Blood samples were taken at days indicated with a circle.

Marathon race (42.6 km)

Changes in numbers of lymphocytes shown on this transparency are not significant.

(Gmünder et al. 1988, 1990)
Effect of prolonged exercise on number of T-lymphocytes

21 km run (workout intensity)

Marathon race (42.6 km)

Changes in numbers of lymphocytes shown on this transparency are not significant.

(Gmünder et al. 1988, 1990)
To activate a T-cell an antigen presenting cell (APC) is mandatory. It takes 3 steps for activation:

1. T-cells bind to APC; 2 signals are needed for successful binding:
   - Recognition of antigen in association with MHC class II (1)
   - Following successful recognition APCs release interleukin-1 (IL-1). IL-1 leads to release of IL-2 in bound T-cells. (2)

2. IL-1 acts as a signal to T-cells to present IL-2 receptors. The IL-1 / IL-2 system acts as an amplifier (3)

3. These steps lead to a rapid, highly amplified response to the trigger stimulus.

Note: MHC II is found only on APCs. MHC I is found on all cells. If immuno competent cells find an antigen in association with MHC II, they „know“ they deal with an APC. If they meet antigens in association with MHC I, they „know“ they docked to a tissue cell infected by a virus. This cell is killed to prevent spreading of infection.
Effect of prolonged exercise on T-lymphocyte activation by Con A (test of lymphocyte function)

21 km run (workout intensity)

In the laboratory activation of T-cells can be measured by exposing T-cells to substances that induce proliferation. No antigen/MHC II is needed in this test. One of these substances is Concanavalin A (Con A). This test is thought to reflect lymphocyte function.

Units on graphs: Internal laboratory standard of normal resting people = 1

Changes in lymphocyte function shown on this transparency are significant and most probably mean decreased immunity.

(Gmünder et al. 1988, 1990)
B-lymphocyte activation

1. Macrophages: Phagocytosis and processing of antigens

2. Antigen presentation to patrolling T- and B-cells (MHC II-restricted). B-cells depend on T-helper cells to start to proliferate and differentiate to antibody producing cells.

3. Clonal proliferation into antibody-forming cells (AFC).

How T-helper cells help: Cell to cell contact and lymphokines
Response of antibody-formation to an antigen challenge

Primary and secondary antibody response.

IgM appear first following exposition to a new antigen. IgG formation is retarded.

However, when the body is exposed a second time to a specific antibody, IgG formation is much faster and more enhanced (s. graph). The reason is memory B-cells.
Effect of prolonged exercise on immunoglobulins

21 km run (workout intensity); immunoglobulin G: Total (g/l)

Changes in subclass II are statistically significant at the 95% level. This could indicate lowered immune defence after the run.

(Gmünder et al. 1988, 1990)
### Overview of findings
(compiled from studies presented here and elsewhere)

<table>
<thead>
<tr>
<th>Acute phase reaction</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of leucocytes</td>
<td>Increase</td>
</tr>
<tr>
<td>Number and function of natural killers</td>
<td>Increase</td>
</tr>
<tr>
<td>Function of macrophages in blood</td>
<td>Increase</td>
</tr>
<tr>
<td>Function of macrophages in tissue</td>
<td>Increase</td>
</tr>
<tr>
<td>Acute phase proteins (CRP, TNF, neopterin)</td>
<td>Increase</td>
</tr>
<tr>
<td>Complement system</td>
<td>Activated</td>
</tr>
<tr>
<td>Interferoneα</td>
<td>Increase</td>
</tr>
<tr>
<td>Interleukin-1 release</td>
<td>Increase</td>
</tr>
<tr>
<td>Interleukin-6 release</td>
<td>Increase</td>
</tr>
</tbody>
</table>

### Specific immune defence

<table>
<thead>
<tr>
<th>Number of lymphocytes in bloodstream</th>
<th>No change or decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of T-cells</td>
<td>No change or decrease</td>
</tr>
<tr>
<td>Number of B-cells</td>
<td>No change or decrease</td>
</tr>
<tr>
<td>Number of helper cells</td>
<td>No change or decrease</td>
</tr>
<tr>
<td>Number of suppressor cells</td>
<td>No change or increase</td>
</tr>
<tr>
<td>Activation of T-cells</td>
<td>Decrease</td>
</tr>
<tr>
<td>Interleukin-2 release</td>
<td>Decrease</td>
</tr>
<tr>
<td>Number of interleukin 2 receptors on T-cells</td>
<td>No change or decrease</td>
</tr>
<tr>
<td>Interferon γ release</td>
<td>No change</td>
</tr>
<tr>
<td>Plasma concentration of immunoglobulins</td>
<td>No significant changes</td>
</tr>
</tbody>
</table>
Interpretation und Discussion
Why does sport initiate an acute phase reaction?

- Damage to tissue: sore muscles, wear and tear
  - antigens get exposed that are normally not (sore muscles)
- Endotoxins: Mechanical damage to the gut by distance running
  - Bacterial endotoxins pass the mucuous membrane of the gut
Why and how the specific immune system becomes inactivated?

✿ Tissue damage (sore muscle, joints, gut etc.) induce an acute phase reaction. A „sterile“ inflammation develops at the sites of damage. Macrophages home in to help to get rid of dead cells, damaged tissue, and probably toxins crossing the gut.

♫ Stress hormones attenuate the response of specific immune cells. This makes sense, since the immune system does not have to fight off a real infection.

As a consequence:

♫ Too much continuous stress could lead to a permanent depression of specific immune functions.
Stress hormones during and after physical activity

Cortisol is known to be more associated with psychological distress. Catecholamines increase mainly with physical stress. You can see that this person probably was distressed before the start.
Psychischer Stress

- **Students: Stress at exams**
  Reduced cellular immunity (Uchakin et al. 2001), reduced response to vaccination (Glaser 1992)

- **Mourning (death of relatives)**
  Reduced lymphocyte activity (Kiecolt-Glaser 2002)

- **General distress**
  Increased susceptibility to infections. Challenge experiments with cold viruses. (Cohen 1998)
The immune system and the nervous system interact

Table 1. Cytokines and Other Mediators of Inflammation That Influence the Hypothalamic–Pituitary–Adrenal Axis.

<table>
<thead>
<tr>
<th>Cytokines</th>
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</thead>
<tbody>
<tr>
<td><strong>Inflammatory cytokines</strong></td>
</tr>
<tr>
<td>Tumor necrosis factor α</td>
</tr>
<tr>
<td>Interleukin-1α and interleukin-1β</td>
</tr>
<tr>
<td>Interleukin-6</td>
</tr>
<tr>
<td><strong>Other cytokines</strong></td>
</tr>
<tr>
<td>Interferon α</td>
</tr>
<tr>
<td>Interferon γ</td>
</tr>
<tr>
<td>Interleukin-2</td>
</tr>
<tr>
<td><strong>Growth factors</strong></td>
</tr>
<tr>
<td>Epidermal growth factor</td>
</tr>
<tr>
<td>Transforming growth factor β</td>
</tr>
<tr>
<td><strong>Lipid mediators</strong></td>
</tr>
<tr>
<td>Prostanoids</td>
</tr>
<tr>
<td>Platelet-activating factor</td>
</tr>
</tbody>
</table>

(Chrousos 1995)
Psychoneuroimmunologie

In a Harvard study of the 1970ies it was found that leukocytes have receptors for neuropeptides (Review: Kiecolt-Glaser et al. 2002).

Hypothesis
Physical activity can affect the control mechanisms shown.
Spezielle Fragestellungen

- Immunomodulation
- Anti-inflammatory effect
- Stress homeostasis
- Immunity and old age
- Multiple sclerosis
- Cancer/HIV

Bedrest/Head down tilt
Surprisingly leads to a reduced T-lymphocyte activation
(Gmünder et al. 1990)
Immunomodulation in Abhängigkeit von Volumen/Intensität

Performance of immune system

Risk of getting infected

Immune system cannot cope any more

Adaptation of immune system

Stressregulation of immune system

Not specific

Intensity and Volume of training and competitions

(Gmünder 1991, Nieman 2003)
Effects of moderate exercise

• **Intervention**
  4 hours cycling at 70% of individual maximal lactate steady state (59% VO$_2$max)

• **Laboratory**
  IL-6, CRP, leukocyte- und lymphocyte populations, NK-activity, neutrophils, monocytes; adrenaline, noradrenaline, cortisol

• **Results**
  Moderate acute-phase-reaction
  Moderate increase in stress hormone levels

• **Conclusions**
  No changes no impairment of immune functions. This is in stark contrast to studies where high intensity or total exhaustion were applied.

• **Do athletes work out at this level of intensity?**

(Scharhag et al. 2005)
Anti-inflammatory effect of sport

A: Time-dependent concentrations of acute phase indicators. Tumour necrosis factor (TNF) and interleukin-1 (IL-1) initiate the inflammation.

B: Acute phase proteins TNF and IL-1 are not released during moderate and regular exercise. Anti-inflammatory cytokines prevail, in particular IL-6.

Anti-inflammatory effect of sport

The following conditions are presently seen as an inflammation:

- Cardio-vascular diseases (atherosclerosis)
- Type-2-diabetes: Because of the cytokine levels this condition is regarded as a permanent systemic low-level inflammation
- Alzheimer

It is interesting to note that

- IL-6 is released by the working muscle
- Moderate exercise has anti-inflammatory properties
- IL-6 modulates glucose and fat metabolism very favourably

Sport and stress homeostasis

• Introduction

• Hypothesis
  – There are persons who apply sports as a sort of self therapy without being aware of the fact. Withdrawal of exercise should increase the symptoms.

• Experiment
  – Psychosocial factors, myalgia, and function of the autonomous nervous system are measured after deprivation of sports. 18 healthy, exercising subjects (≥ 4 h/week) had to do without workouts for 1 week.

• Results
  – 8 out of the 18 people showed an increase in symptoms. Only this subset showed lower cortisol levels, NK-activity, and function of the autonomous nervous system before the test.

• Conclusion
  – People with reduced stress management abilities unconsciously control stress homeostasis by regular exercise to suppress symptoms. Giving up sports can affect their well being.
Immunity and old age

Physical exercise

- Reduced efficacy of influenza vaccination in 65 years old people.
- The effect of moderate exercise was investigated. Intervention consisted of 3 aerobic classes per week for 10 months. Control group did not work out.
- Intervention: Flu vaccination before and after Training period.

Baseline experiment in year 2000 (graph to the left)
Controls and intervention group (no training in 2000) did not differ significantly 4 weeks and 3 months after being vaccinated (MFI: Manifold increase in titer).

Intervention in 2001 (graph to the left)
Intervention group did develop higher antibody titers following intervention than controls. Young adults showed a very high response even without working out.

(Kohut and Senchina 2004
Kohut et al. 2004)
Physical or psychological factors?

The increase in numbers of successfully vaccinated elderly people could be related to psychological factors as well, not only to physical factors (Kohut et al., 2005).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control pre-intervention</th>
<th>Exercise pre-intervention</th>
<th>Control post-intervention</th>
<th>Exercise post-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>76.05 ± 18.5</td>
<td>84.6 ± 17.8</td>
<td>76.4 ± 18.0</td>
<td>82.6 ± 17.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 6.0</td>
<td>28.5 ± 4.8</td>
<td>27.4 ± 5.3</td>
<td>27.8 ± 5.1</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>137.1 ± 16.0</td>
<td>141.5 ± 17.7</td>
<td>135.9 ± 15.4</td>
<td>138.5 ± 10.3</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>81.2 ± 10.8</td>
<td>83.4 ± 8.0</td>
<td>79.0 ± 7.1*</td>
<td>77.6 ± 10.3*</td>
</tr>
<tr>
<td>6 min walk (yards)</td>
<td>615 ± 109</td>
<td>636 ± 58</td>
<td>632 ± 109</td>
<td>716 ± 78**</td>
</tr>
<tr>
<td>Sense of coherence</td>
<td>75.9 ± 8.5</td>
<td>70.3 ± 8.9</td>
<td>72.1 ± 10.8</td>
<td>72.8 ± 7.2**</td>
</tr>
<tr>
<td>Depression</td>
<td>2.8 ± 3.1</td>
<td>3.8 ± 2.0</td>
<td>4.2 ± 3.0</td>
<td>3.1 ± 2.8**</td>
</tr>
</tbody>
</table>

| Influenza A H1N1          | 5.7 ± 0.32               | 5.2 ± 0.30                 | 6.0 ± 0.32                | 7.3 ± 0.51                 |
| Week 4 post               | 85%                      | 86%                        | 58%                       | 85%                        |
| Influenza A H1N1          | 6.5 ± 0.32               | 6.6 ± 0.29                 | 5.8 ± 0.33                | 7.0 ± 0.54                 |
| Week 12 post              | 77%                      | 65%                        | 35%                       | 79%                        |

* Main effect of time (change occurred in both exercise and control groups, p < .05).
** Treatment by time interaction (improvement in exercise group > control group, p < .05).
Sport and multiple sclerosis

• Introduction
  – Originally, it was thought that physical inactivity is the best therapy to avoid escalating episodes. Beginning with the 1980ies, fitness training was discovered as a means to treat the disease efficiently.

• Hypothesis
  – Physical activity improves coordinative performances. Quality of life, and immunoenocrine functions (Schulz et al. 2004). The questions arose whether IL-6 and sIL-6R (HAP-axis) have a neurotrophic effect.

• Experiment
  – Coordinative performance, quality of life, IL-6, sIL-6R, nerve growth factor, and brain derived neurotrophic factor was determined prior to and after exercise. In total, 39 patients were involved. The intervention group did workouts on 2 days per week for 8 weeks for 30 minutes at 75% maximal performance.

• Results
  – Coordinative performance, and quality of life were better after intervention. IL-6, sIL-6R, nerve growth factor, and brain derived neurotrophic factor were not affected.

• Conclusion
  – The positive effect of sports was corroborated. Anti-inflammatory effects were not found.
Sports, cancer, and HIV

- Depending on the study design and the hypothesis tested, studies with animals showed reduced growth of tumours and metastases – or no effect at all. (Colbert et al. 2000, Davis et al. 1998, Woods et al. 1994, Zielinski et al. 2004)

- With humans the effect of sports is still being debated. In some studies no effect was found, in others a positive effect was found. Study designs are sometimes mediocre due to low numbers of persons tested. No intervention studies, only epidemiological data available. (Torti und Matheson 2004, Fairey et al. 2000, Westerlind 2003)

- Moderate exercise has no negative affect on HIV-infection and AIDS. Quality of life is improved. (Shephard 1998, Stringer et al. 1998)

- Hypothesis: Light to moderate exercise improves immunity as long as you like doing sports. Sport can be part of the therapy:
  - With people who have cancer
  - With people who have an HIV-infection or AIDS has developed

  If you feel uncomfortable doing sports, you perceive working out as a stress. This could harm the function of the immune system.
Tipps for training and competition

• Overtraining
• Training, competition and illness
• Nutrition and rehydration
Overtraining

- Regular exhausting training without sufficient recovery and rehabilitation can lead to overtraining (overtraining syndrome).

- Microlesions in muscles and connective tissue lead to chronic, systemic inflammation (s. www.svl.ch/Overtraining).
Overtraining syndrome

Table 1 - The major symptoms and signs of overtraining.

<table>
<thead>
<tr>
<th>Alteration of physiological functions and adaptation to performance</th>
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</thead>
<tbody>
<tr>
<td>Decreased performance</td>
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<tr>
<td>Decreased muscular strength</td>
</tr>
<tr>
<td>Muscle soreness and tenderness</td>
</tr>
<tr>
<td>Reduced toleration of loading</td>
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<tr>
<td>Recovery prolonged</td>
</tr>
<tr>
<td>Chronic fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Sleep-wake cycle abnormalities</td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
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<tr>
<td>Alteration of sexual functions</td>
</tr>
<tr>
<td>Changes in blood pressure and heart rate</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Psychological symptoms</th>
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</thead>
<tbody>
<tr>
<td>Feelings of depression</td>
</tr>
<tr>
<td>General apathy</td>
</tr>
<tr>
<td>Difficulty in concentrating</td>
</tr>
<tr>
<td>Emotional instability</td>
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<tr>
<td>Fear of competition</td>
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<tr>
<td>Loss of appetite</td>
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<tr>
<td>Excitation and restlessness</td>
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<tr>
<td>Phlegmatic behaviour and inhibition</td>
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<table>
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<tr>
<th>Immunological dysfunction</th>
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<tbody>
<tr>
<td>Increased susceptibility to and severity of bacterial infections</td>
</tr>
<tr>
<td>Reactivation of herpes viral infections</td>
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<tr>
<td>Decreased functional activity of neutrophils</td>
</tr>
<tr>
<td>Decreased total lymphocyte counts</td>
</tr>
<tr>
<td>Decreased production and secretion of immunoglobulins</td>
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<table>
<thead>
<tr>
<th>Biochemical alterations</th>
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</thead>
<tbody>
<tr>
<td>Decreased hemoglobin, serum iron and ferritin</td>
</tr>
<tr>
<td>Negative nitrogen balance</td>
</tr>
<tr>
<td>Increased urea levels</td>
</tr>
<tr>
<td>Increased uric acid productions</td>
</tr>
<tr>
<td>Decreased glutamine concentrations</td>
</tr>
<tr>
<td>Mineral depletion (Zn, Co, Al, Mn, Se, Cu, etc.)</td>
</tr>
<tr>
<td>Low free testosterone</td>
</tr>
<tr>
<td>Decreased free testosterone to cortisol ratio of more than 30%</td>
</tr>
</tbody>
</table>

**Diagnosis**

- Difficult. There is no reliable, specific test
- Best indicators: hormone levels before and after exercise

**Therapy**

- Rest
- Very light exercise in different sport can be considered

(Table: Angeli et al., 2004; Urhausen und Kindermann, 2002)

Also s. www.svl.ch/Overtraining)
Consequences of Overtraining

a) Open-window hypothesis: An infection is more likely 3–72 hours after excessive performance.

b) Hypothesis cumulative effects: Excessive exercise in combination with lack of sufficient recovery and rehabilitation leads to chronic changes in immune functions.

Graph: Smith (2003)
(a) Pedersen and Ullum (1994)
(b) Mackinnon (1999)
Training, competition, and illness
Training and competitions with a fever?

- Intensive exercise enable viruses to cross mucous membranes in the respiratory and digestive tract more efficiently. Once in the bloodstream, it is more likely that the heart becomes infected (cardiotropic viruses).

- Excessive and exhausting exercise increase the likelihood of permanent damage to heart muscle and valves as a consequence of this infection.
  - There are many sports celebrities and young aficionados (mostly men) who continued to work out hard with a virus infection and/or fever. This can result in instant death. Examination of the heart showed permanent damage as a consequence of repeated viral infections.

- Recommendations
  - No training with a fever
  - No training with colds when throat hurts
  - If there is no fever and no symptoms in the throat, just a running nose you may work out lightly in the aerobic range. No anaerobic loads.
Nutrition and rehydration

- Undernourishment is very common among athletes. Caloric deficiency (!), iron, zinc, vitamins A, E, B6 und B12
  ETH-conference on applied sports nutrition 2003 und 2005

- Megadoses of vitamins and trace minerals can cause damage

- Working out with insufficient carbohydrate uptake (low blood glucose):
  - Increased stress hormone levels (cortisol, catecholamines)
  - Effect on a variety of immune parameters
  Gleeson et al. 2004
  - No effect of carbohydrate drink on oral immunity (IgA)
  Tzai-Li and Gleeson 2005

- Antioxidants could have beneficial effect on exercise-induced immunodepression
  Gleeson 2006

- Carbohydrate supply:
  30 – 70 g h⁻¹ as a sports drink (60 – 90 g l⁻¹ sugar)
References (1)

References (2)

References (3)

Thanks!