Sports and Immunity

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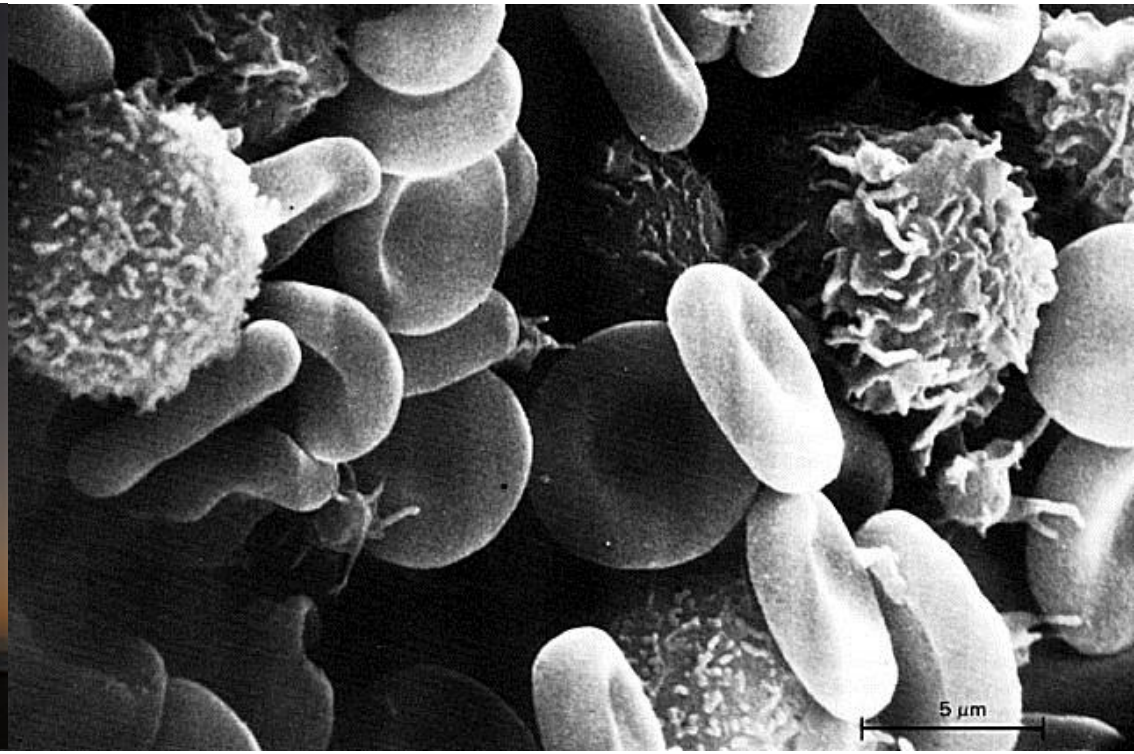

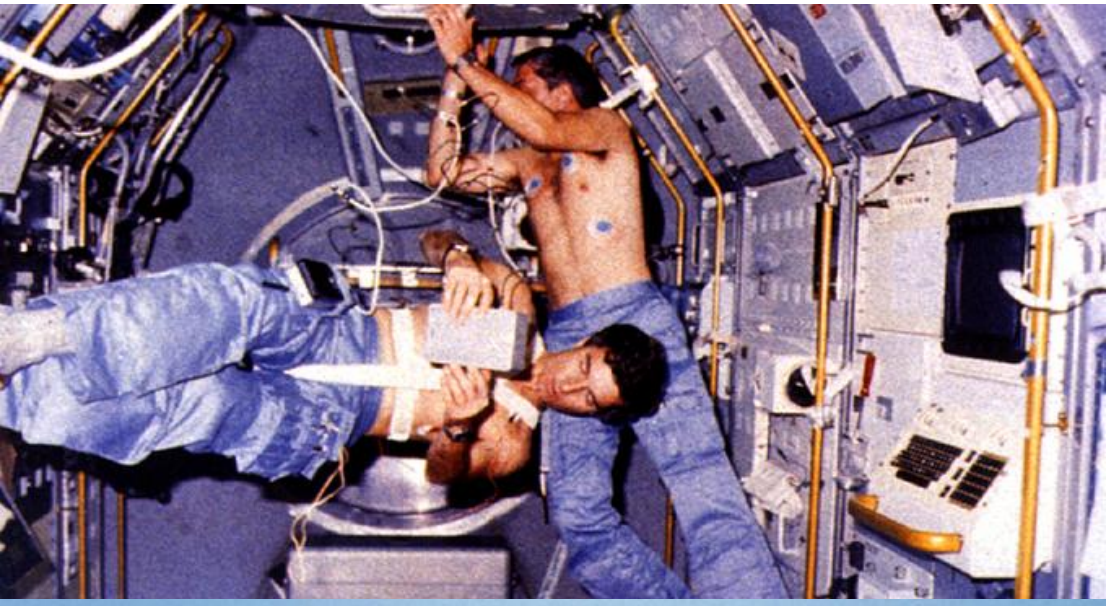


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Sports: Does it enhance or impair immunity?

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?


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Observations / anecdotic reports are contradictive

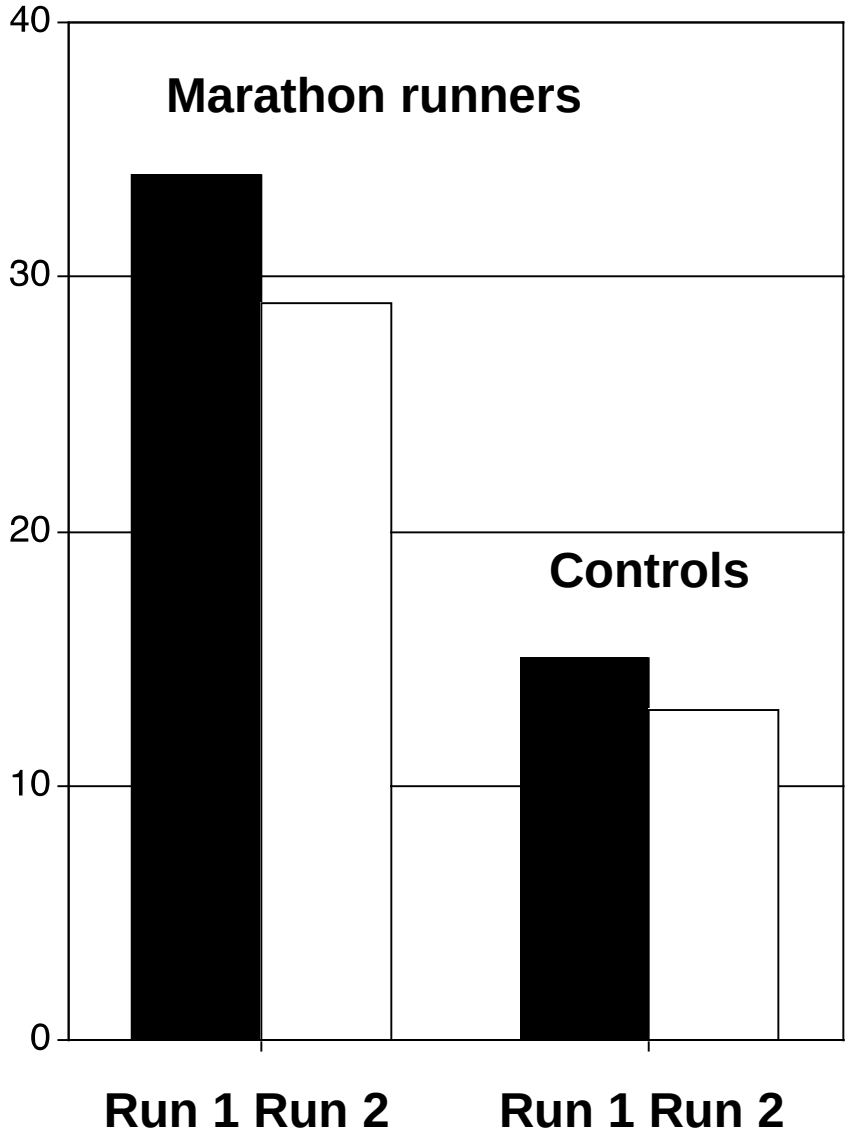
- **Anecdotic reports of coaches: Athletes are more susceptible to infectious diseases during and following important competitions (cold, diarrhoea).**

- **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)

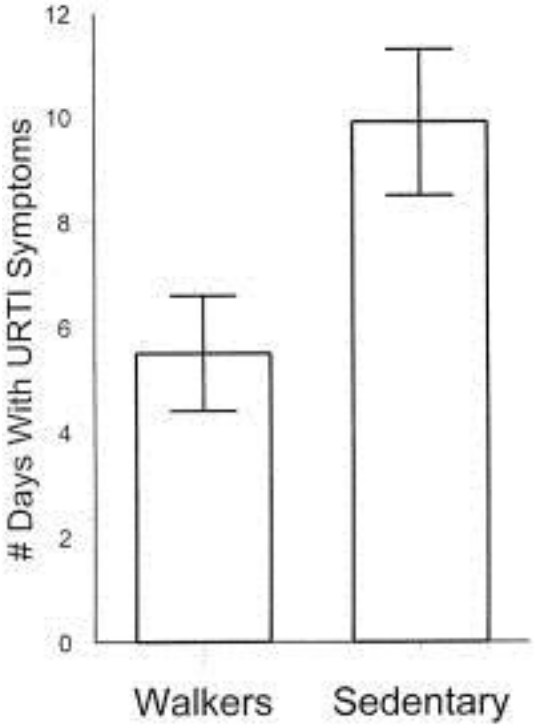
Number of colds in relation to physical activity

Nieman et al. 1998a+b

126 women

45 min walking for 5 days per week

URTI: Upper respiratory tract infections

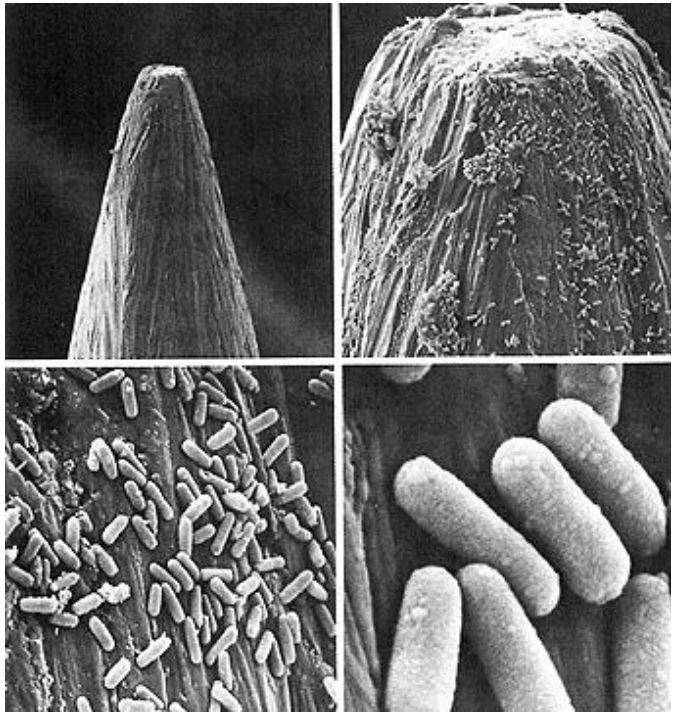


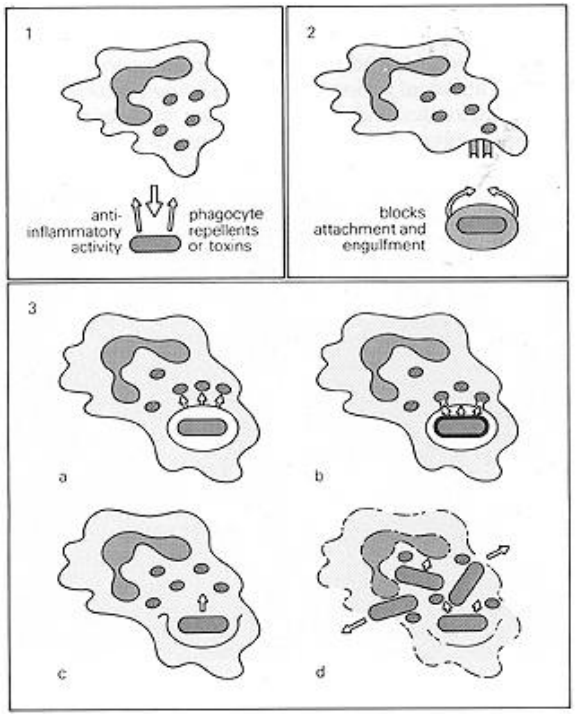
Nieman et al. 1993

Number of people who took a cold (during a period of 12 weeks)

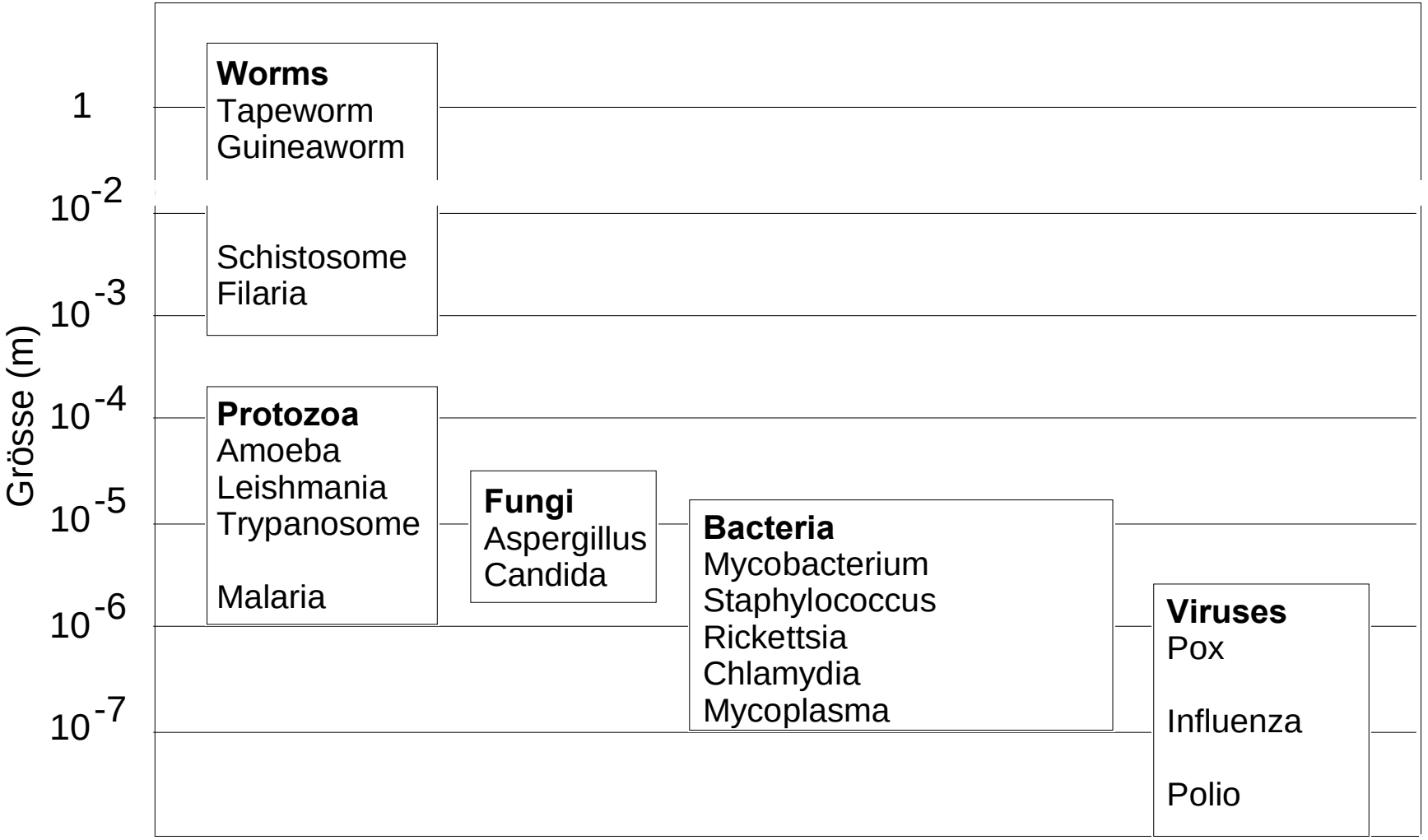
Very active and fit	8 %
Moderately active and fit	21 %
Inactive, less fit	50 %

Introduction into Immunology





The range of infectious agents which challenge the immune system



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

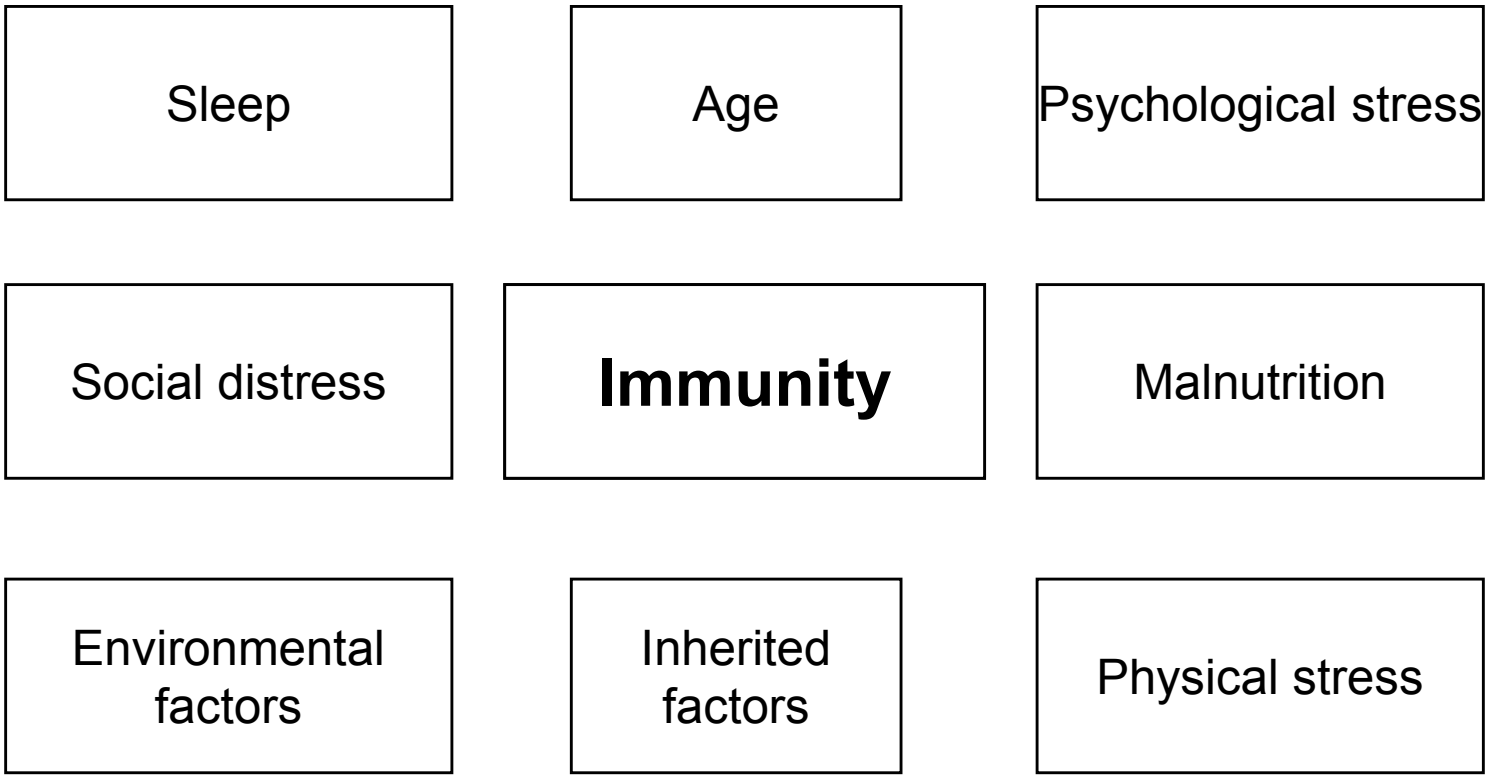
The immune system has the following tasks:

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.**

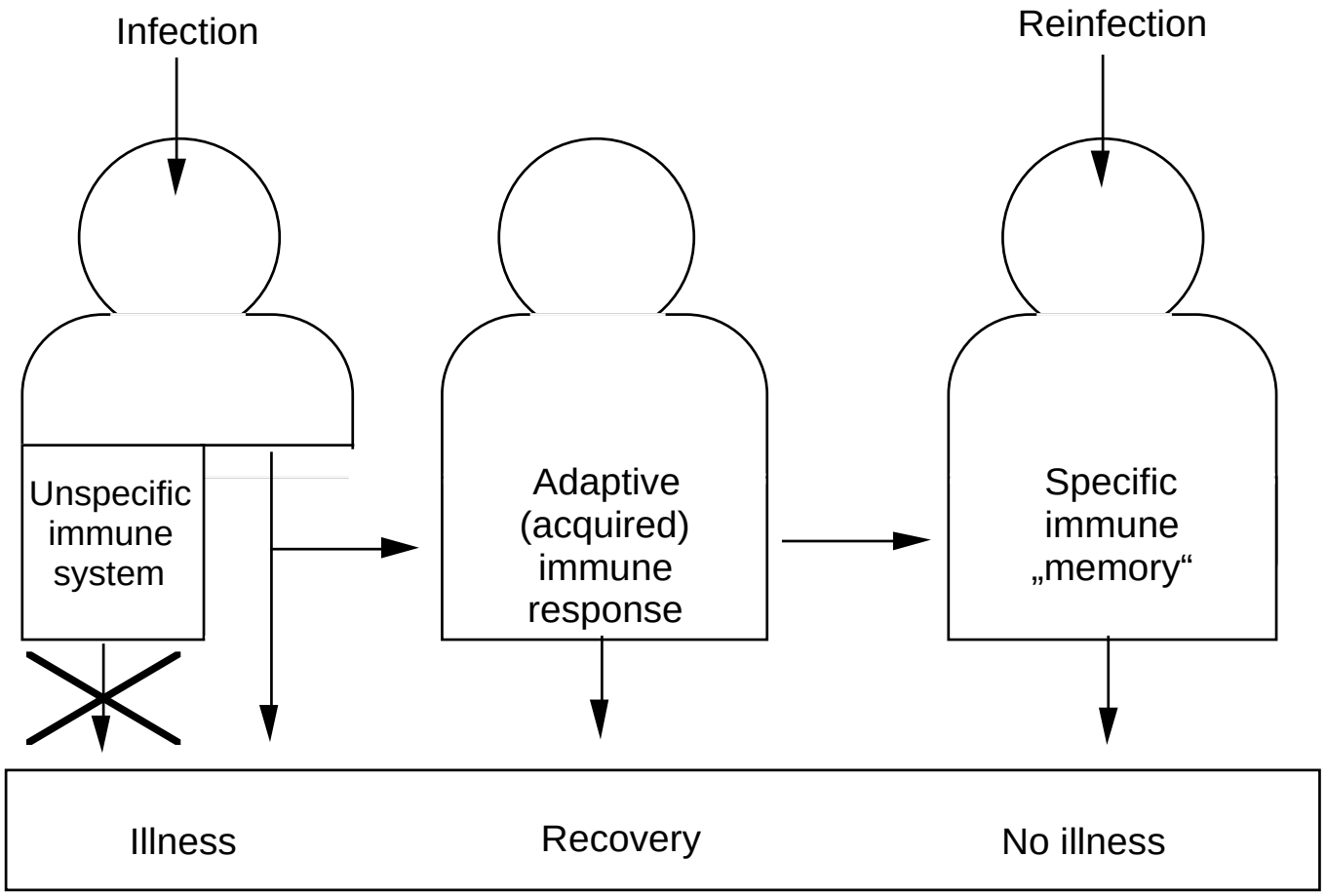
The proper function of the immune system depends on many factors such as



The immune system is made up of many „subsystems“

	Unspecific immune system	**Specific, adaptive immune system**
	Susceptibility does not change with repeated infection	Susceptibility decreases with repeated infection
Soluble (humoral) defence mechanisms	Complement, lysozyme, interferon	Antibodies (Immunoglobulins, secreted by B-lymphocytes)
Cellular defence mechanisms	Phagocytes, natural killers	T-lymphocytes helper cells cytotoxic cells

Challenge by an infectious agent – do I get ill or not?

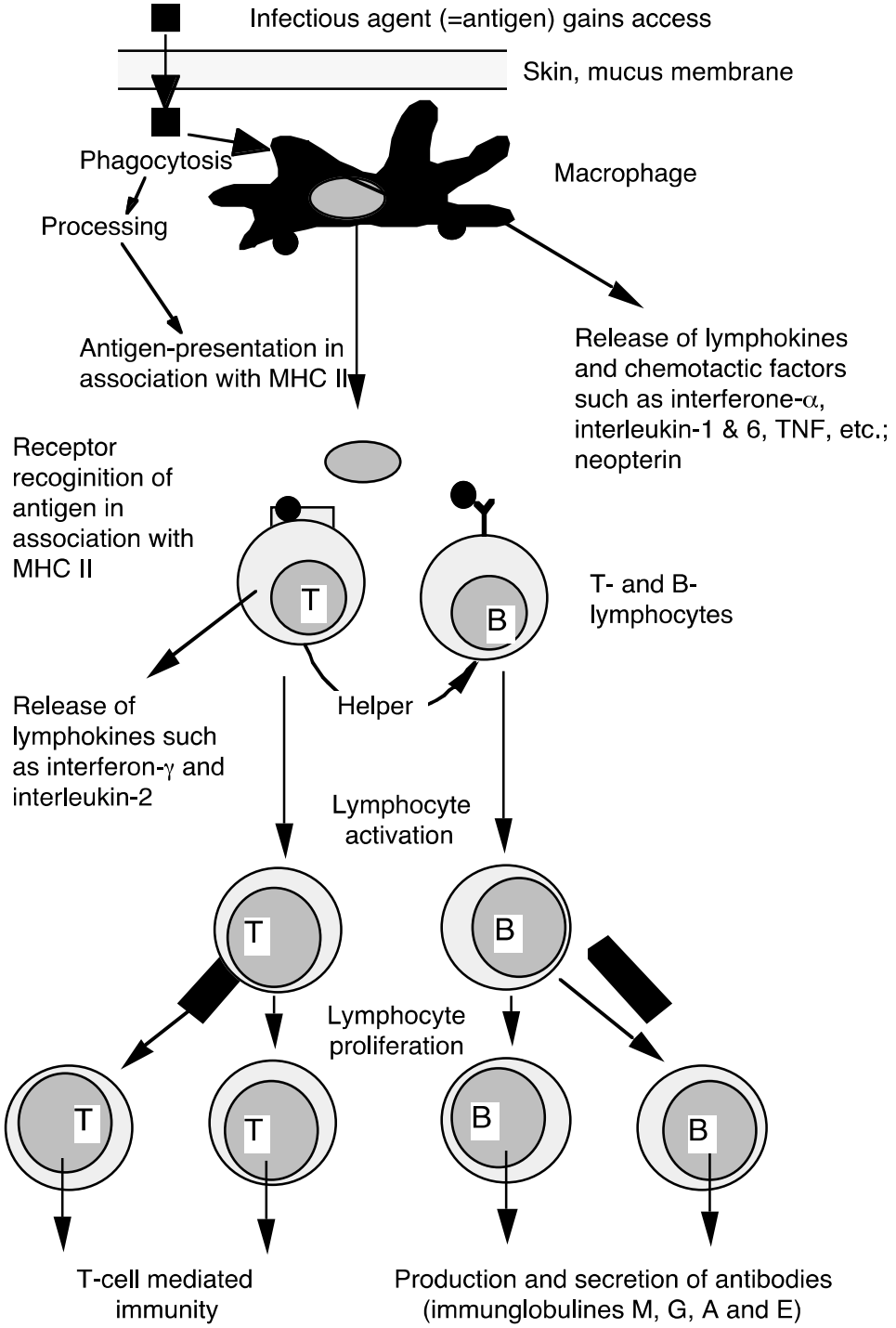


If an infectious agent gains access to the body, it may be stopped by:

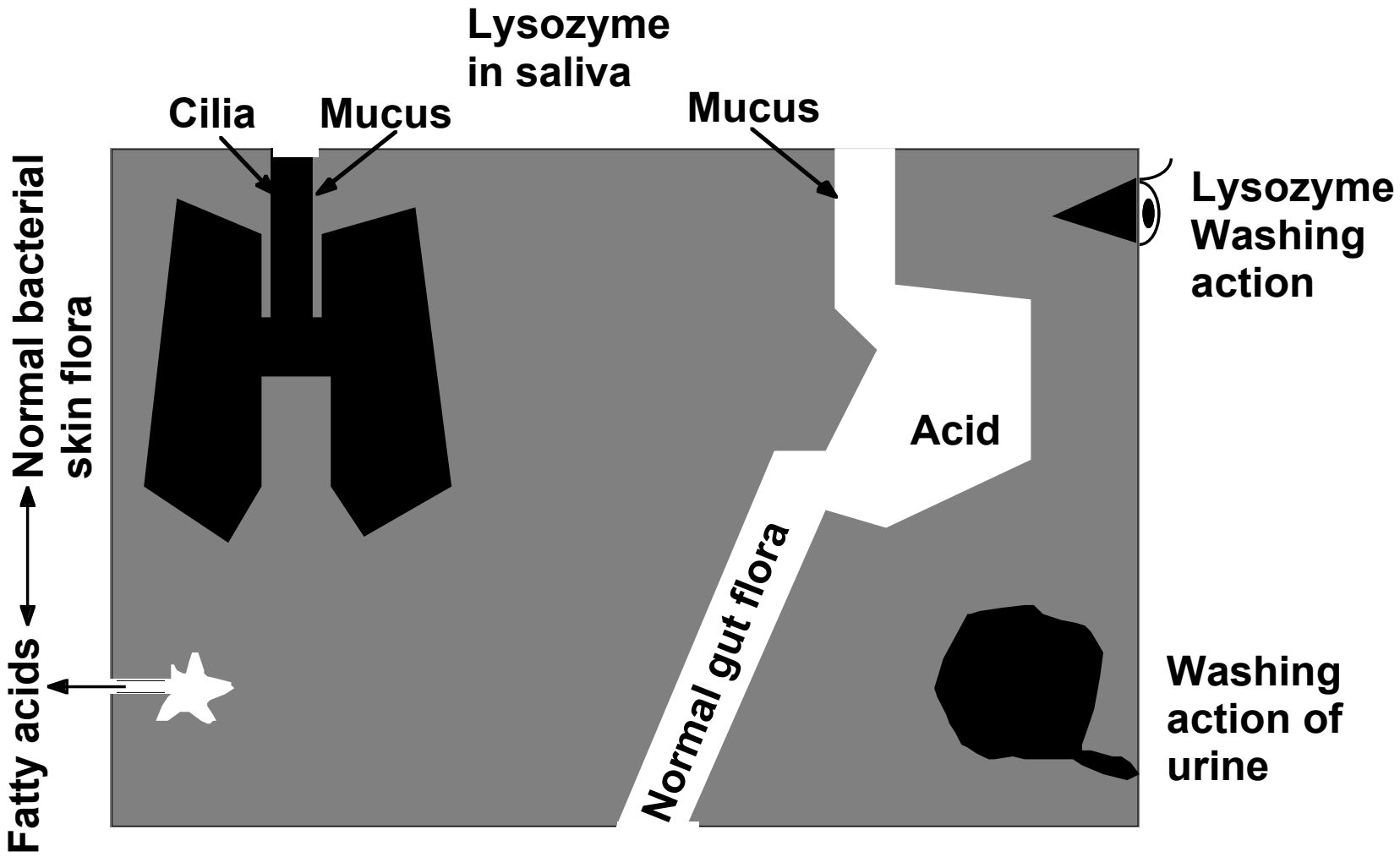
- body surface
- unspecific immune system

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



The first lines of defence: External body surfaces



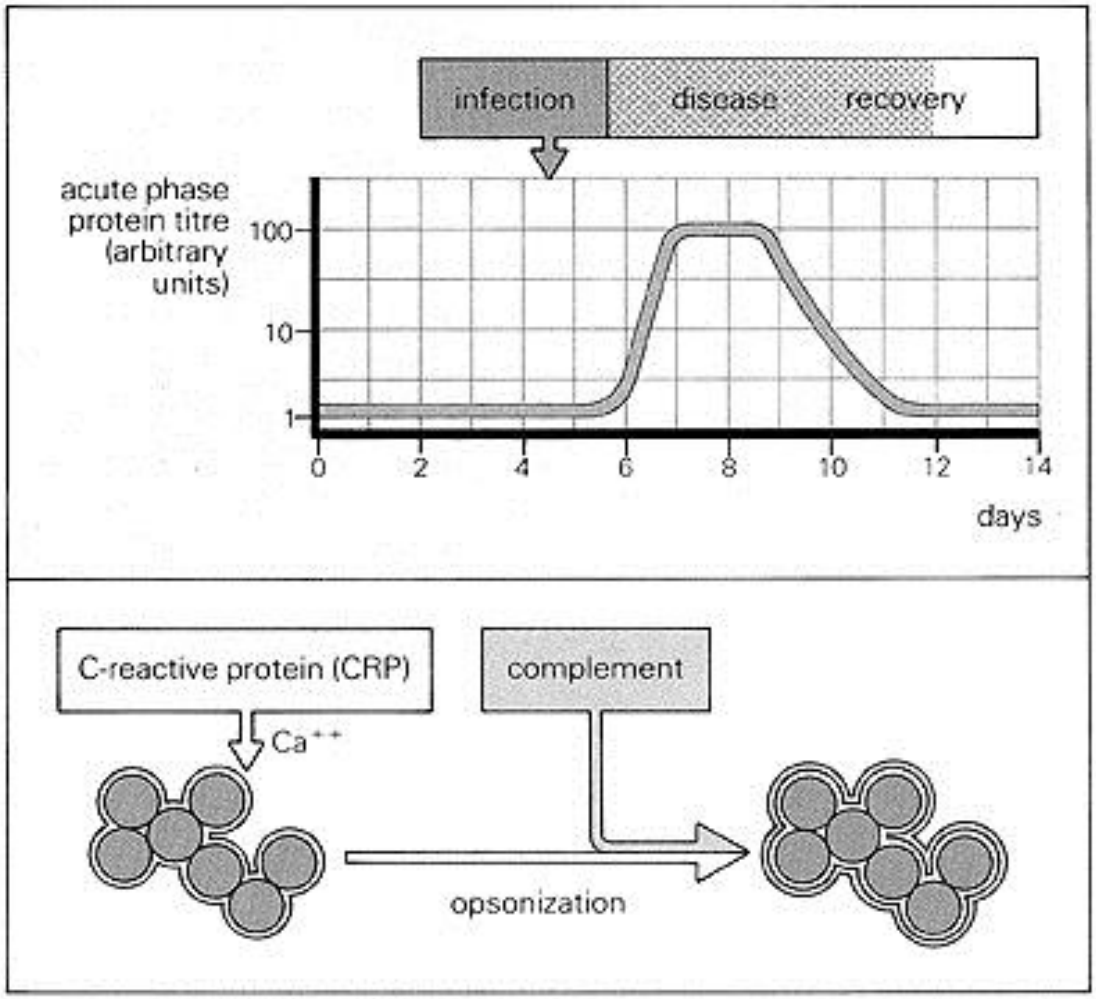
More unspecific defence lines:

- 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.

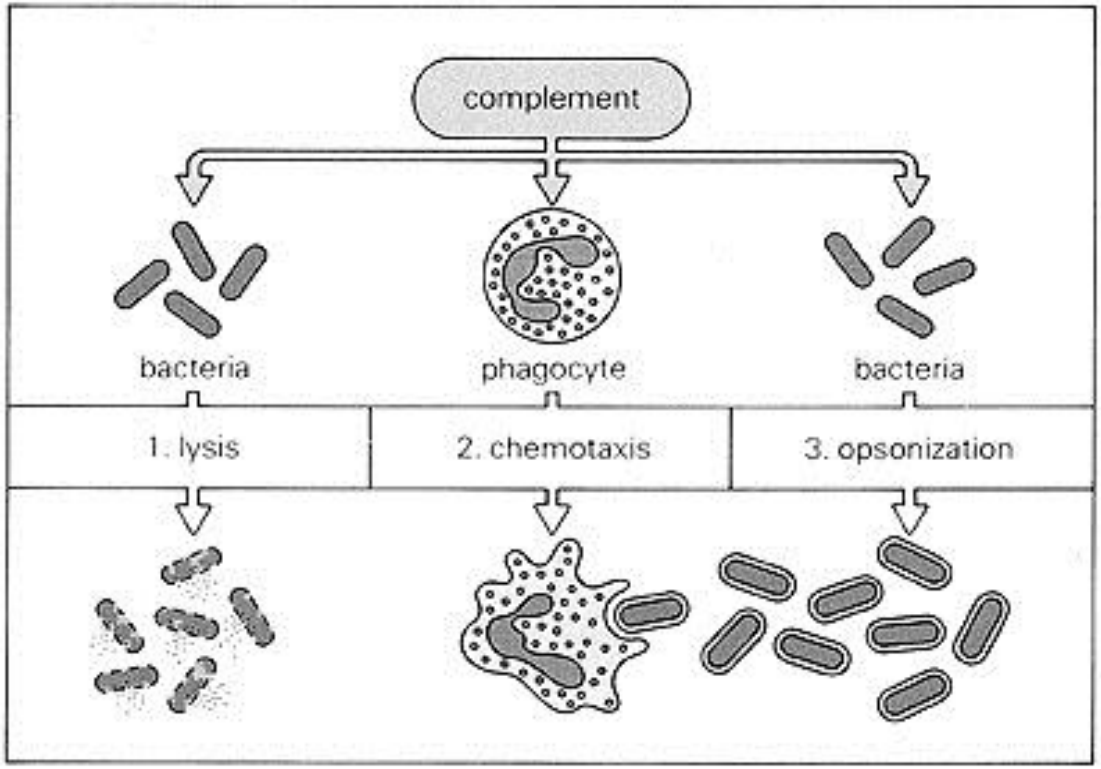
Inflammation: Acute phase proteins



- **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.**

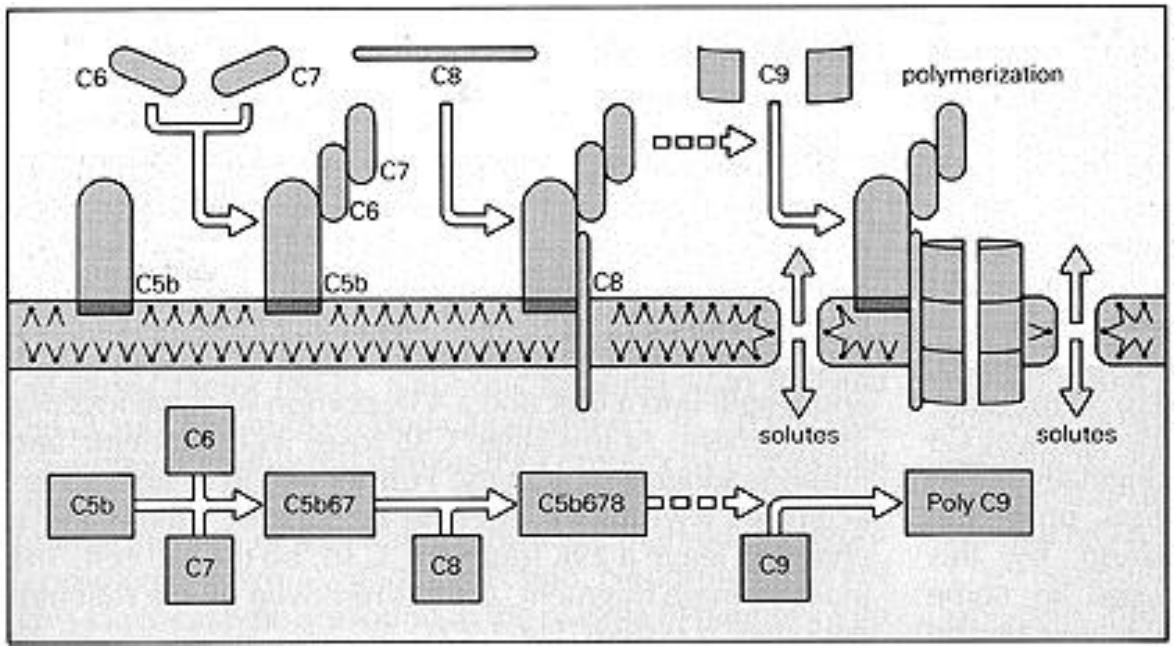
(Gabriel et. al. 2000)

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.**

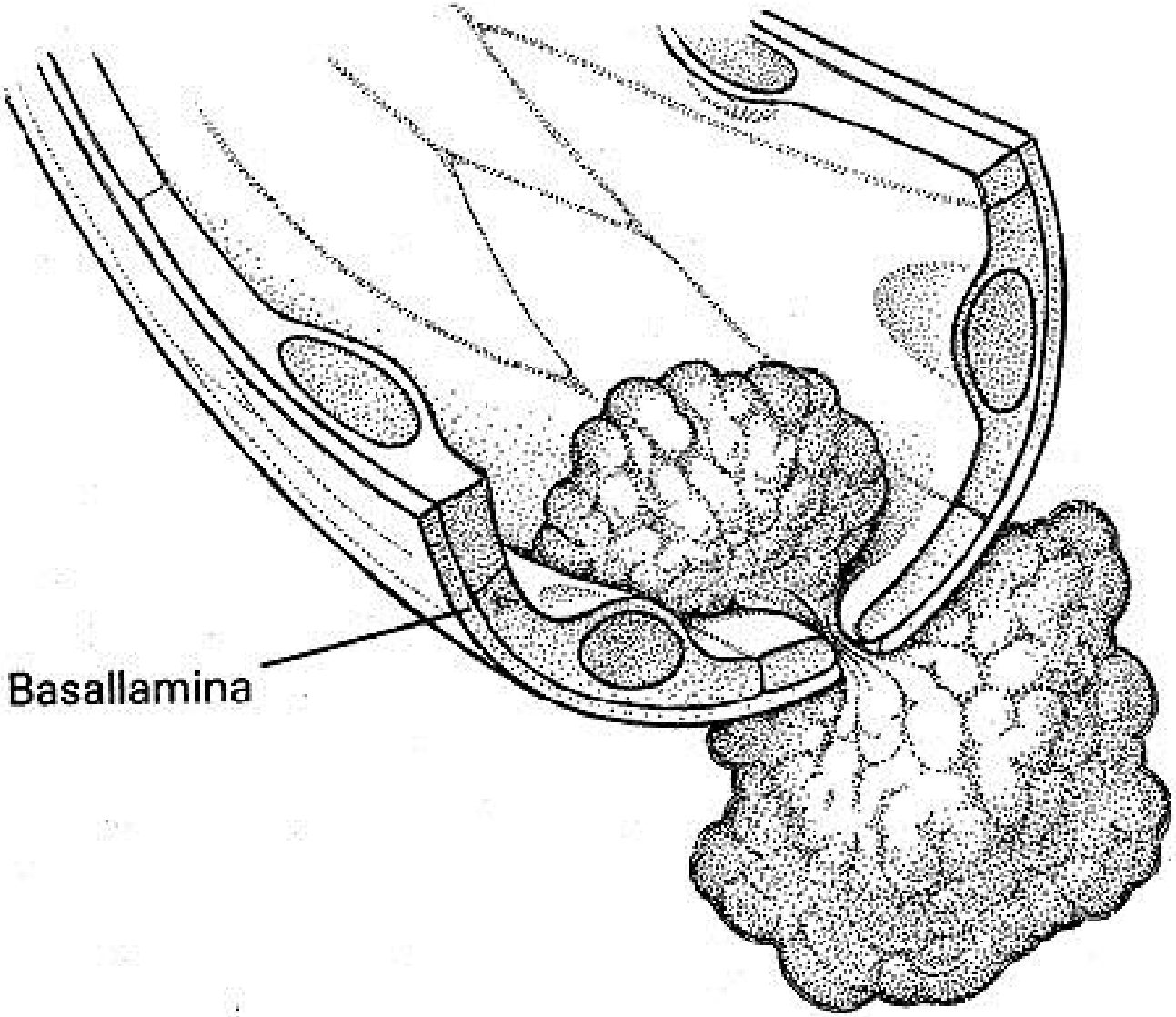
1) Bacterial killing by complement fragments



How complement may kill bacteria:

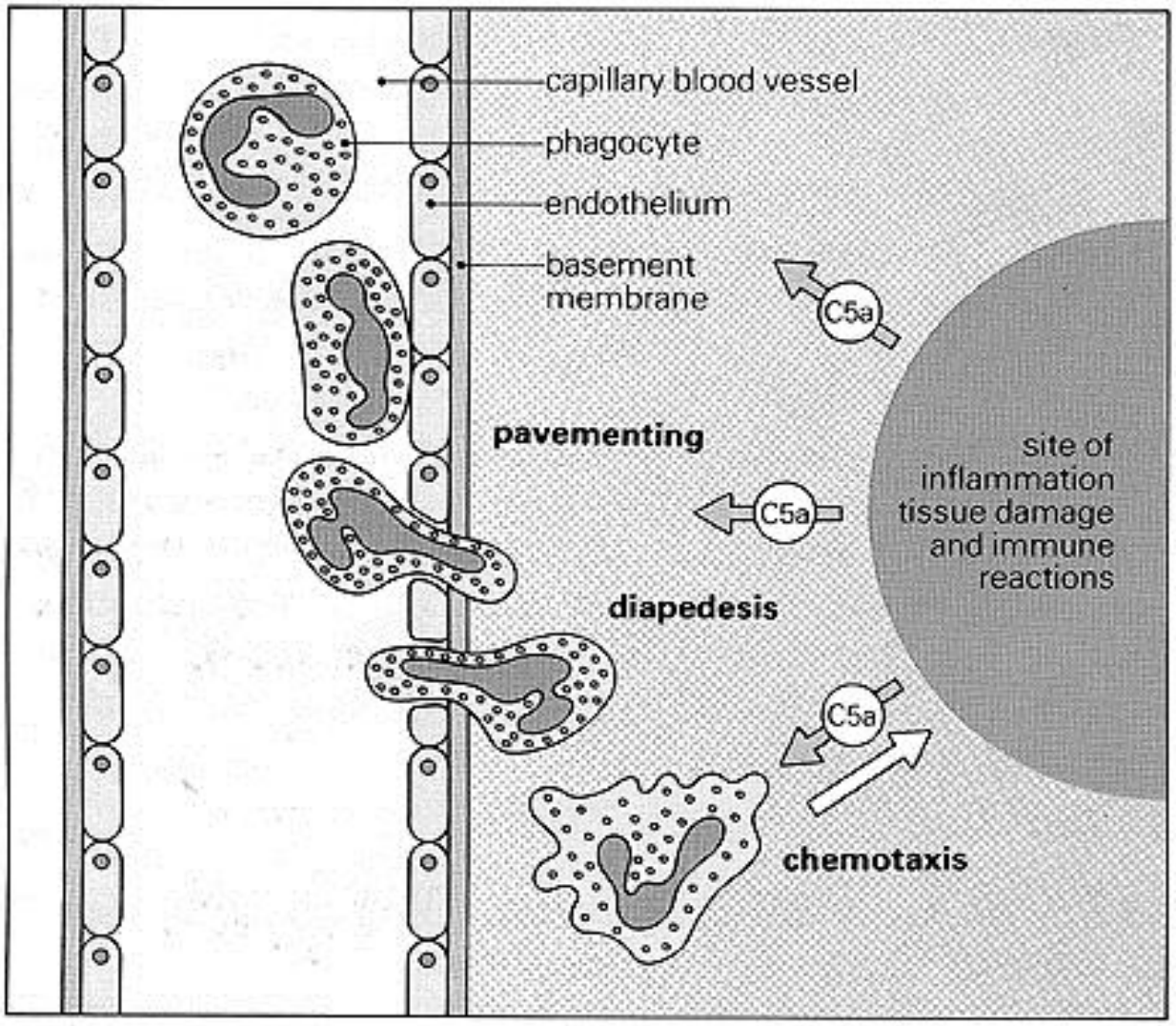
- **C5b binds to a bacterium**
- **C6 and C7 bind to C5b**
- **C8 binds to C5b and penetrates the cell wall**
- **C5b678 catalyzes the polymerisation of C9**
- **C9 forms an annular cylinder across the bacterial cell wall**
- **Pore formation initiates cell lysis (loss of solutes). Breakdown of the chemoosmotic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

2) Chemotaxis



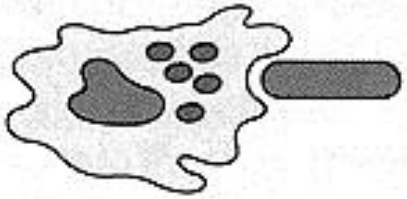
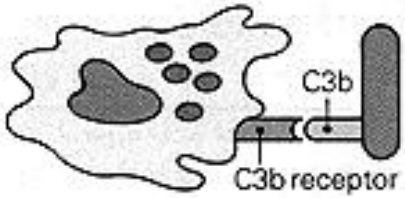
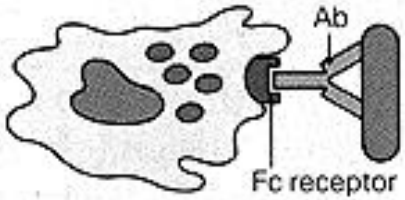
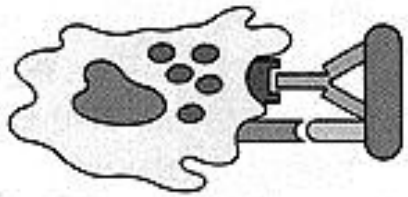
A leukocyte is attracted by a chemical signal (chemotaxis) and by squeezing between endothelial cells gets to the site of infection.

2) Chemotaxis: Come to help!



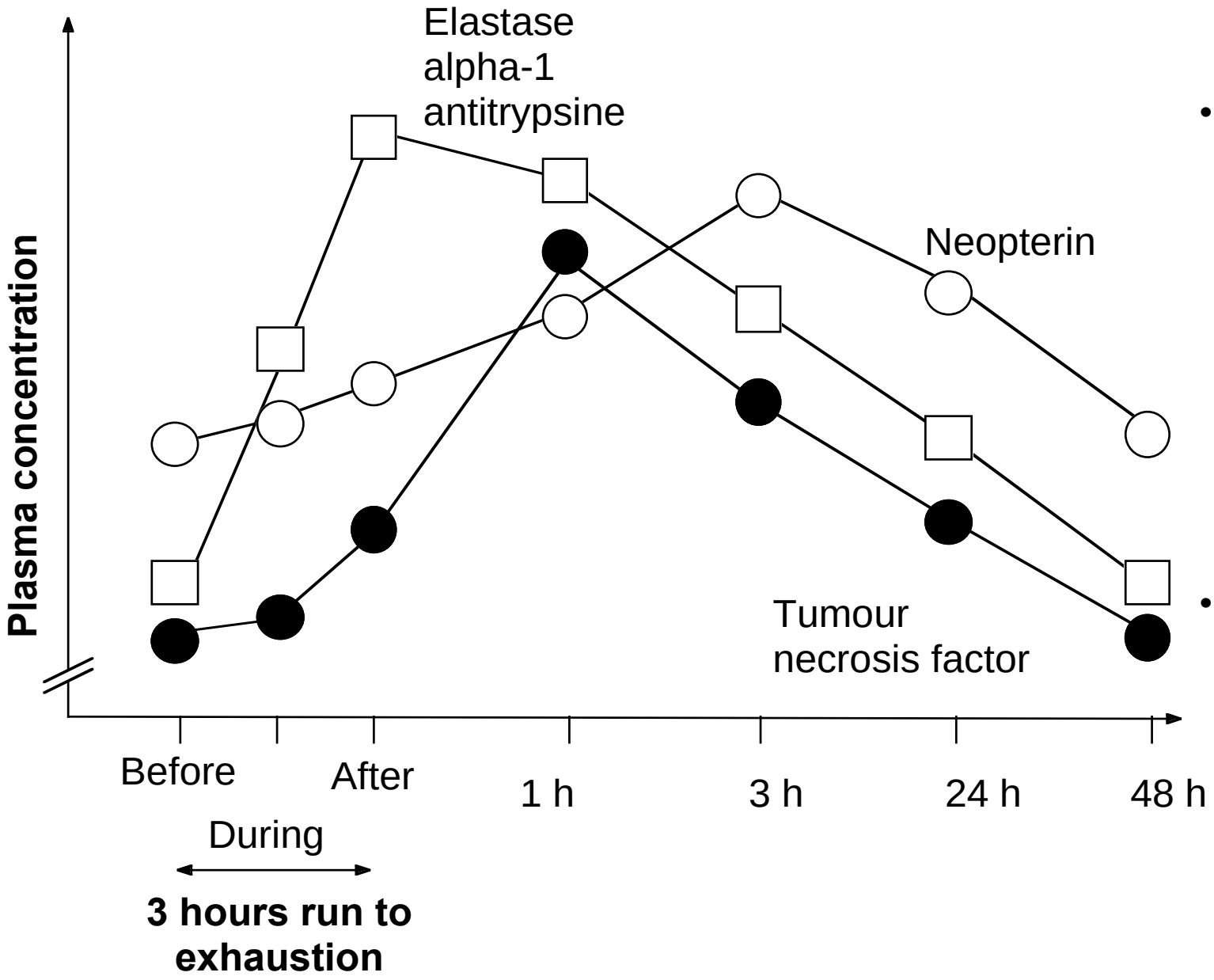
- **Bacteria and traumas damage tissue cells. Lysed cells trigger a number of reactions which are known as inflammation (in medical terms: rubor, calor, dolor and tumor)**
- **Fragments of the complement system, in particular C5a, attract phagocytes along a concentration gradient, This process is called 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.**
- **Chemotaxis:“Navigation“ by concentration gradient.**

3) Opsonization: Flavouring of intruders

phagocyte	opsonin	binding
1 	–	±
2 	complement C3b	+ +
3 	antibody	+
4 	antibody and complement C3b	+ + + +

- **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:

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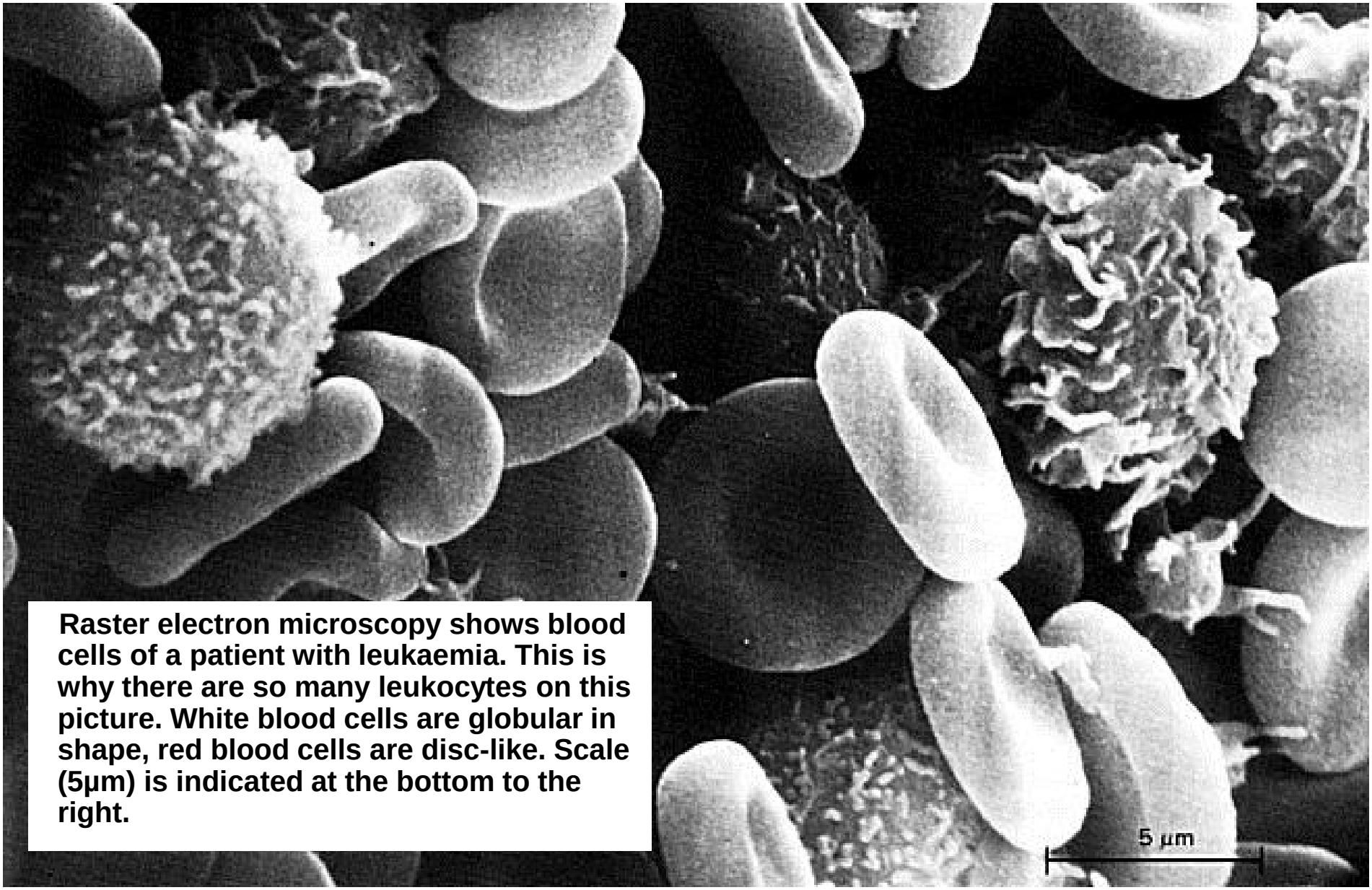
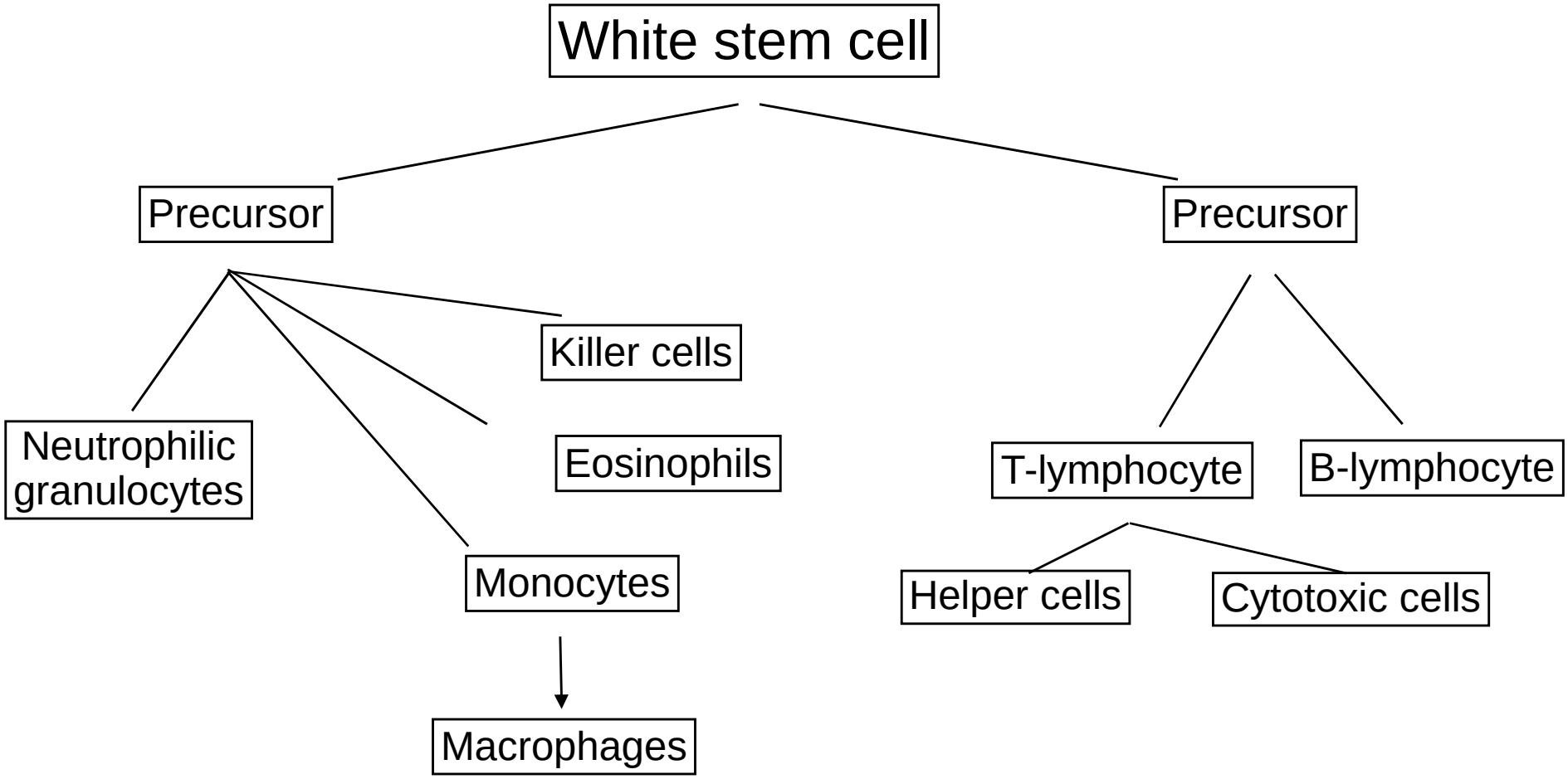
- **Changes in rate of decomposition (e.g. liver)**
- **Changes in rate of elimination (e.g. urine, sweat)**

- **Measuring hematocrite (blood centrifugation, percentage of particles) allows compensation for loss of water.**



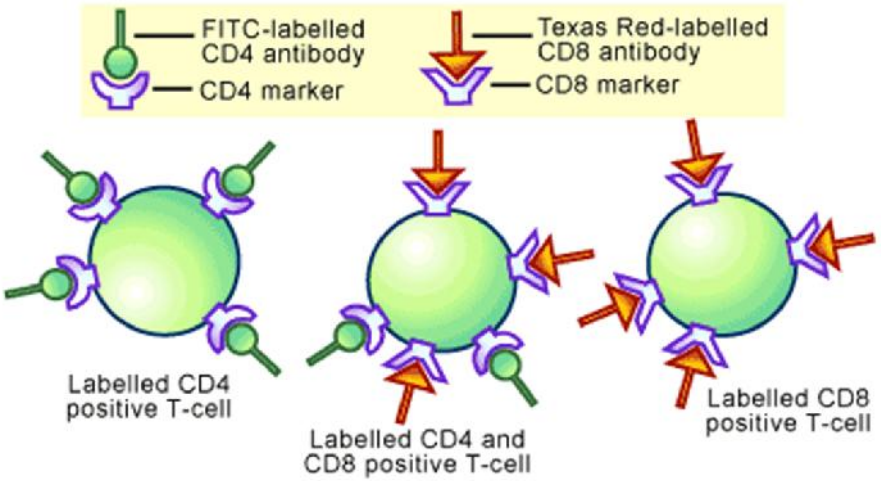
Raster electron microscopy shows blood cells of a patient with leukaemia. This is why there are so many leukocytes on this picture. White blood cells are globular in shape, red blood cells are disc-like. Scale (5µm) is indicated at the bottom to the right.

White blood cells: Most important players

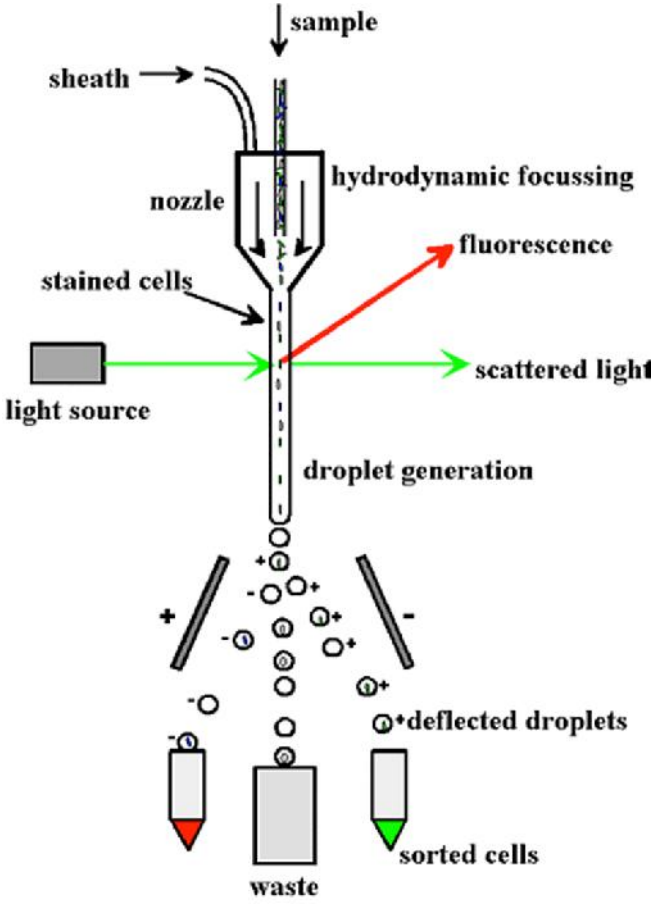


Differentiation of white blood cells

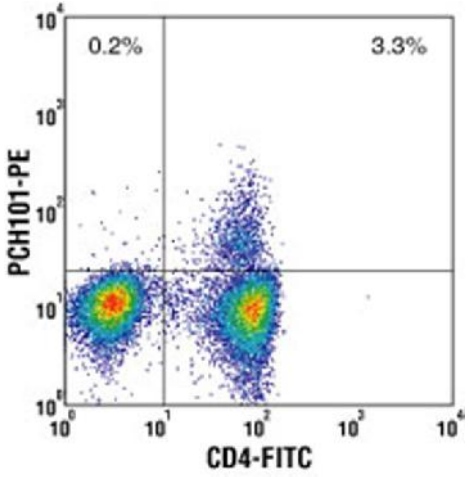
- **Flow Cytometry / Cell Sorting**



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)

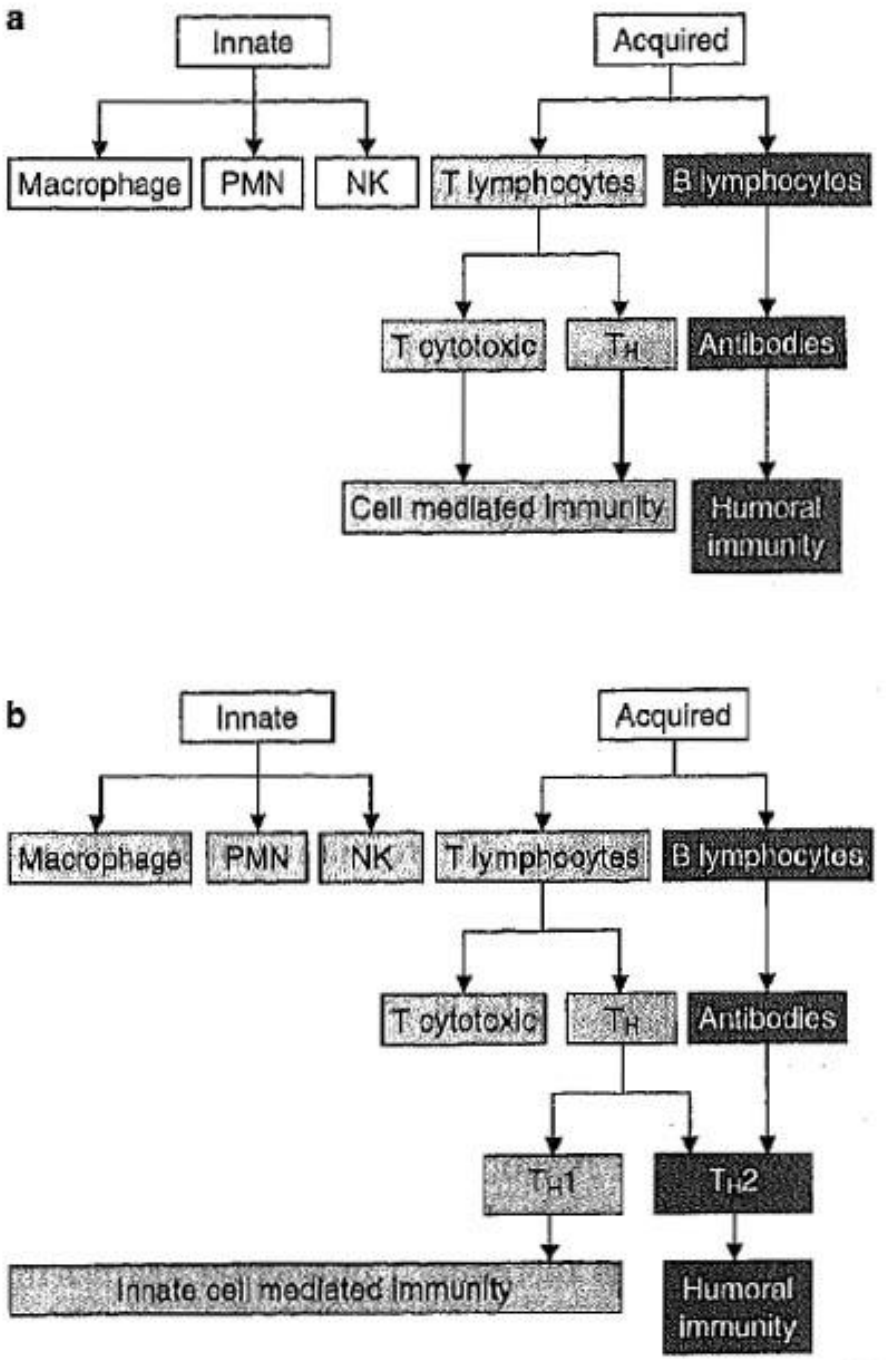
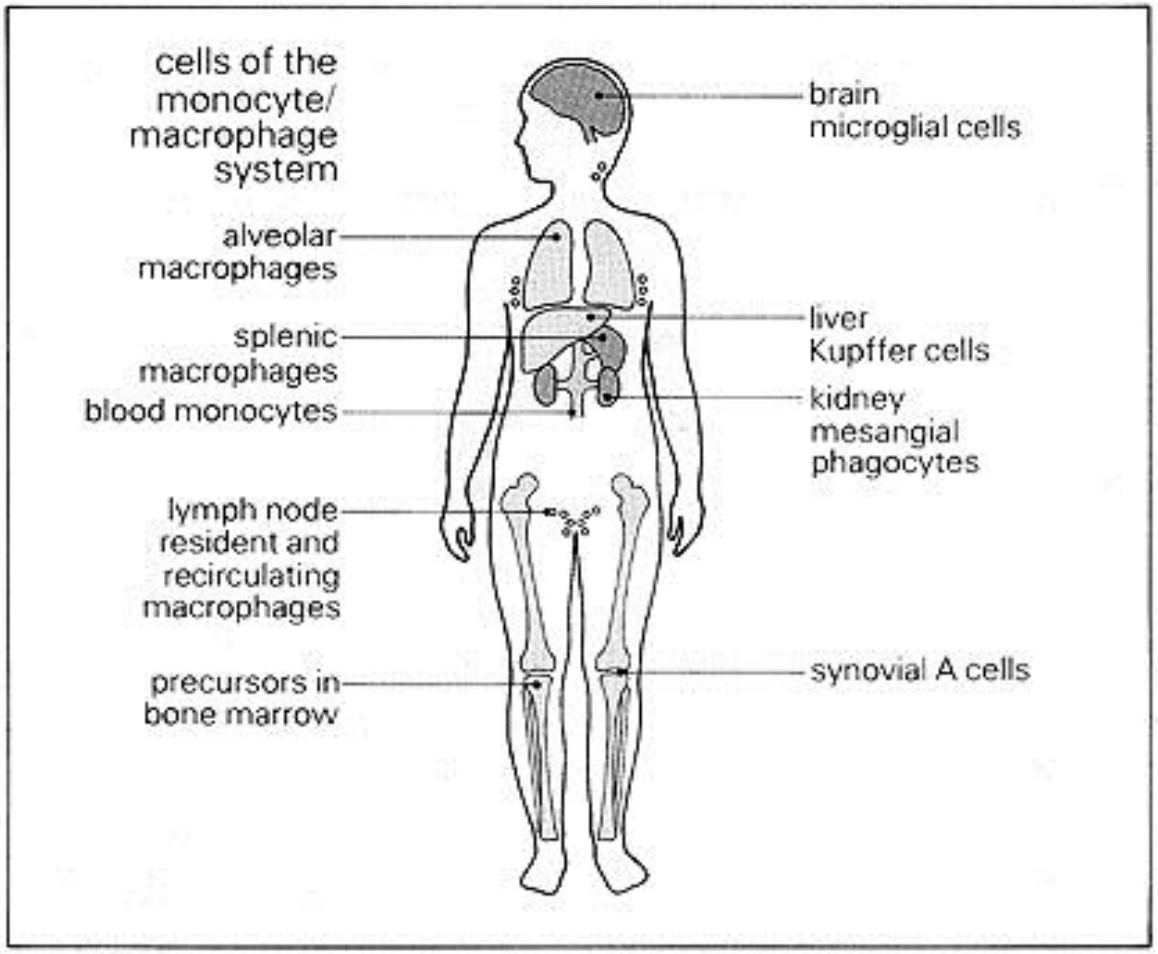


Fig. 2. (**a**) Traditional view of divisions of the immune system. (**b**) Revised view of divisions of the immune system.[55] **NK** = natural killer cells; **PMN** = polymorphonuclear; **T_H1** = T helper-1 cells; **T_H2** = T helper-2 cells.

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)

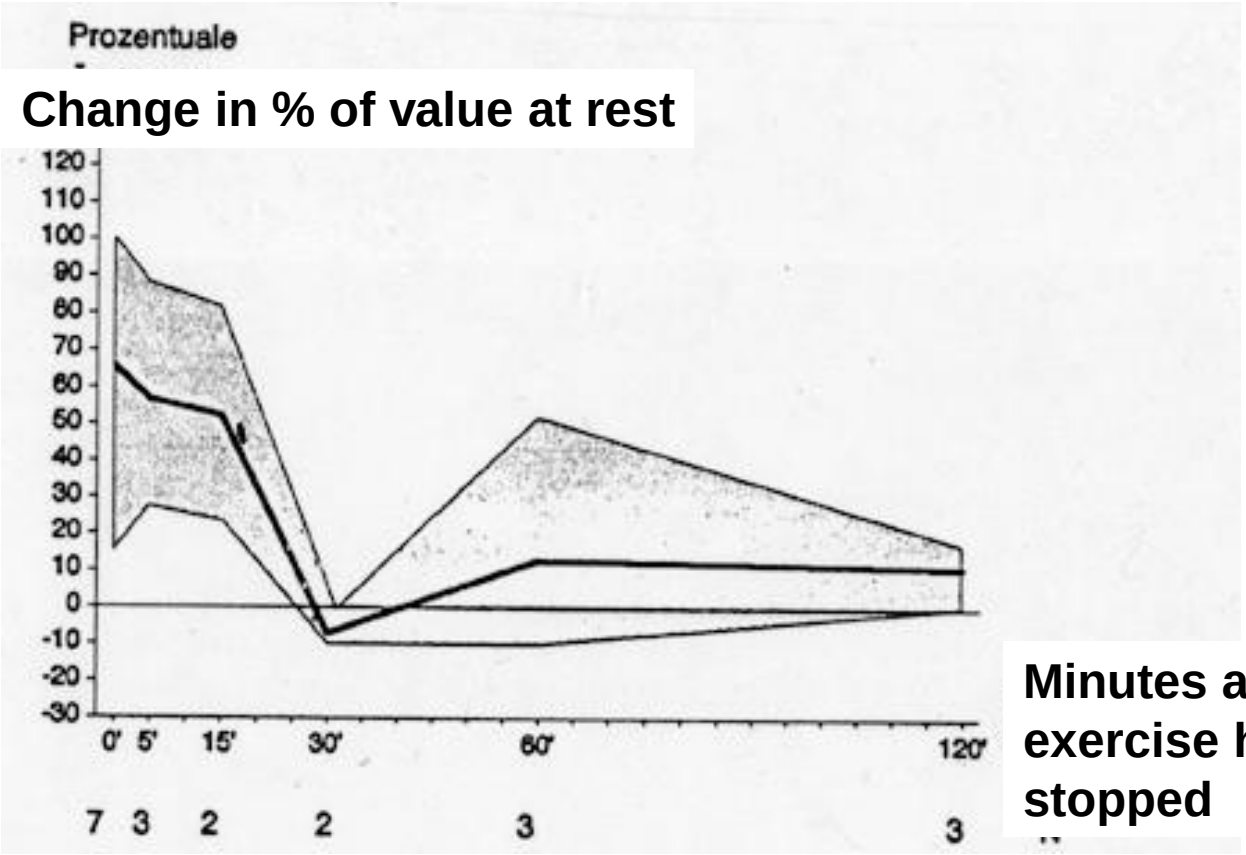
- **Lungs: Alveolar macrophages**
- **Spleen: Macrophages**
- **Blood: Monocytes**
- **Lymph nodes: Resident and recirculating macrophages**
- **Precursor cells in bone marrow**

(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



N, number of studies performed

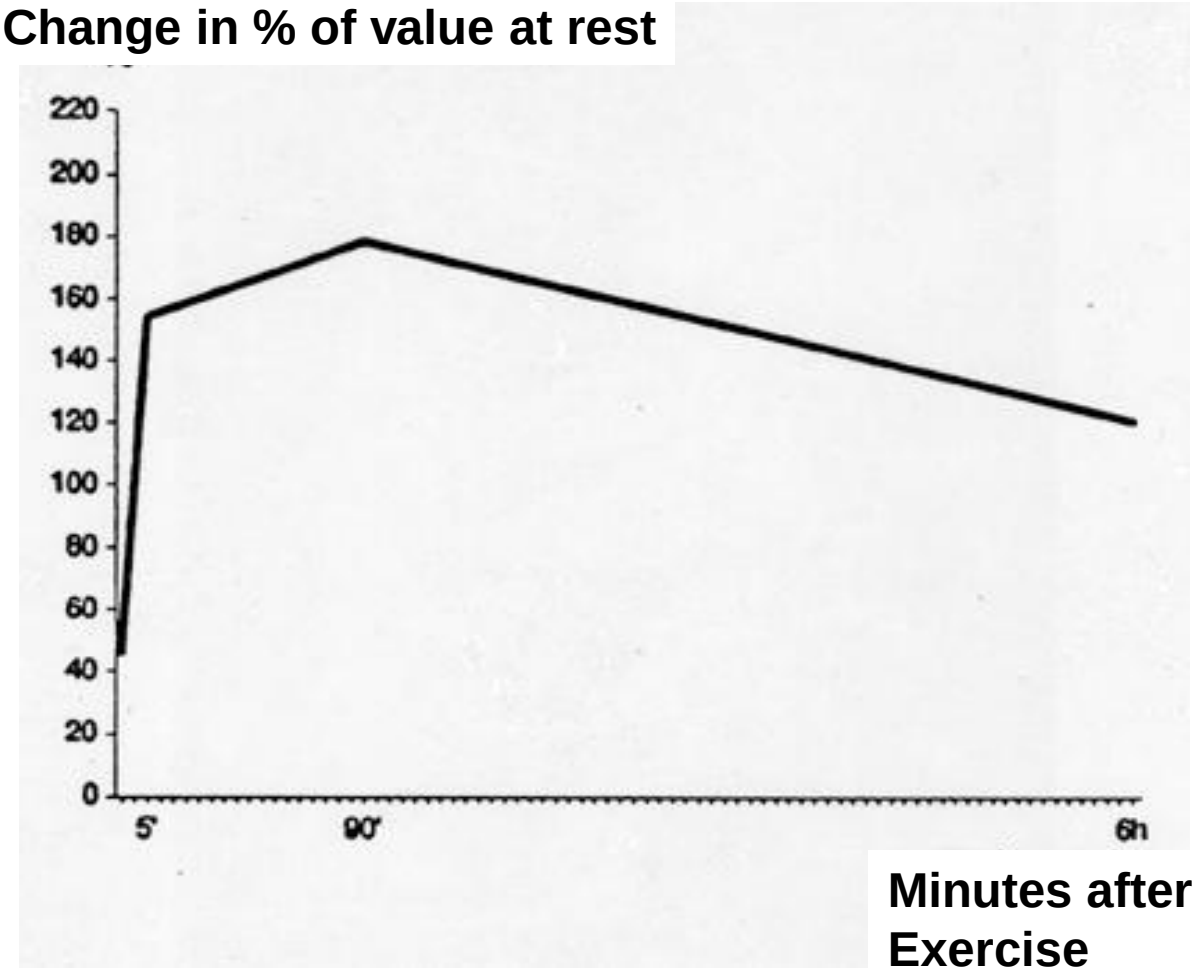
(D. Escher, 1992)

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 - $10 \cdot 10^9$ 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).

Effect of prolonged exercise (3 h) on the number of leucocytes



(D. Escher, 1992)

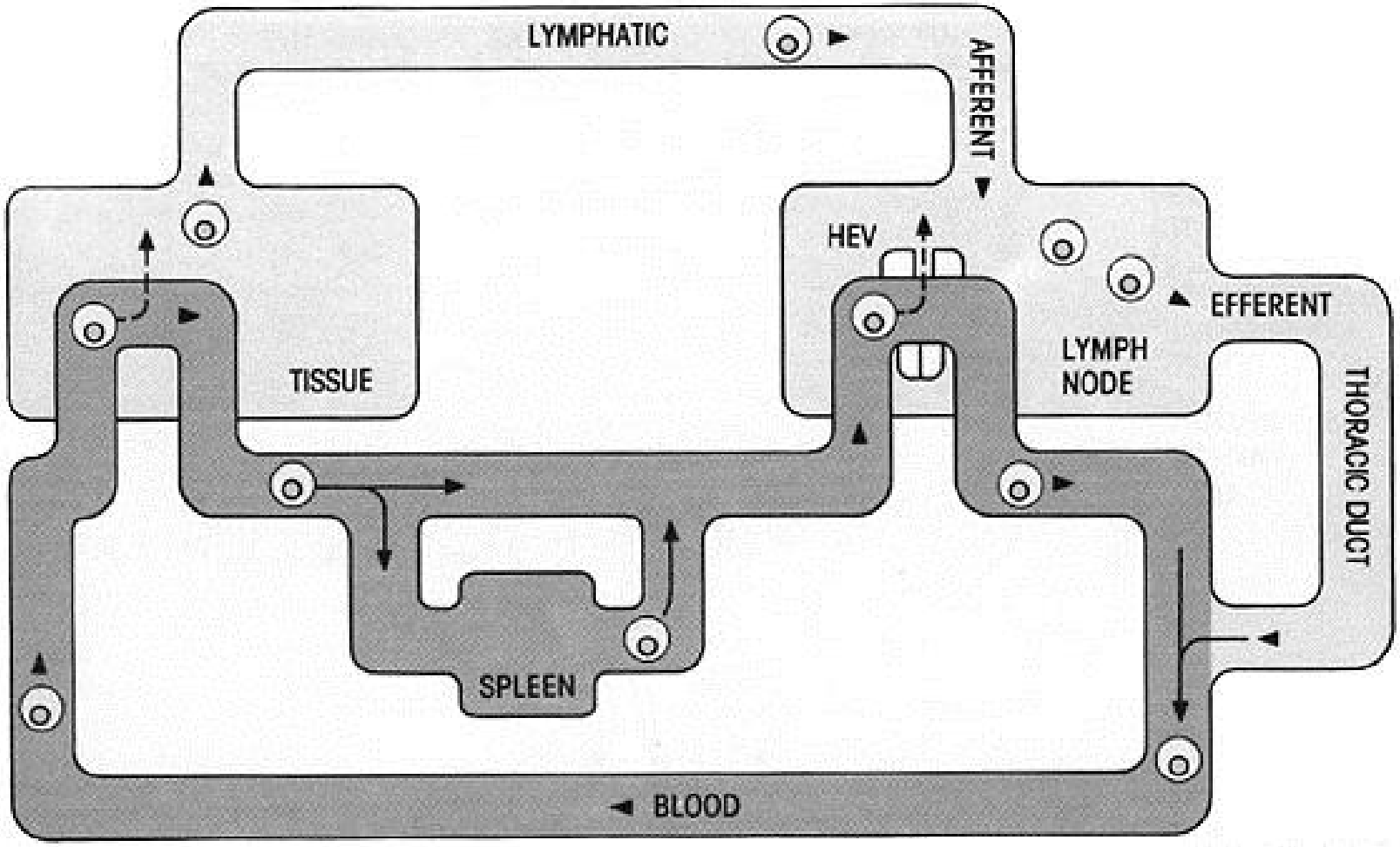
The graph shows the average of increase in leukocyte numbers as a percentage of the resting value following a 3 hours run. The increase is more enhanced, continues to rise even following the run, and it takes much more time to recover as compared to short bouts of exercise.

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).

Lymphocytes

- **Lymphocytes belong to white blood cells**
  - **White blood cells: 4 - 10 · 10^9 per litre (=Giga)**
  - **Lymphocytes: 1.5 - 4 · 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 · 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.**

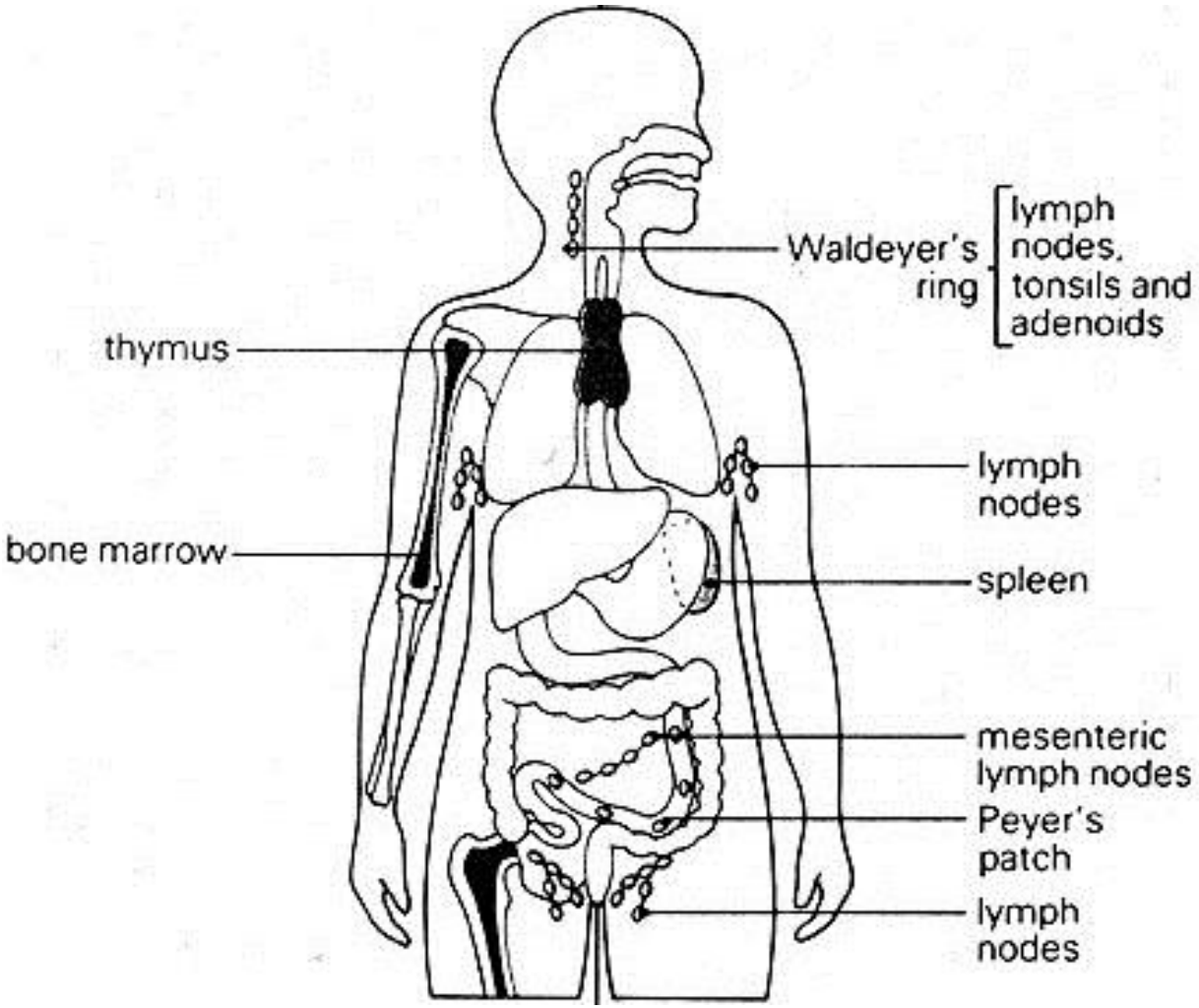
Lymphocyte trafficking



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

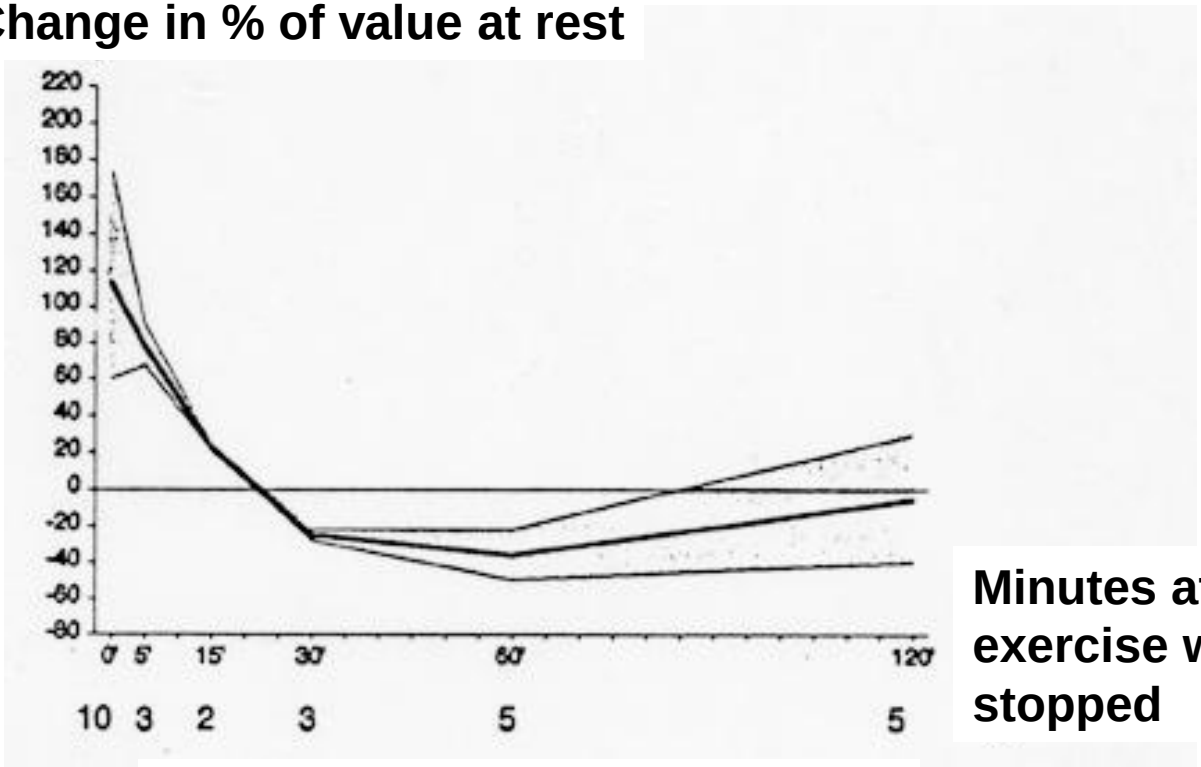
Primary ... **secondary lymph organs**



- **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



Minutes after exercise was stopped

N, number of studies performed

(D. Escher, 1992)

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).

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)

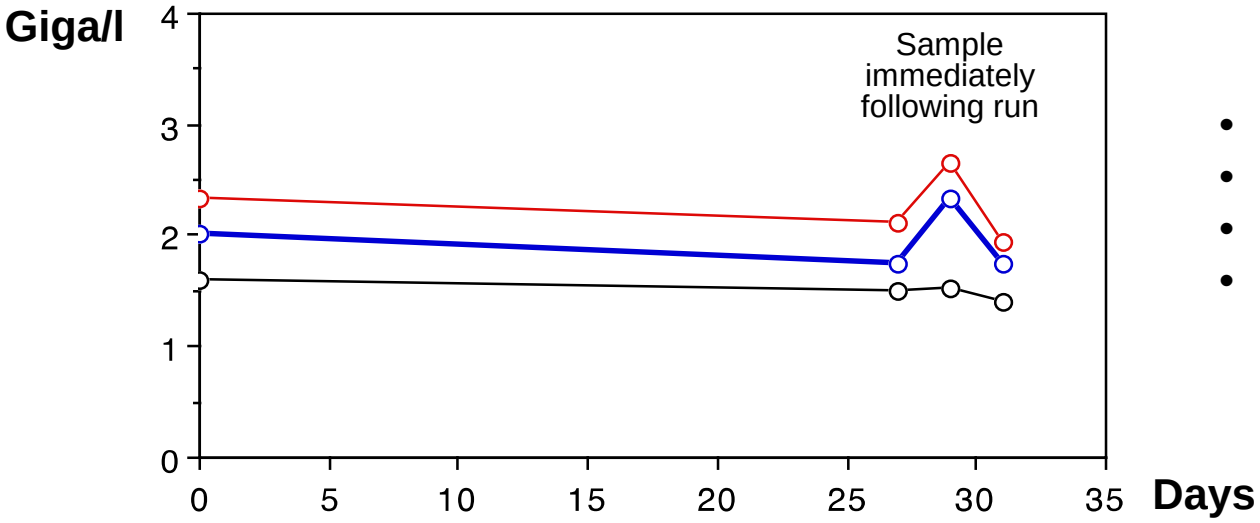
Possible mechanisms at molecular level:

- 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)

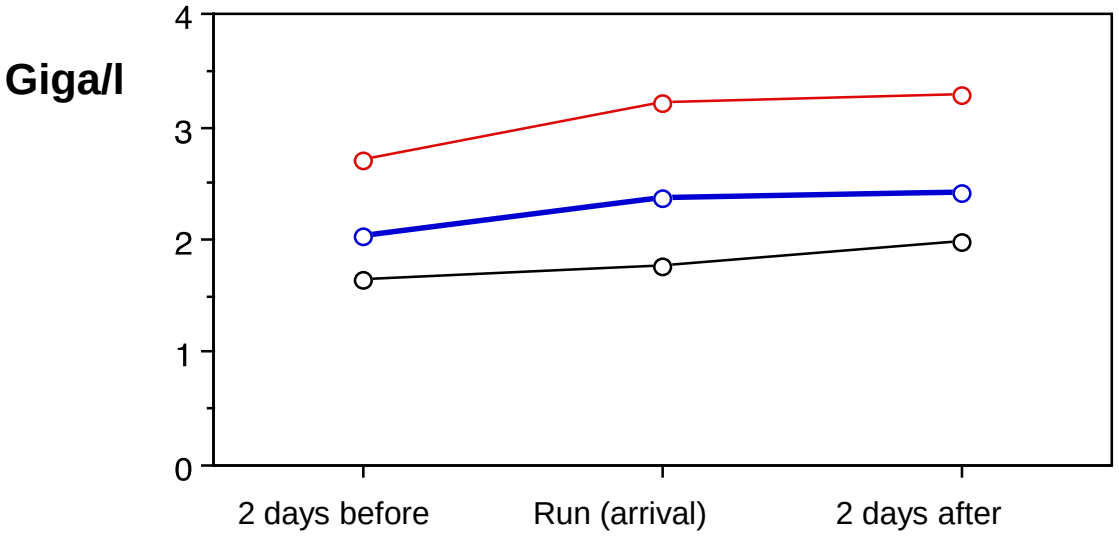
Effect of prolonged exercise on number of lymphocytes

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)

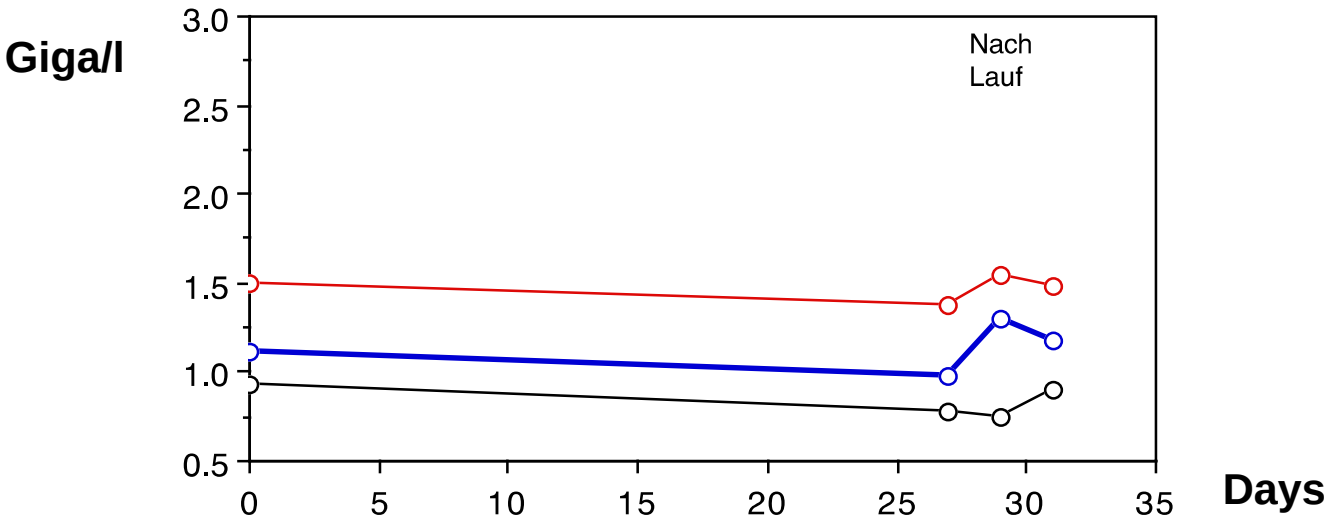


Changes in numbers of lymphocytes shown on this transparency are not significant.

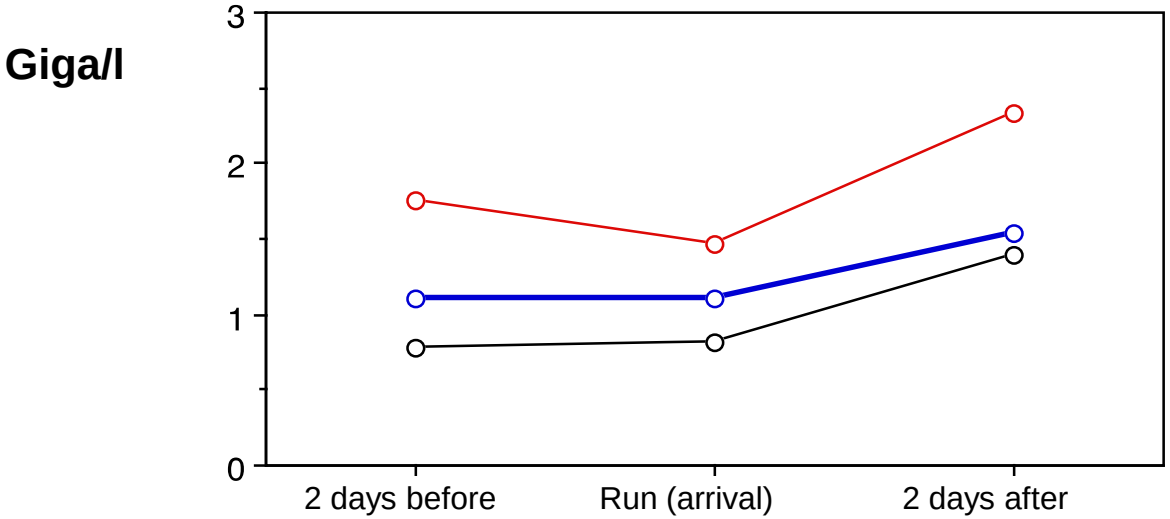
(Gmünder et al. 1988, 1990)

Effect of prolonged exercise on number of T-lymphocytes

21 km run (workout intensity)



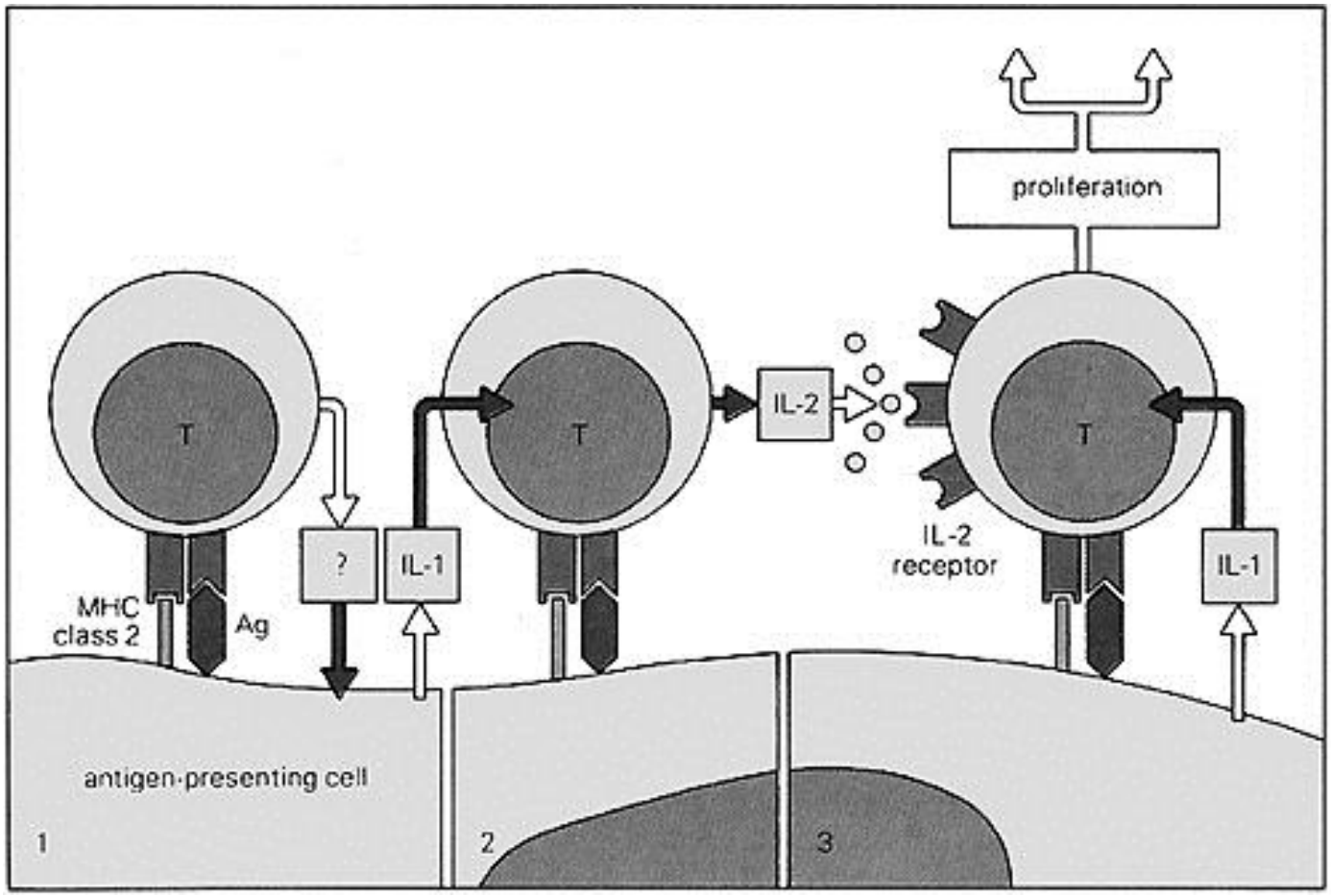
Marathon race (42.6 km)



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

(Gmünder et al. 1988, 1990)

T-lymphocyte activation



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)**

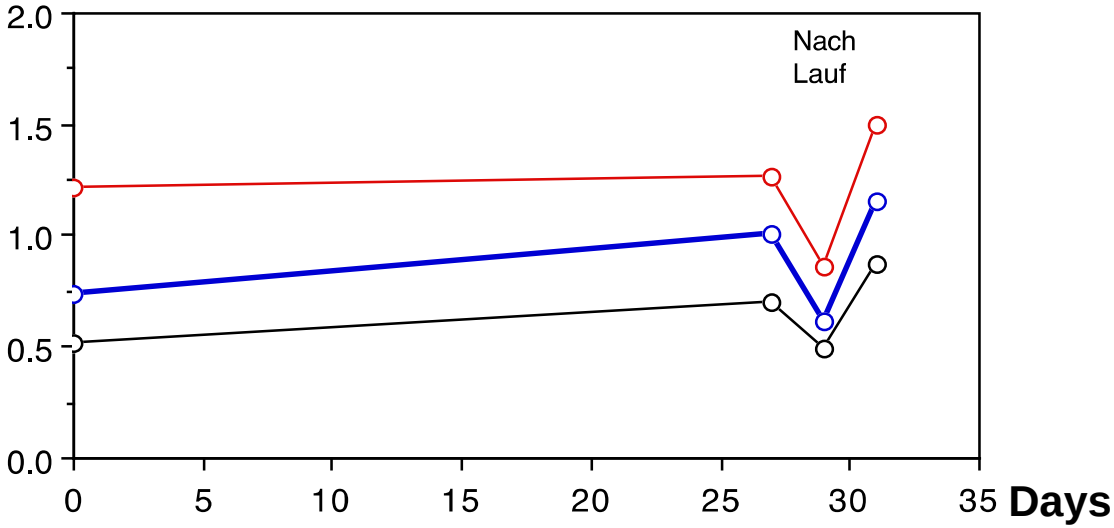
2 **IL-1 acts as a signal to T-cells to present IL-2 receptors. The IL-1 / IL-2 system acts as an amplifier (3)**

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

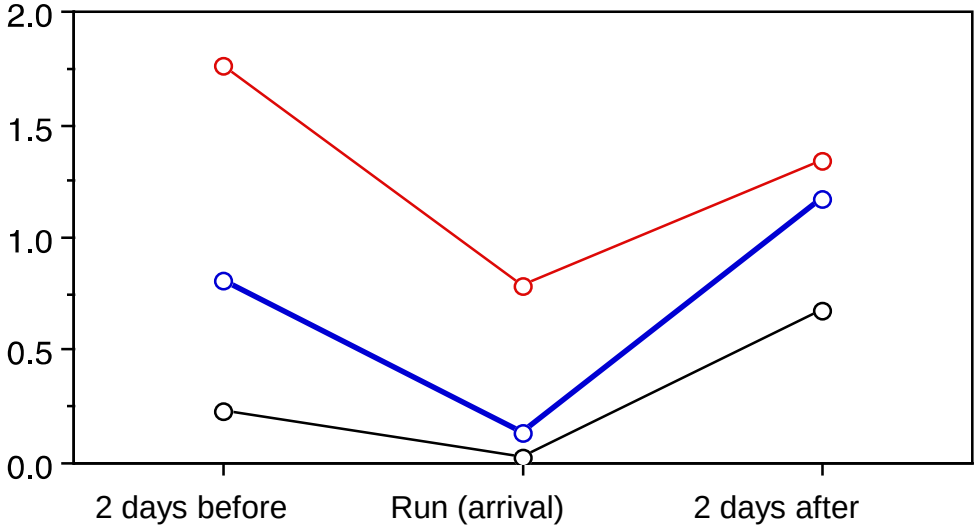
Note: MHC II is found only on APCs. MHC I is found on all cells. If immuno competent cells find an antigen in association with MHC II, they „know“ they deal with an APC. If they meet antigens in association with MHC I, they „know“ they docked to a tissue cell infected by a virus. This cell is killed 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)



Marathon race (42.6 km)



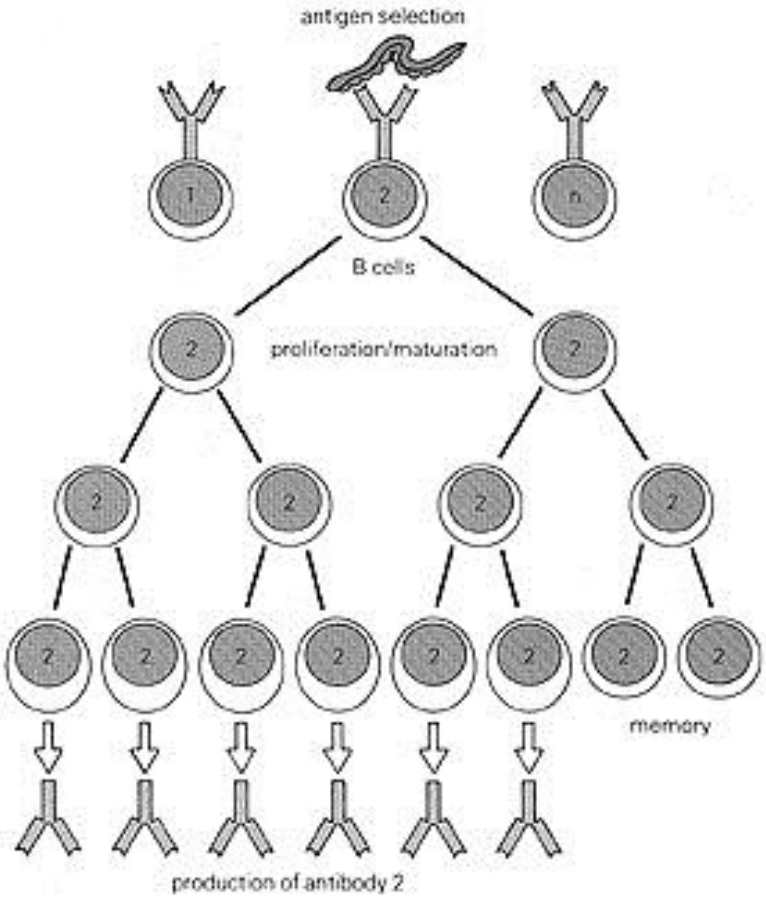
In the laboratory activation of T-cells can be measured by exposing T-cells to substances that induce proliferation. No antigen/MHC II is needed in this test. One of these substances is Concanavalin A (Con A). This test is thought to reflect lymphocyte function.

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

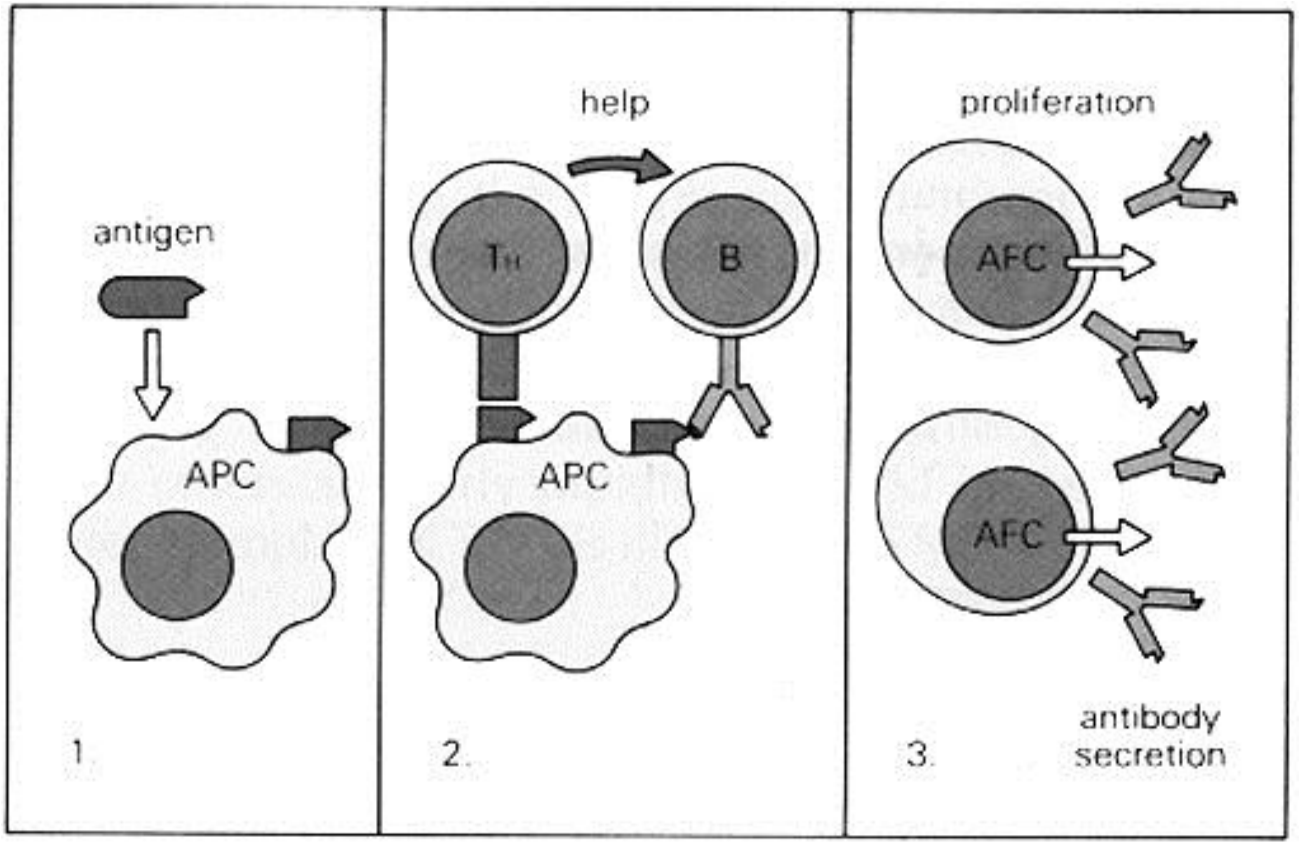


1 **Macrophages: Phagocytosis and processing of antigens**

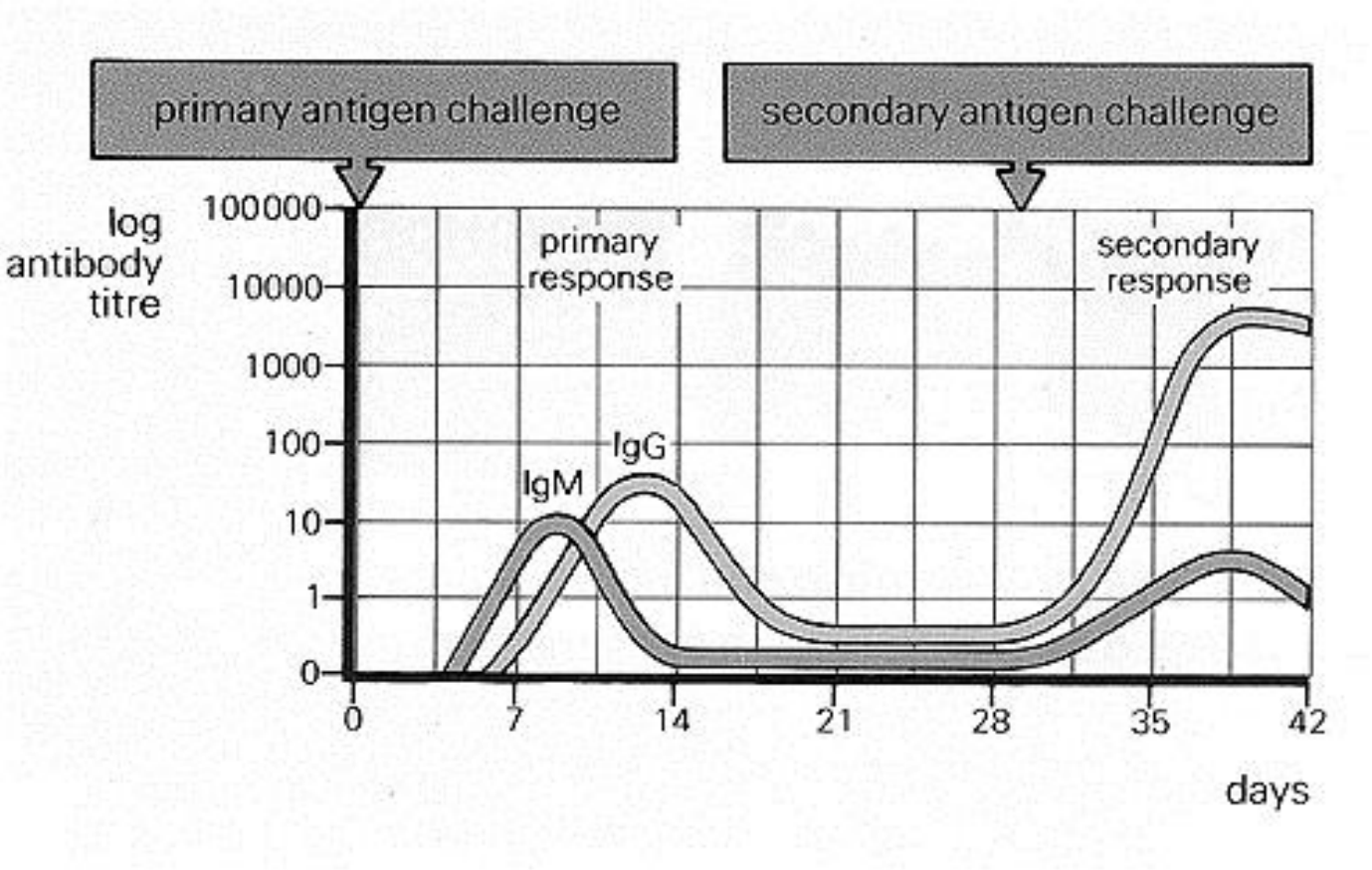
2 **Antigen presentation to patrolling T- and B-cells (MHC II-restricted). B-cells depend on T-helper cells to start to proliferate and differentiate to antibody producing cells.**

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



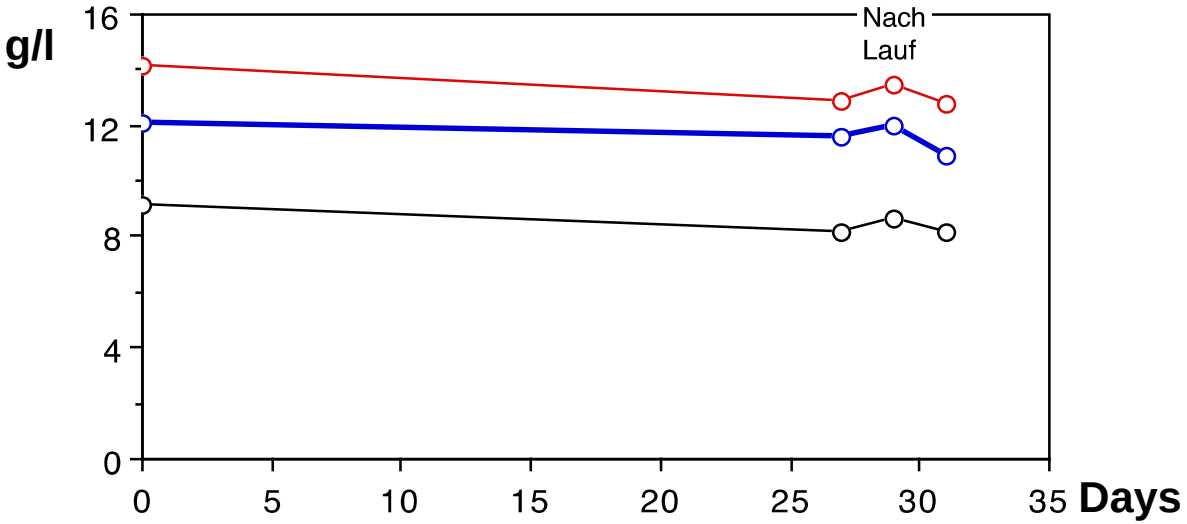
Primary and secondary antibody response.

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

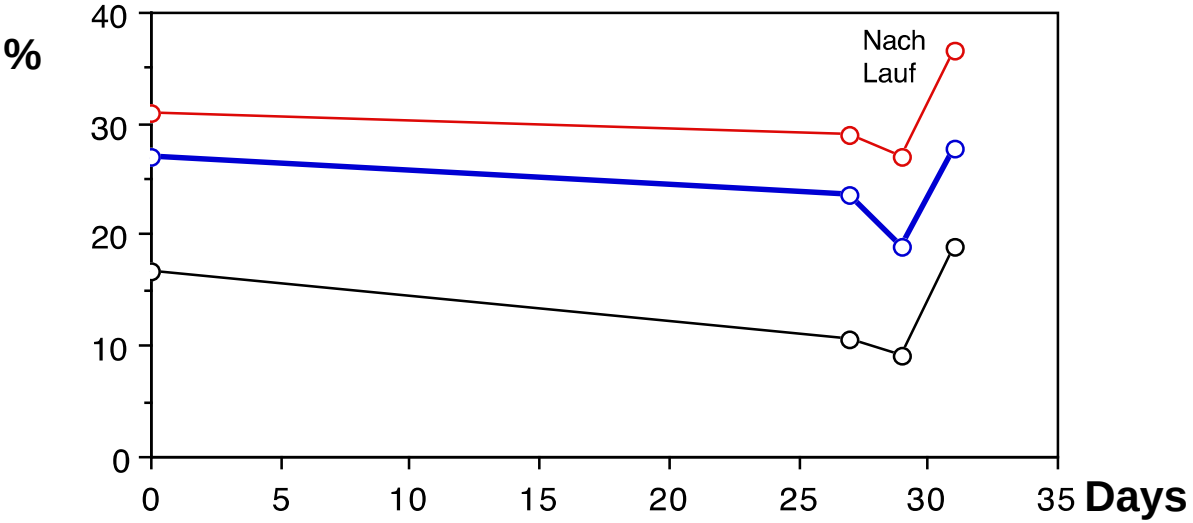
However, when the body is exposed a second time to a specific antibody, IgG formation is much faster and more enhanced (s. graph). The reason is memory B-cells.

Effect of prolonged exercise on immunoglobulins

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



21 km run (workout intensity); immunglobulin G: subclass II (%)



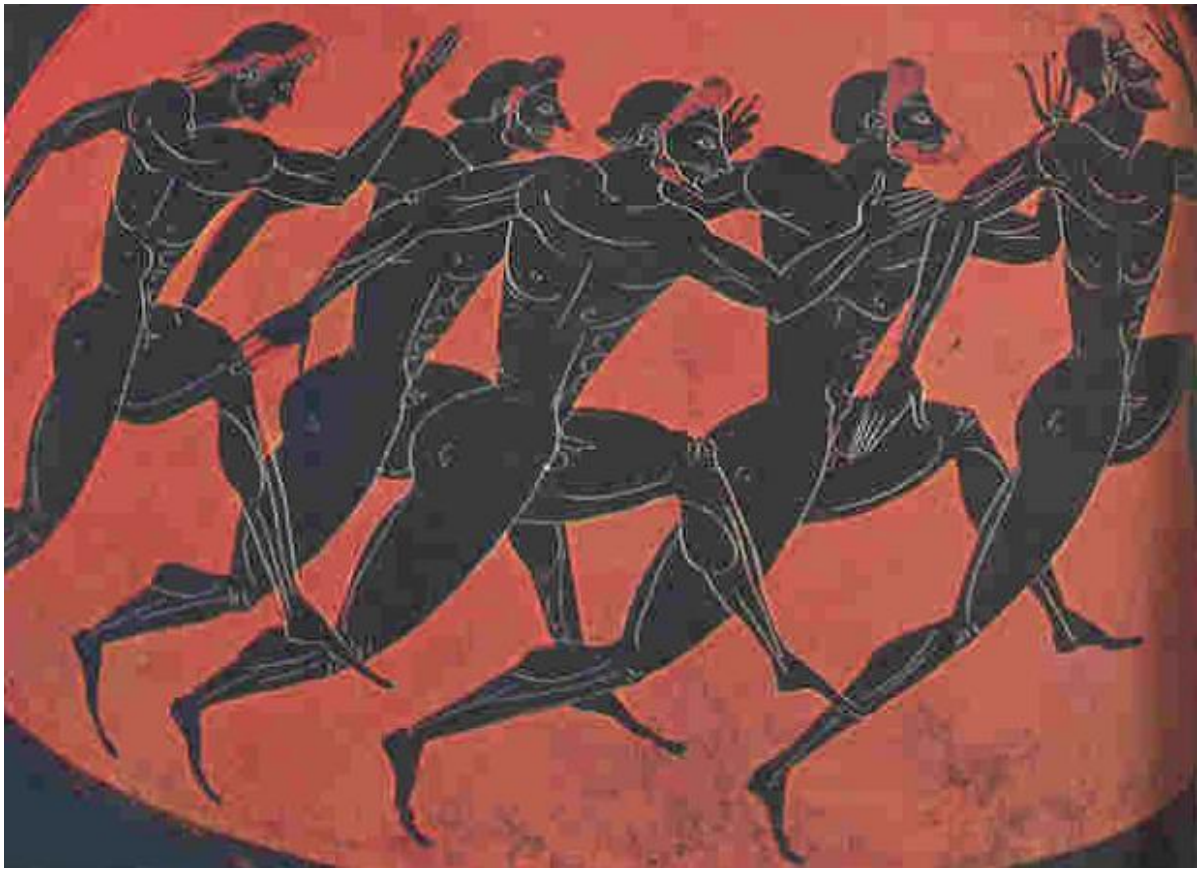
Changes in subclass II are statistically significant at the 95% level. This could indicate lowered immune defence after the run.

(Gmünder et al. 1988, 1990)

Overview of findings (compiled from studies presented here and elsewhere)

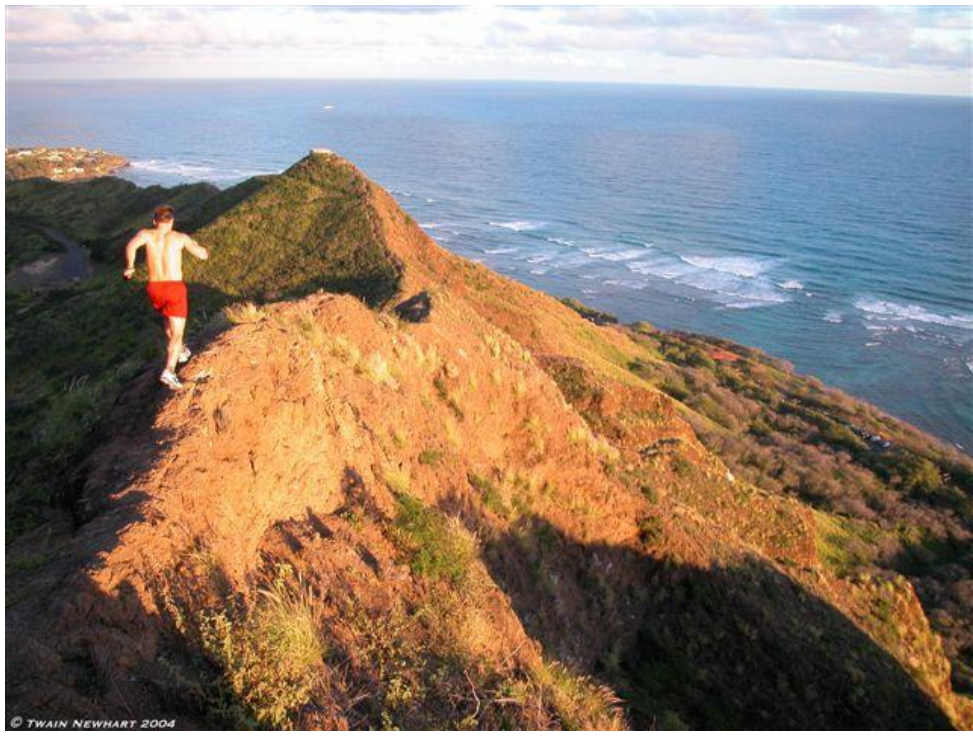
Acute phase reaction	
Number of leucocytes	Increase
Number and function of natural killers	Increase
Function of macrophages in blood	Increase
Function of macrophages in tissue	Increase
Acute phase proteins (CRP, TNF, neopterin)	Increase
Complement system	Activated
Interferoneα	Increase
Interleukin-1 release	Increase
Interleukin-6 release	Increase
Specific immune defence	
Number of lymphocytes in bloodstream	No change or decrease
Number of T-cells	No change or decrease
Number of B-cells	No change or decrease
Number of helper cells	No change or decrease
Number of suppressor cells	No change or increase
Activation of T-cells	Decrease
Interleukin-2 release	Decrease
Number of interleukin 2 receptors on T-cells	No change or decrease
Interferon γ release	No change
Plasma concentration of immunoglobulins	No significant changes

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?

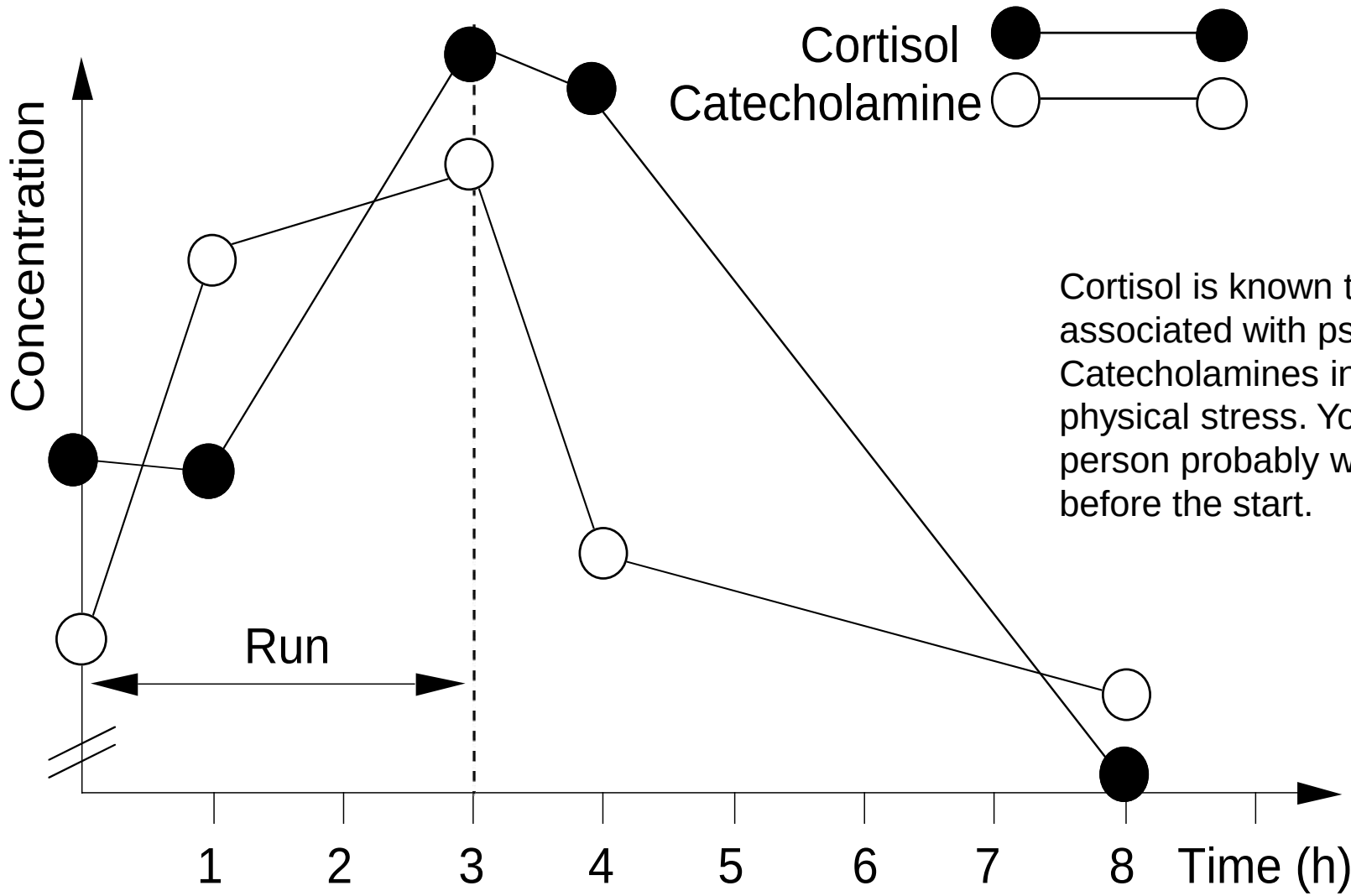
- ☆ **Tissue damage (sore muscle, joints, gut etc.) induce an acute phase reaction. A „sterile“ inflammation develops at the sites of damage. Macrophages home in to help to get rid of dead cells, damaged tissue, and probably toxins crossing the gut.**

- 🕐 **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

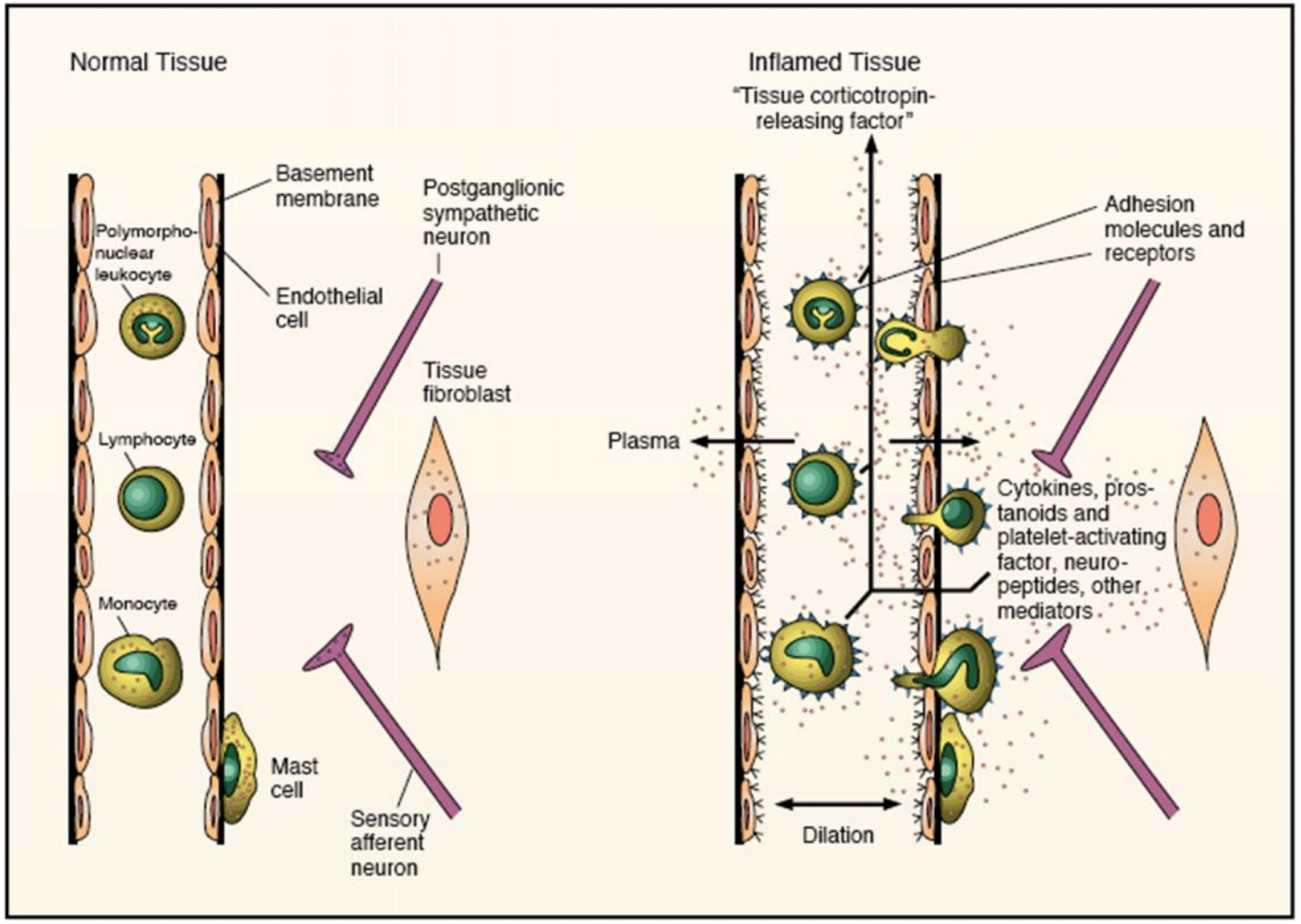


Figure 3. Components and Events of Inflammation.

Quiescent circulating leukocytes, local immune accessory cells, and the terminals of peripheral postganglionic sympathetic and sensory afferent neurons are shown in normal tissue (left-hand panel). In inflamed tissue (right-hand panel), there is vasodilation, increased permeability of the vessel, and exudation of plasma. Activated leukocytes and endothelial cells express adhesion molecules and adhesion-molecule receptors. Cells attach to the vessel wall and diapedesis takes place, with chemotaxis toward a chemokine gradient at the focus of inflammation. Activated circulating cells, migrant cells, local immune accessory cells, and peripheral nerves secrete cytokines, prostanoids, platelet-activating factor, neuropeptides, and other mediators of inflammation. Some of these substances, such as interleukin-6, leukotrienes, complement component 5α, corticotropin-releasing hormone, and transforming growth factor β, have chemokinetic activity. Some substances, such as the inflammatory cytokines tumor necrosis factor α, interleukin-1, and interleukin-6, escape into the systemic circulation, causing systemic symptoms and activating the hypothalamic–pituitary–adrenal axis. Because of such effects, these substances have been called "tissue corticotropin-releasing factor."

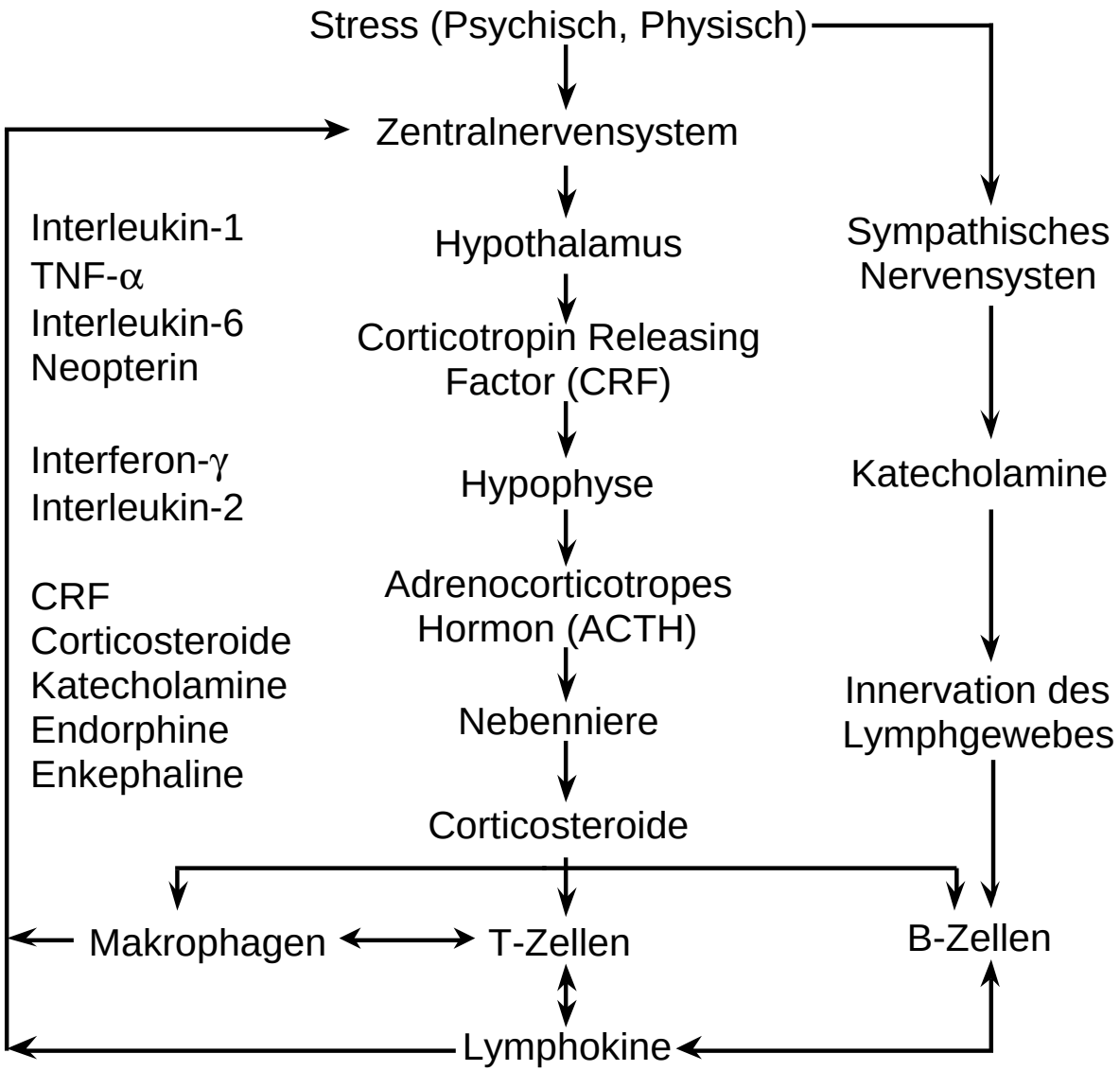
Table 1. Cytokines and Other Mediators of Inflammation That Influence the Hypothalamic–Pituitary–Adrenal Axis.

Inflammatory cytokines
Tumor necrosis factor α
Interleukin-1α and interleukin-1β
Interleukin-6
Other cytokines
Interferon α
Interferon γ
Interleukin-2
Growth factors
Epidermal growth factor
Transforming growth factor β
Lipid mediators
Prostanoids
Platelet-activating factor

(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**).**

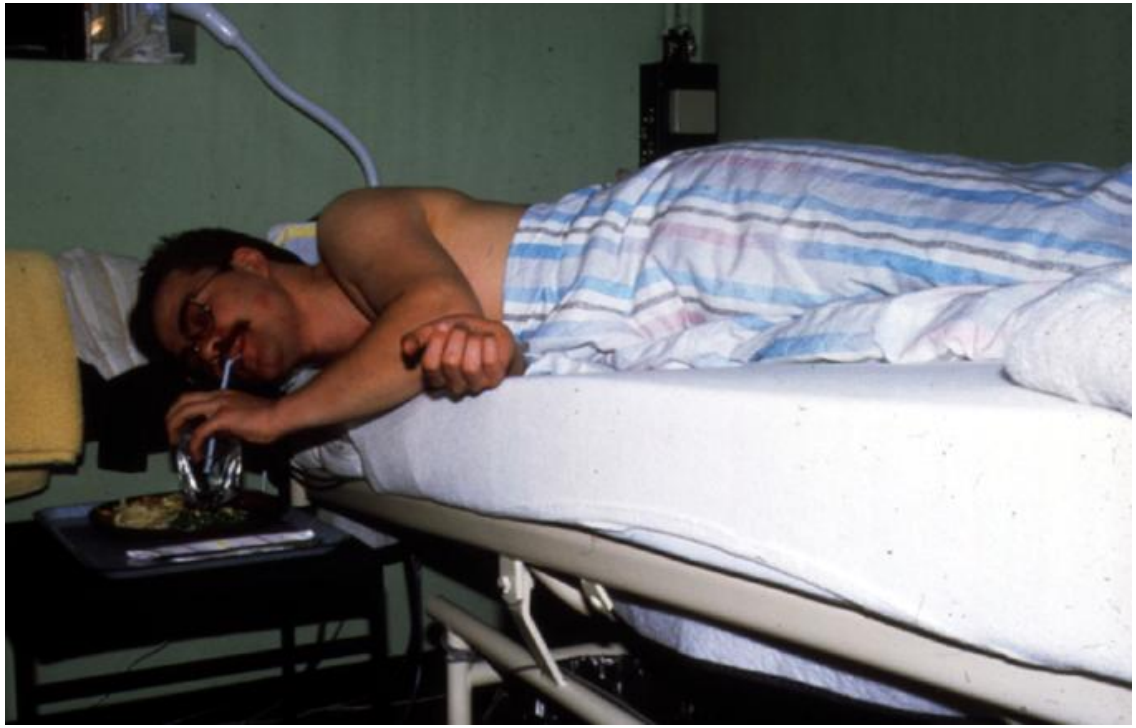


Hypothesis
Physical activity can affect the control mechansims shown.

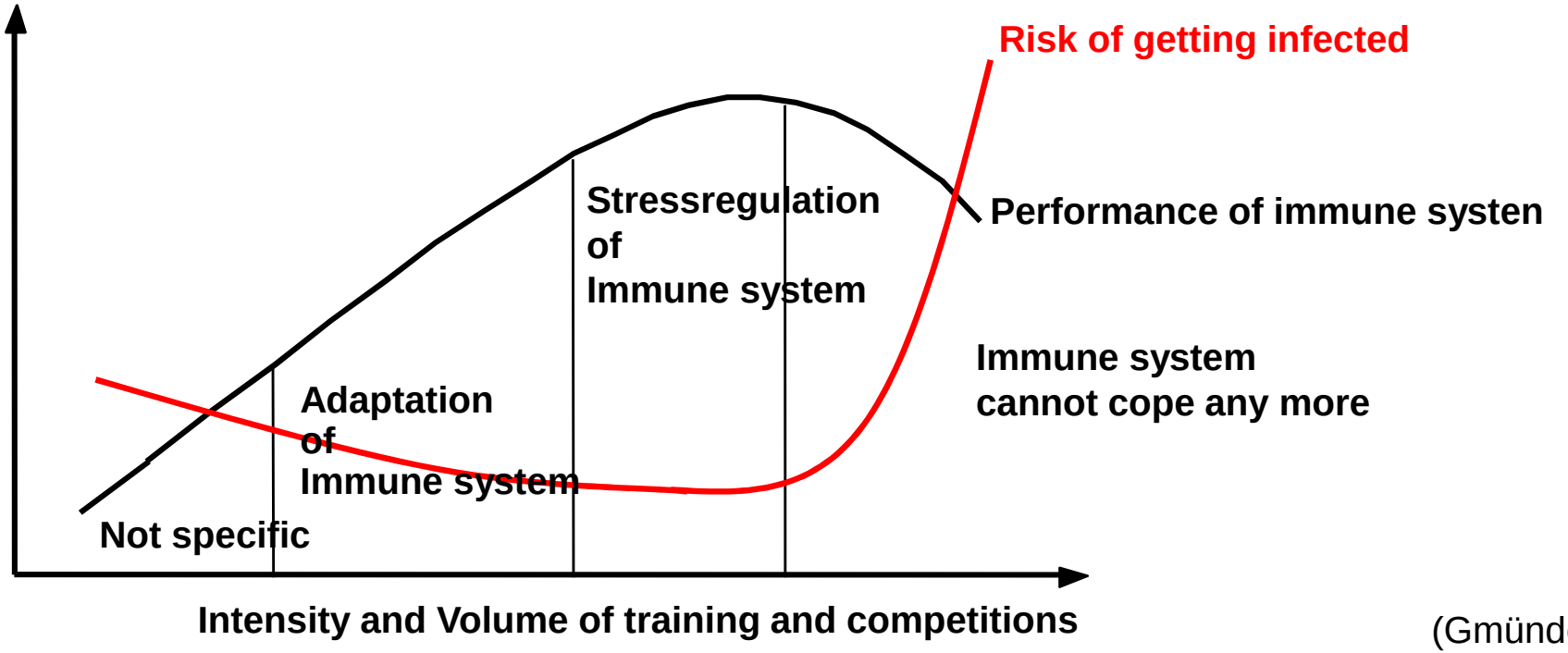
Spezielle Fragestellungen

- 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



(Gmünder 1991, Nieman 2003)

Effects of moderate exercise

- **Intervention**
  4 hours cycling at 70% of individual maximal lactate steady state (59% VO_2max)

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

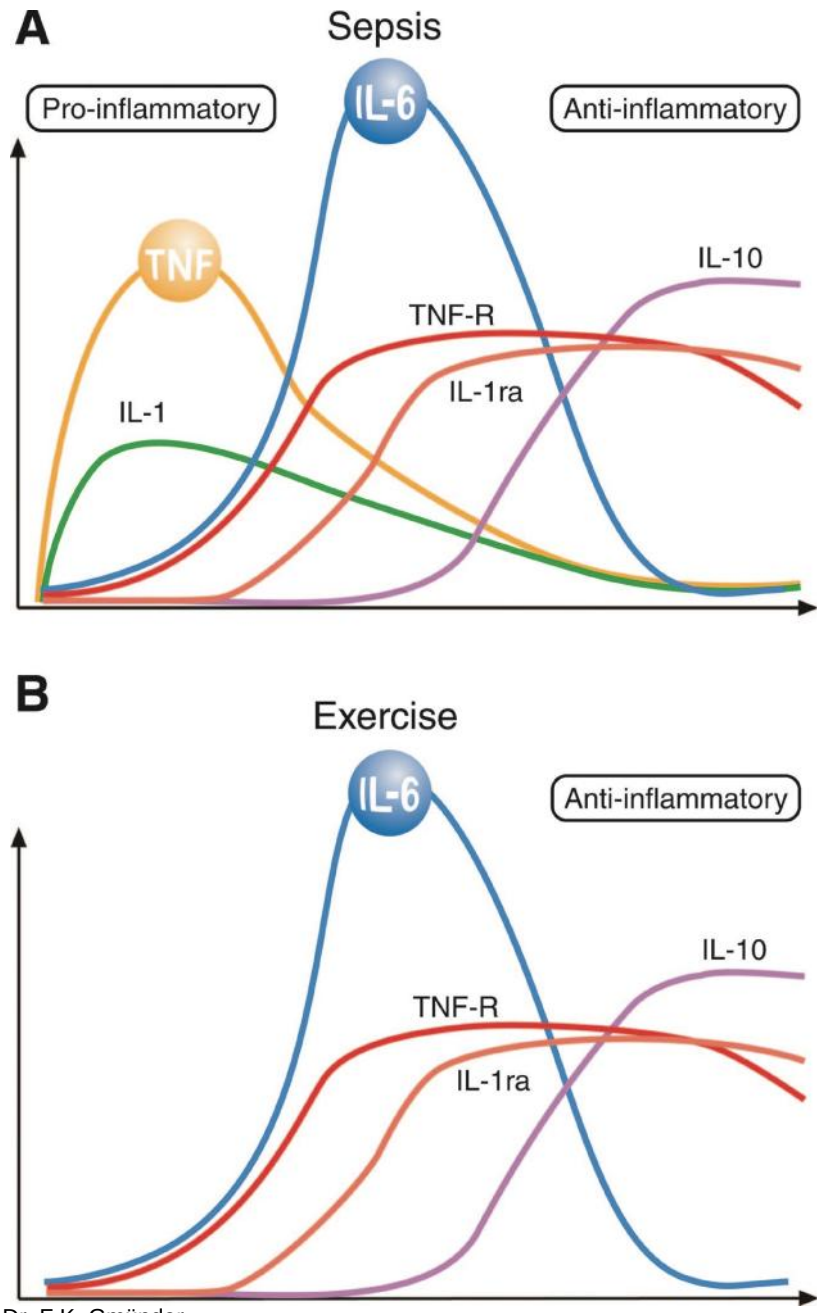
- **Results**
  Moderate acute-phase-reaction
  Moderate increase in stress hormone levels

- **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 prpteins TNF and IL-1 are not released during **moderate and regular exercise**. Anti-inflammatory cytokines prevail, in particular IL-6.

(Woods 2005, Petersen and Pedersen 2005)

Anti-inflammatory effect of sport

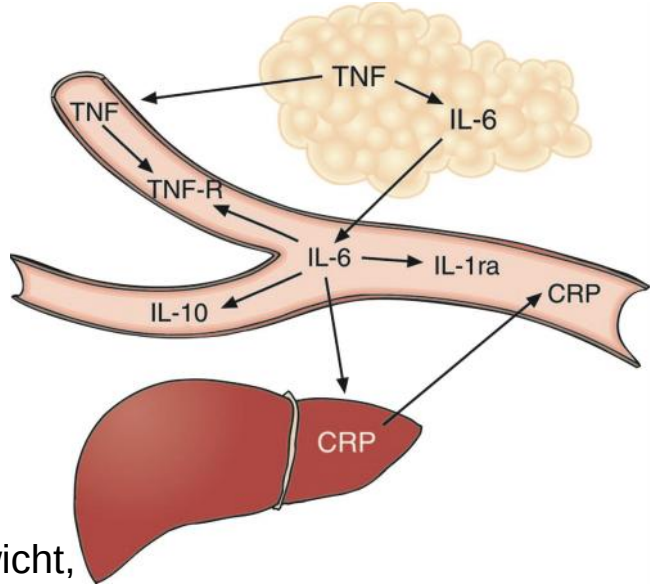
The following conditions are presently seen as an inflammation:

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

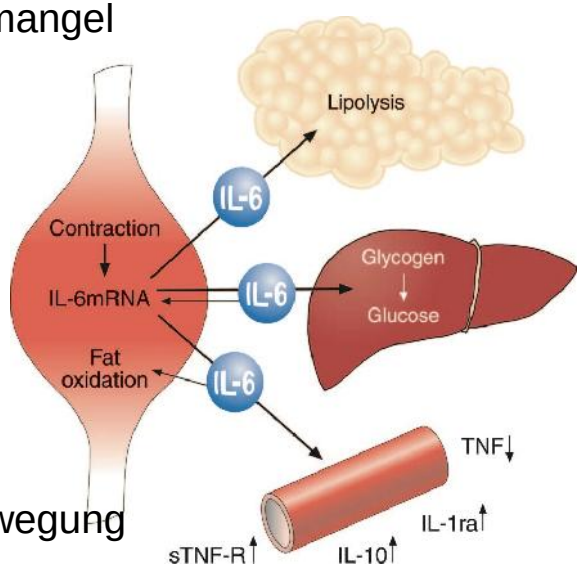
It is interesting to note that

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

(Woods 2005, Petersen and Pedersen 2005)



Übergewicht, Bewegungsmangel



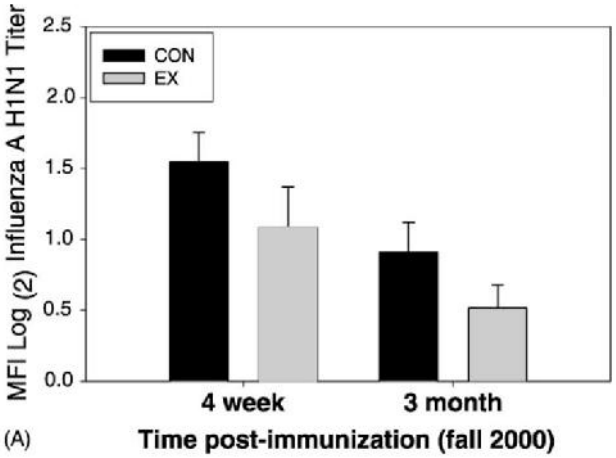
Genügend Bewegung

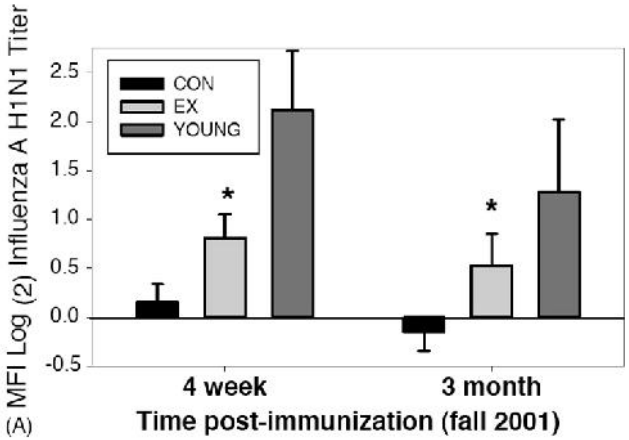
Sport and stress homeostasis

- **Introduction**
  - **Mood, chronic fatigue syndrome, irritability, and fibromyalgia are regulated via the hypothalamic - pituitary - adrenal axis (HPA-system). Patients often show abnormal stress management via the HPA-axis** (Chrousos 1995, Glass et al. 2004).
- **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).

Health, fitness, psychosocial, and immune variables (results shown as means ± Std. Dev.; influenza results shown as $\log_2$ HI titer means ± SEM and % subjects with "protective" titer defined as HI > 40)

Variable	Control pre-intervention	Exercise pre-intervention	Control post-intervention	Exercise post-intervention
Weight (kg)	76.05 ± 18.5	84.6 ± 17.8	76.4 ± 18.0	82.6 ± 17.4
BMI (kg/m^2)	27.5 ± 6.0	28.5 ± 4.8	27.4 ± 5.3	27.8 ± 5.1
Systolic BP	137.1 ± 16.0	141.5 ± 17.7	135.9 ± 15.4	138.5 ± 10.3
Diastolic BP	81.2 ± 10.8	83.4 ± 8.0	79.0 ± 7.1*	77.6 ± 10.3*
6 min walk (yards)	615 ± 109	636 ± 58	632 ± 109	716 ± 78**
Sense of coherence	75.9 ± 8.5	70.3 ± 8.9	72.1 ± 10.8	72.8 ± 7.2**
Depression	2.8 ± 3.1	3.8 ± 2.0	4.2 ± 3.0	3.1 ± 2.8**
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 immuno-endocrine 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.

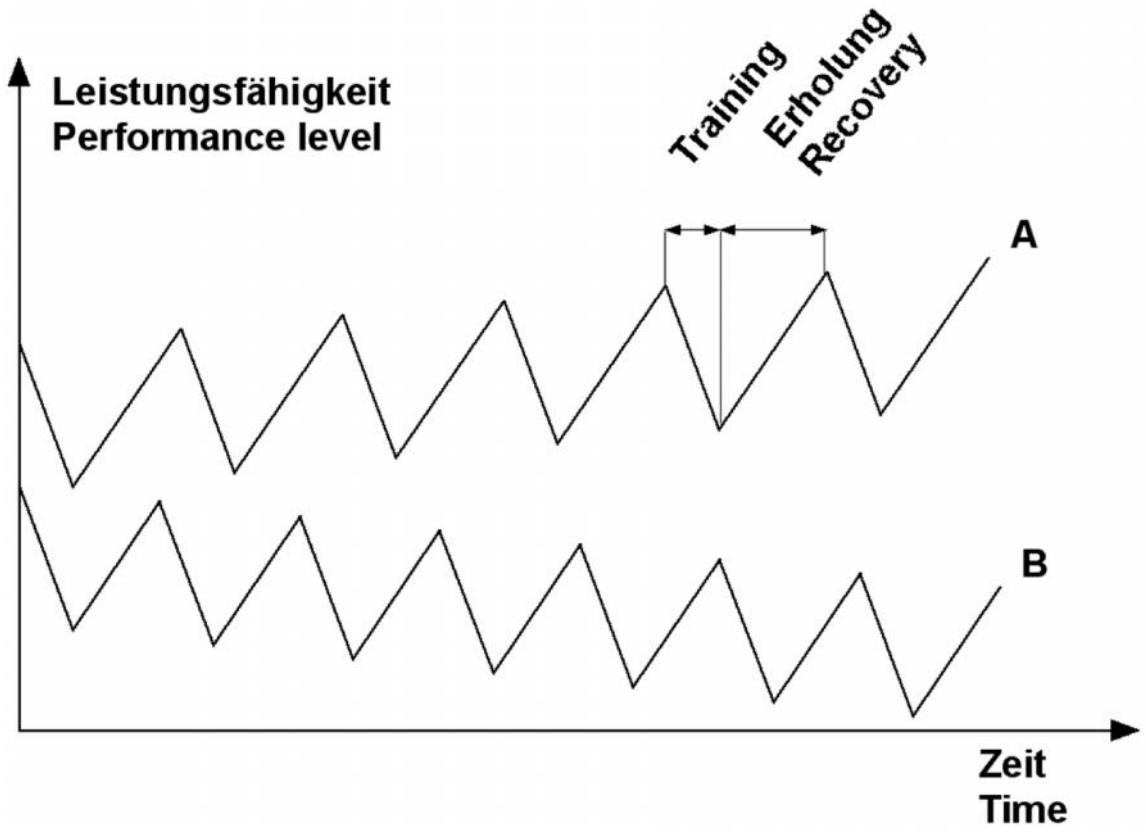
Tipps for training and competition

- 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.*

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

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

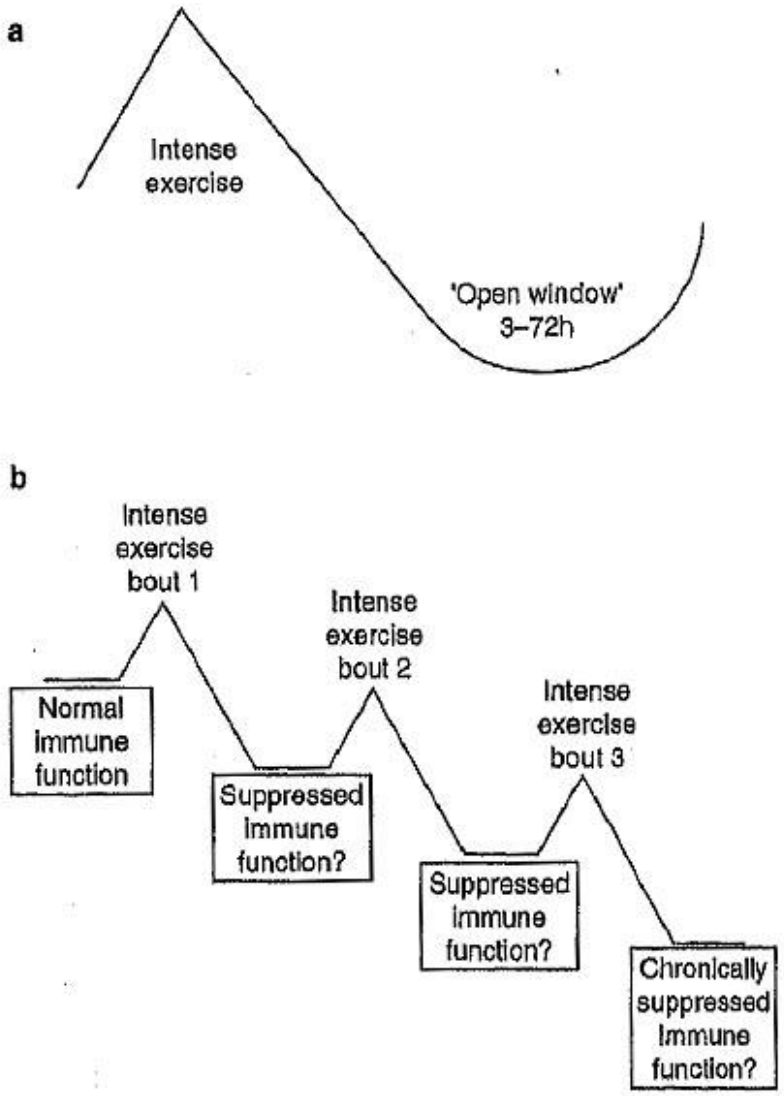


Fig. 1. (a) The 'open window' is believed to occur between 3–72 hours after excessive exercise. It is theorised that athletes are susceptible to illness during this period.[30] **(b)** Cumulative effects: extremely intense exercise, without insufficient recovery time, may result in chronically altered immune function.[8]

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
  http://www.svl.ch/reports/TagungSporternaehrung2003.html
  http://www.svl.ch/reports/Sporternaehrung_2005.html
- **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)

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Thanks!